ADMIN

Memo/Agenda
Minutes
Botanicals
Re-Review Summaries
- Polyvinylpyrrolidone
- Retinol and Retinyl Palmitate

CIR EXPERT PANEL MEETING

SEPTEMBER 9-10, 2013

MEMORANDUM

To: CIR Expert Panel Members and Liaisons
From: Director, CIR
Subject: 128th Meeting of the CIR Expert Panel — Monday and Tuesday, September 9-10, 2013
Date: August 16, 2013

Enclosed are the agenda and accompanying materials for the 128th CIR Expert Panel Meeting to be held September 9-10, 2013. The location again is the Madison Hotel, 1177 Fifteenth Street, NW, Washington, DC 20005. Phone: (202) 862-1600. Fax: (202) 785-1255. The meeting agenda includes consideration of 17 ingredient groups advancing in the process, 1 re-review, 2 re-review summaries, and a review of the botanical boiler plate.

Schedule and hotel accommodations

We have reserved rooms for the nights of Sunday, September 8 and Monday, September 9 at the Madison. If you encounter any travel problems, please contact me on my cell phone at 410-299-0777.

Team meetings

Re-reviews - there is one safety assessment to re-review and make a determination on the need to reopen to revise the conclusion. There are no ingredients to add.

1. Iodopropynyl Butylcarbamate (agenda and flash drive name - butylcarbamate) was reviewed previously (published in 1998) with a conclusion of safe as used in cosmetics at concentrations ≤0.1%. Additionally, the Panel concluded that Iodopropynyl butylcarbamate should not be used in products intended to be aerosolized. Use concentrations reported in 2013 indicate that iodopropynyl butylcarbamate was being used at concentrations up to 0.05% in cosmetic products. The Panel should decide whether to reaffirm the current conclusion or to re-open and issue an amendment.

Draft reports - there are 3 draft reports for review.

1. Alkyl Betaines (agenda and flash drive name – alkyl betaines) - This is the first time that the Panel is seeing this report addressing 11 ingredients. A Scientific Literature Review was announced for public comment May 14, 2013. Technical comments and unpublished data received from the Council have been incorporated into the report. The Council notified CIR that additional data on betaine and the analogs have been submitted to REACH and are located on the European Chemical Agency's (ECHA) website for your review. Do we need more data or can we proceed to issue a tentative report?

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2. Phytosterols (agenda and flash drive name – phytosterols) - This is the first time that the Panel is seeing this report addressing 27 ingredients. The Scientific Literature Review was issued on June 7, 2013. The Panel previously reviewed (2004) the safety of PEG soy sterols that included data on phytosterols/soy sterols and phytosterol esters, and concluded that these ingredients are safe for use in cosmetic products. Summaries of the relevant data were included in the report. Do we need more data or can we proceed to issue a tentative report?

3. Rosmarinus Officinalis (agenda and flash drive name – rosmarinus) - This is the first time that the Panel is seeing this report addressing 12 ingredients. The Scientific Literature Review was issued on June 7, 2013. Technical comments from the Council have been addressed and unpublished data were added. Industry questioned the inclusion strategy for constituents of Rosmarinus in this report. Should the carboxylic acid ingredients be included in this report? Do we need more data or can we proceed to issue a tentative report?

Tentative report – there are 5 draft tentative reports.

1. Amino Acid Alkyl Amides (agenda and flash drive name – alkyl amides) – At the June 2013 meeting, the Panel issued an insufficient data announcement on the safety of amino acid alkyl amide ingredients. The Panel requested dermal irritation and sensitization data at the highest use concentration for (1) lauroyl lysine (45%) and (2) sodium lauroyl glutamate (40%). Data received from industry have been incorporated in the report and technical comments have been considered. If the information is still insufficient, then a tentative conclusion of insufficient data should be issued. If the information now available is sufficient, the Panel should issue a Tentative Report with an appropriate discussion/conclusion.

2. *Anthemis Nobilis*-Derived Ingredients (agenda and flash drive name – *anthemis nobilis*) – At the June 2013 meeting, the Panel issued an insufficient data announcement on the safety of *Anthemis nobilis*-derived ingredients in cosmetic products. Except for the flower oil, the Panel requested composition data on all *Anthemis nobilis*-derived ingredients, and sensitization data on all ingredients at the use concentration of 10%. We did not receive those data. If the information is still insufficient, the Panel should issue a Tentative Report with an insufficient data conclusion.

3. *Chamomilla recutita*-Derived Ingredients (agenda and flash drive name – *chamomile*) – At the June 2013 meeting, the Panel determined that the data are insufficient for evaluating the safety of *Chamomilla recutita*-derived ingredients in cosmetic products. The Panel requested skin irritation and sensitization data on *Chamomilla recutita* (matricaria) flower extract at a use concentration of 10%. Skin irritation and sensitization data at use concentrations of 0.3% and 0.2%, respectively, were provided. The Panel should confirm that the new data satisfy (or don't satisfy) the needs of the Panel. The Panel should review the draft tentative conclusion and the discussion section which presents the rationale for the conclusion.

4. Formic Acid and Sodium Formate (agenda and flash drive name – formic acid) – At the June 2012 meeting, the Panel reopened the safety assessment of formic acid to consider new data on the new use as a preservative and a fragrance, and to consider adding sodium formate. This report includes data received on the new functions of formic acid and sodium formate. The Panel should confirm that the data is sufficient to issue an amended tentative report with a safe as used or safe with qualifications conclusion.

5. Hydrolyzed Wheat Protein and Hydrolyzed Wheat Gluten (agenda and flash drive name – hydrolyzed wheat proteins) – At the March 2013, meeting, the Panel tabled the animal- and plant-derived hydrolyzed proteins report to allow for reorganization and further analysis of data from Japan. This report groups hydrolyzed wheat protein and hydrolyzed wheat gluten. Prior to tabling the report, the Panel issued an insufficient data announcement and requested data on (1) methods of manufacturing; and (2) composition and characterization specifications of hydrolyzed wheat protein from several suppliers. Technical comments were considered and updated VCRP

data have been incorporated into the report. No additional new unpublished data were received. Do we need more data or can we proceed to issue as tentative report?

Final reports - there are 9 final reports for consideration. After reviewing these drafts, especially the rationale in the discussion section, the Panel should issue them as final reports.

1. Achillea Millefolium (Yarrow)-Derived Ingredients (agenda and flash drive name – *achillea*) – At the June 2013 meeting, the Panel issued a tentative amended report with a conclusion that these ingredients are safe in the present practices of use and concentration in cosmetics. Technical comments received from the Council were considered.

2. Alkyl PEG/PPG Ethers (agenda and flash drive name – PEG-PPG ethers) – At the June 2013 meeting, the Panel issued a tentative report with a conclusion that these ingredients are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating. Technical comments from the Council were addressed.

3. Alumina and Aluminum Hydroxide (agenda and flash drive name – alumina) – At the June 2013 meeting, the Panel issued a tentative report with a conclusion of safe in cosmetics in the present practices of use and concentration in cosmetics. Technical comments received from the Council were addressed. No additional data were received. The report addresses the Panel's request for additional information on the connection between aluminum and Alzheimer's disease.

4. Dialkyl Sulfosuccinate Salts (agenda and flash drive name – sulfosuccinates) – At the June 2013 meeting, the Panel issued a tentative amended report with a conclusion of safe in the present practices of use an concentration in cosmetics when formulated to be non-irritating. The Panel confirmed the existing safe conclusion for diethylhexyl sodium sulfosuccinate and added 7 dialkyl sulfosuccinate salts. Technical comments received from the Council have been addressed.

5. Hydroxypropyl bis(*N*-Hydroxyethyl-*p*-Phenylenediamine) HCl (agenda and flash drive name – hair dye) – In June 2013, the Panel issued a tentative report with a conclusion of safe in the present practices of use and concentration in hair dyes. Technical comments received from the Council have been addressed. No additional data were received.

6. Isethionate Salts (agenda and flash drive name – isethionate) – At the June 2013 meeting, the Panel issued a tentative amended report with a conclusion of safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating. Technical comments received from the Council were considered. No additional data were received.

7. Methyl Glucose Polyethers and Esters (agenda and flash drive name – methyl glucose) – At the June 2103 meeting, the Panel issued a revised tentative report with a conclusion of safe in the present practices of use and concentration in cosmetics. The Council commented that language in the Discussion should reflect the Panel's conclusion that the data submitted on the toxicity potential of these ingredients were sufficient to support the safety of these ingredients in cosmetics. Additional information relating to skin sensitization of methyl glucose dioleate has been added.

8. Polyquaternium-22 and Polyquaternium-39 (agenda and flash drive name – polyquats) – At the June 2013 meeting, the Panel issued a tentative report with a conclusion of safe in the present practices of use and concentration in cosmetics. Technical comments received from the Council were addressed. New VCRP data have been included in the report. No other comments were submitted.

9. Tromethamine, Aminomethyl Propanediol, and Aminoethyl Propanediol (agenda and flash drive name – tromethamine) – In June 2013, the Panel issued a tentative report with a conclusion of safe in the present practices of use and concentration in cosmetics. Technical comments received from the Council were addressed. Updated concentrations of use data for aminomethyl propanediol and aminoethyl propanediol have been included. There is still no reported use of aminoethyl propanediol.

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 9 reports to be issued as final safety assessments, followed by the rest of the reports advancing in the process, and finish with a discussion of the botanical boiler plate.

The bulk of the agenda is the final reports, but there are almost as many draft and tentative reports combined. It is still likely that the full Panel session will conclude before lunch on day 2, so plan your travel accordingly.

Have a safe journey.

Agenda
128th Cosmetic Ingredient Review Expert Panel Meeting
September 9-10, 2013

Monday, September 9

8:00 am **CONTINENTAL BREAKFAST**

8:30 am **WELCOME TO THE 128th EXPERT PANEL TEAM MEETINGS** **Drs. Bergfeld/Gill**

8:45 am **TEAM MEETINGS** **Drs. Marks/Belsito**

	Dr. Marks' Team		**Dr. Belsito's Team***
FR (LB)	tromethamine	FR (WJ)	methyl glucose
FR (LB)	alumina	FR (WJ)	polyquats
FAR (LB)	*achillea*	TR (WJ)	*chamomile*
FR (LB)	hair dye	TR (WJ)	*anthemis nobilis*
DR (LB)	phytosterols	TAR (WJ)	formic acid
Admin (LB/IB)	Botanical BP	RR (WJ)	butylcarbamate (re-review)
FR (MF)	PEG-PPG ethers	RRsum (LG)	Re-review summaries (2)
FAR (MF)	sulfosuccinates	FAR (CB)	isethionate
DR (MF)	*rosmarinus*	TR (CB)	alkyl amides
FR (WJ)	methyl glucose	DR (CB)	alkyl betaines
FR (WJ)	polyquats	DR (CB)	hydrolyzed wheat proteins
TR (WJ)	*chamomile*	FR (MF)	PEG-PPG ethers
TR (WJ)	anthemis nobilis	FAR (MF)	sulfosuccinates
TAR (WJ)	formic acid	DR (MF)	*rosmarinus*
RR (WJ)	butylcarbamate (re-review)	FR (LB)	tromethamine
RRsum (LG)	Re-review summaries (2)	FR (LB)	alumina
FAR (CB)	isethionate	FAR (LB)	*achillea*
TR (CB)	alkyl amides	FR (LB)	hair dye
DR (CB)	alkyl betaines	DR (LB)	phytosterols
DR (CB)	hydrolyzed wheat proteins	Admin (LB/IB)	Botanical BP

Noon **Lunch for Panel, liaisons, and staff**

1:00 pm **Team meetings - continue as needed**

5:00 pm **ADJOURN DAY 1 SESSION**

FR: Final report
FAR: Final amended report
TR: Tentative report
TAR: Tentative amended report
DR: Draft report
RR: Re-review

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.

* Team moves to breakout room.

Tuesday, September 10			
8:00 am	**CONTINENTAL BREAKFAST**		
8:30 am	**WELCOME TO THE 128th FULL CIR EXPERT PANEL MEETING**		
8:45 am	Admin	**MINUTES OF THE June 2013 EXPERT PANEL MEETING**	**Dr. Bergfeld**
9:00 am	**DIRECTOR'S REPORT**		**Dr. Gill**
9:30 am	**FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, RE-REVIEWS, and OTHER DISCUSSION ITEMS**		
		Final Reports	
	FAR (CB)	Isethionate - Dr. Belsito reports	
	FR (LB)	Alumina - Dr. Marks reports	
	FAR (LB)	*Achillea* - Dr. Belsito reports	
	FR (LB)	Tromethamine - Dr. Marks reports	
	FR (LB)	Hair dye - Dr. Belsito reports	
	FAR (MF)	Sulfosuccinates - Dr. Marks reports	
	FR (MF)	PEG-PPG Ethers - Dr. Belsito reports	
	FR (WJ)	Methyl glucose - Dr. Marks reports	
	FR (WJ)	Polyquats - Dr. Belsito reports	
		Reports Advancing	
	DR (LB)	Phytosterols - Dr. Marks reports	
	DR (MF)	*Rosmarinus* - Dr. Belsito reports	
	DR (CB)	Alkyl betaines - Dr. Marks reports	
	TR (CB)	Hydrolyzed wheat proteins - Dr. Belsito reports	
	TR (CB)	Alkyl amides - Dr. Marks reports	
	TAR (WJ)	Formic Acid - Dr. Belsito reports	
	TR (WJ)	*Chamomile* - Dr. Marks reports	
	TR (WJ)	*Anthemis nobilis* - Dr. Belsito reports	
		Re-reviews	
	RR (WJ)	Butylcarbamate - Dr. Marks reports	
	Admin (LG)	re-review summaries (2) - Dr. Gill reports	
		New Data	
	Admin (LB/IB)	Botanical BP - Dr. Belsito reports	

ADJOURN - Next meeting *Monday and Tuesday, December 9-10, 2013*

FR: Final report
FAR: Final amended report
TR: Tentative report
TAR: Tentative amended report
DR: Draft report
RR: Re-review

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.

ONE HUNDRED TWENTY-SEVENTH MEETING

OF THE

EXPERT PANEL

June 10-11, 2013

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.

Adopted (Date)

Wilma F. Bergfeld, M.D.

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Others Present at the Meeting

F. Alan Andersen	CIR
Yutaka Aoki	Kanebo Cosmetics
Robeena Aziz	FDA
Lillian Becker	CIR
Don Bjerke	Procter & Gamble
Ivan Boyer	CIR
Christina Burnett	CIR
Kapal Dewan	FDA
Monice Fiume	CIR
Paul Donald Forbes	Toxarus, Inc.
Kevin Fries	CIR
Lillian Gill	CIR
Robert Golden	Toxlogol
Britiny Hawkins	EWG
Bart Heldreth	CIR
Brian Hughes	Dow Chemical Co.
Carla Jackson	CIR
Wilbur Johnson, Jr.	CIR
Javauh Juanbe	EWG
Akiho Kinoshita	Shiseido
Dennis Laba	Presperse
Beth Lange	Mary Kay, Inc.
Stanley R. Milstein	FDA
Lauren Nardella	The Rose Sheet
Damani Parran	Akzo Nobel
John Paul Pestano	EWG
Thomas Re	L'Oreal
Diego Rua	FDA
Noriko Shibuya	Shiseido
David Steinberg	Steinberg & Associates
Brian Xu	Ashland

CHAIRMAN'S OPENING REMARKS

The 127th meeting of the CIR Expert Panel was called to order at 8:30 a.m. by Dr. Wilma Bergfeld on Tuesday, June 11, 2013. She then recalled the grand retirement celebration for Dr. Andersen that was held on yesterday evening and the book of tributes that was presented as a token of appreciation for his tenure at CIR. Regarding today's agenda, Dr. Bergfeld noted that a total of 18 ingredient reports are scheduled for review. Of these, 5 and 10 reports are expected to advance to the final and tentative report stages, respectively. Re-review documents will also be considered to determine whether or not the published final reports associated with these documents should be re-opened.

Dr. Bergfeld mentioned that CIR had received a request to review formaldehyde again, and that a presentation on this ingredient was given by Dr. Robert Golden prior to Team meetings on the preceding day **(Slide presentation at end of minutes)**. She also noted that re-review cycles, the toxicity of botanical mixtures, and CIR's heavy metals/pesticides boilerplate were among the topics discussed during yesterday's Team meetings, and will likely be included in today's Panel discussions.

APPROVAL OF MINUTES

The minutes of the March 10-11, 2013 CIR Expert Panel meeting were unanimously approved.

DIRECTOR'S REPORT

Dr. Andersen introduced Dr. Beth Lange, Mary Kay, the new chair of the Council's CIR Science and Support Committee and welcomed her ongoing participation with the Panel.

He described the safety assessments included in the most recent issue of the *International Journal of Toxicology* and noted that the interval between completion of reports by the Panel and their appearance in the Journal was decreasing significantly. He reviewed the ongoing efforts of Dr. Ivan Boyer, CIR's senior toxicologist, along with Dr. Bart Heldreth, CIR chemist, to develop alternative methods for assessing potential toxicity of cosmetic ingredients. Building on the presentation by EPA's Dr. Ann Richards on her program's efforts in computational toxicology, CIR has expanded the thinking about possible collaboration to include both FDA and CIR interacting with the EPA program.

Dr. Andersen thanked the Panel for participating in the celebration of his career at CIR. He echoed the oft-stated observation that the work of the Panel exceeds the sum of its parts. He explained that the extraordinary efforts of the industry trade association some 37 years ago to establish an independent safety review group and the unwavering commitment to the program over the intervening years, along with all the individuals that make up the CIR Expert Panel and the CIR staff, made his 20 years in the job a real pleasure. This was the final meeting for Dr. Andersen, who is retiring. CIR Deputy Director, Dr. Lillian Gill will move into the Director position in July.

Final Safety Assessments

Animal- and Plant-derived Amino Acids

The 21 animal- and plant-derived amino acids ingredients listed below are safe in the present practices of use and concentration as described in the safety assessment.

apricot kernel amino acids*
collagen amino acids
corn gluten amino acids*
elastin amino acids*
garcinia mangostana amino acids*
hair keratin amino acids
jojoba amino acids*
keratin amino acids
lupine amino acids
lycium barbarum amino acids*
milk amino acids
oat amino acids
rice amino acids
sesame amino acids*
silk amino acids
soy amino acids
spirulina amino acids*
sweet almond amino acids*
vegetable amino acids
wheat amino acids
yeast amino acids*

**Not reported to be in current use. Were 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 this group.*

These animal- and plant-derived amino acids function as skin and hair conditioning agents. The safety of α-amino acids as direct food additives has been well established based on extensive research through acute and chronic dietary exposures. The Panel focused its

review on dermal irritation and sensitization data relevant to the use of these ingredients in topical cosmetics and relied on its past findings on the safety of α-amino acids.

The discussion addressed the potential that incomplete enzymatic hydrolysis of the parent proteins may lead to residual di- or tripeptides. Concern was expressed over potential that such small peptides could cause allergic reactions in sensitive individuals. The Panel stated that industry should continue to manufacture plant- and animal-derived amino acids in a way that minimizes residual peptides.

The Panel reiterated that a safety assessment for hydrolyzed protein ingredients from plant and animal sources will be developed on a separate track.

Boron Nitride

Boron nitride is safe in the present practices of use and concentration in cosmetics.

This ingredient is an inorganic compound with a crystalline form that can be hexagonal or cubic, and is reported to function in cosmetics as a slip modifier (i.e., it has a lubricating effect). Boron nitride is a chemically inert and insoluble ingredient, and its crystalline lattice structure makes it a very large molecule that is not expected to penetrate the skin. While the highest reported concentration of use of boron nitride is 25% in eye shadow formulations and sensitization data were only available at a maximum concentration of 18.7% in formulation, boron nitride was not expected to cause sensitization because the stratum corneum would act as an effective barrier.

***Hypericum perforatum*-derived ingredients (amended)**

The 7 ingredients listed below are safe in the present practices of use and concentration in cosmetics.

hypericum perforatum extract
hypericum perforatum flower extract
hypericum perforatum flower/leaf extract*
hypericum perforatum flower/leaf/stem extract
hypericum perforatum flower/twig extract*
hypericum perforatum leaf extract*
hypericum perforatum oil

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

This is an amended safety assessment. One common name for this plant is St. John's wort. These ingredients function in cosmetics as skin-conditioning agents – miscellaneous and antimicrobial agents, but are used at low concentrations. The Panel reviewed relevant animal and human data. Because formulators may use more than one botanical ingredient in a formulation, caution was urged to avoid levels of toxicological and allergenic concern for plant constituents, such as hypericin. The Panel also reiterated that all botanical ingredients can contain pesticide residues and heavy metals as impurities, and that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulations.

Nitrocellulose and Collodion

Nitrocellulose and collodion are safe in the present practices of use and concentration in cosmetics.

Nitrocellulose is used almost exclusively in nail products. The maximum reported use concentration of nitrocellulose is 41% in "nail stickers" made of dried nail polish; the maximum reported use concentration in nail polish and enamels is 22%. Collodion is reported to have a maximum concentration of use of 14% in nail polish and enamel. While it appeared that collodion might properly be considered a mixture containing nitrocellulose, collodion is a listed cosmetic ingredient and has reported uses. So, collodion was added to the title of this report. The molecular weight and chemical properties of nitrocellulose suggested little likelihood of significant dermal absorption, and there is little possibility of biotransformation were any penetration to occur.

Tentative Safety Assessments

***Achillea millefolium*-Derived Ingredients**

The Panel issued a tentative safety assessment for public comment with the conclusion that these 3 Achillea millefolium-derived ingredients listed below were safe as cosmetic ingredients in the present practices of use and concentration.

achillea millefolium extract
achillea millefolium flower/leaf/stem extract
achillea millefolium flower extract

These ingredients may function in cosmetics as skin-conditioning agents – miscellaneous, skin-conditioning agents – humectants; and fragrance ingredients. The Panel reviewed relevant animal and human data to determine their safety in cosmetics. Achillea millefolium extract was reported to be used in 135 cosmetic products, including 83 leave-on products up to 0.04% and 47 rinse-off products up to 0.03%. There were no uses reported for achillea millefolium flower extract and achillea millefolium flower/leaf/stem extract, but were they to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to achillea millefolium extract.

The Panel stressed that there may be an accumulation of constituents of toxicological and allergenic concern (e.g., hydroquinone, linalool) when multiple botanical ingredients containing these constituents are used in the same formulation. The Panel also reiterated that all botanical ingredients can contain pesticide residues and heavy metals as impurities, and that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

Alkyl PEG/PPG Ethers

The Panel issued a tentative safety assessment for public comment with the conclusion that the 131 alkyl PEG/PPG ethers listed below are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

PEG-4-PPG-7 C13/C15 alcohol*
PEG/PPG-3/6 dimethyl ether*
PEG/PPG-7/12 dimethyl ether*
PEG/PPG-9/2 dimethyl ether
PEG/PPG-14/7 dimethyl ether
PEG/PPG-17/4 dimethyl ether
PEG/PPG-22/40 dimethyl ether*
PEG/PPG-27/14 dimethyl ether*
PEG/PPG-35/40 dimethyl ether
PEG/PPG-36/41 dimethyl ether
PEG/PPG-50/40 dimethyl ether
PEG/PPG-52/32 dimethyl ether*
PEG/PPG-55/28 dimethyl ether
PEG/PPG-4/2 propylheptyl ether*
PEG/PPG-6/2 propylheptyl ether*
PEG-7/PPG-2 propylheptyl ether*
PEG/PPG-8/2 propylheptyl ether*
PEG/PPG-10/2 propylheptyl ether*
PEG/PPG-14/2 propylheptyl ether*
PEG/PPG-40/2 propylheptyl ether*
PPG-2-ceteareth-9
PPG-4-ceteareth-12*
PPG-10-ceteareth-20*
PPG-1-ceteth-1*
PPG-1-ceteth-5*
PPG-1-ceteth-10*
PPG-1-ceteth-20*
PPG-2-ceteth-1*
PPG-2-ceteth-5*
PPG-2-ceteth-10
PPG-2-ceteth-20*
PPG-4-ceteth-1*
PPG-4-ceteth-5*
PPG-4-ceteth-10*
PPG-4-ceteth-20
PPG-5-ceteth-20
PPG-8-ceteth-1
PPG-8-ceteth-2*
PPG-8-ceteth-5*
PPG-8-ceteth-10
PPG-8-ceteth-20
PPG-2 C9-11 pareth-5*
PPG-2 C9-11 pareth-7*
PPG-2 C9-11 pareth-8*
PPG-2 C9-11 pareth-11*
PPG-2 C12-13 pareth-8
PPG-2 C12-15 pareth-6*
PPG-4 C13-15 pareth-15*
PPG-5 C9-15 pareth-6*
PPG-6 C9-11 pareth-5*
PPG-6 C12-15 pareth-12*
PPG-6 C12-18 pareth-11*
PPG-3 C12-14 sec-pareth-7*
PPG-4 C12-14 sec-pareth-5*
PPG-5 C12-14 sec-pareth-7*
PPG-5 C12-14 sec-pareth-9*
PPG-1-deceth-4*
PPG-1-deceth-5*
PPG-1-deceth-6*
PPG-1-deceth-7*
PPG-2-deceth-3
PPG-2-deceth-5*
PPG-2-deceth-7*
PPG-2-deceth-8*
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PPG-2-deceth-12
PPG-2-deceth-15*
PPG-2-deceth-20*
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PPG-2-deceth-50*
PPG-2-deceth-60*
PPG-4-deceth-4*
PPG-4-deceth-6*
PPG-6-deceth-4*
PPG-6-deceth-9*
PPG-8-deceth-6*
PPG-14-deceth-6*
PPG-6-decyltetradeceth-12*
PPG-6-decyltetradeceth-20
PPG-6-decyltetradeceth-30
PPG-13-decyltetradeceth-24
PPG-20-decyltetradeceth-10
PPG-9-ethylhexeth-5*
PPG-1-isodeceth-4*
PPG-1-isodeceth-6*
PPG-1-isodeceth-7*
PPG-1-isodeceth-9*
PPG-2-isodeceth-4*
PPG-2-isodeceth-6*
PPG-2-isodeceth-8*
PPG-2-isodeceth-9*
PPG-2-isodeceth-10*
PPG-2-isodeceth-12
PPG-2-isodeceth-18*
PPG-2-isodeceth-25*
PPG-3-isodeceth-1*
PPG-4-isodeceth-10*
PPG-3-isosteareth-9
PPG-2-laureth-5*
PPG-2-laureth-8*
PPG-2-laureth-12*
PPG-3-laureth-8*
PPG-3-laureth-9*
PPG-3-laureth-10*
PPG-3-laureth-12*
PPG-4 laureth-2*
PPG-4 laureth-5*
PPG-4 laureth-7*
PPG-4-laureth-15*
PPG-5-laureth-5
PPG-6-laureth-3*
PPG-25-laureth-25
PPG-3-myreth-3*
PPG-3-myreth-11*
PPG-2-PEG-11 hydrogenated lauryl alcohol ether*
PPG-3-PEG-6 oleyl ether*
PPG-9-steareth-3*
PPG-23-steareth-34*
PPG-30 steareth-4*
PPG-34-steareth-3
PPG-38 steareth-6*
PPG-1 trideceth-6
PPG-1 trideceth-13*
PPG-4 trideceth-6*
PPG-6 trideceth-8*
propylene glycol capreth-4*
propylene glycol isodeceth-4*
propylene glycol isodeceth-12*
propylene glycol laureth-6*
propylene glycol oleth-5*

**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 maximum reported leave-on use concentrations are up to 10% PPG-5-ceteth-20 in "other" fragrance preparations and in tonics, dressings, and other hair grooming aids and up to 7% PEG/PPG-14/7 dimethyl ether in face and neck, and body and hand products.

These ingredients are similar to the alkyl PEG ether ingredients that have already been reviewed and found safe when formulated to be non-irritating by the CIR Expert Panel. The principle differences between the alkyl PEG ethers and the alkyl PEG/PPG ethers are the polypropylene glycol (PPG) repeat units that are included to fine tune the surfactant properties of these ingredients. Inclusion of the PPGs did not raise any additional safety concerns because the PPGs were reviewed recently by the CIR and found safe when formulated to be non-irritating. While there were few data available on the individual alkyl PEG/PPG ethers, the existing data on the analogues support the safety of this ingredient family. Additionally, concerns, such as the possibility of the presence of the residual starting materials ethylene oxide and propylene oxide or the potential by-product 1,4-dioxane, and the possibility that these ingredients can be penetration enhancers, will be addressed in the safety assessment as done previously in the alkyl PEG ethers report.

Alumina and Aluminum Hydroxide

The Panel issued a tentative safety assessment for public comment with the conclusion that alumina and aluminum hydroxide are safe in the present practices of use and concentration in cosmetics.

Alumina was reported to be used in 523 leave-on products at concentrations up to 60%, and in 40 rinse-off products at concentrations up to 30%. Aluminum hydroxide was reported to be used in 572 leave-on products at concentrations up to 10.1% and 6 rinse-off products at concentrations up to 8.8%. In addition to published safety data, the Panel relied on the FDA's conclusion of safety for the use of alumina in medical devices (i.e., replacement knees and dental implants). The Panel also considered the FDA's approval of aluminum hydroxide in over-the-counter drugs (i.e., antacids) as well as in colors used in medical devices (i.e., sutures and bone cement).

Because the names of these ingredients may raise a concern that use in cosmetics would involve exposure to aluminum, the Panel directly addressed that concern. Acknowledging the ongoing scientific debate about aluminum's connection to Alzheimer's disease and breast cancer, the Panel suggested that this was not relevant to these ingredients because these two ingredients are not the same as the elemental aluminum and aluminum. Use of alumina and aluminum hydroxide in cosmetics would not result in significant systemic availability of aluminum.

Dialkyl Sulfosuccinate Salts

The Panel issued a tentative amended safety assessment for public comment with the conclusion that the 8 dialkyl sulfosuccinate salts listed below are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

ammonium dinonyl sulfosuccinate*
diamyl sodium sulfosuccinate*
dicapryl sodium sulfosuccinate*
diethylhexyl sodium sulfosuccinate
diheptyl sodium sulfosuccinate*
dihexyl sodium sulfosuccinate*
diisobutyl sodium sulfosuccinate*
ditridecyl sodium sulfosuccinate*

**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 re-opened the safety assessment of diethylhexyl sodium sulfosuccinate (previously named dioctyl sodium sulfosuccinate; last reviewed in 1998) to add an additional seven dialkyl sulfosuccinate salts, and issued the tentative amended report. The Expert Panel found the existing data on diethylhexyl sodium sulfosuccinate sufficient to evaluate the safety of the other diesters, and issued a tentative amended safety assessment for public comment. Diethylhexyl sodium sulfosuccinate is the only alky sulfosuccinate salt named in this report that is in use, and the greatest maximum reported leave-on use concentration is 4.4% in eyebrow pencil formulations.

The Panel stated that diethylhexyl sodium sulfosuccinate is a reasonable representative of all of the diesters. All of the diesters named above are of a similar alkyl chain length and are symmetrically substituted, and all have similar functions in cosmetic formulations. The re-review document presented to the Panel originally suggested including monoesters in addition to the diesters. However, the Panel did not find that diethylhexyl sodium sulfosuccinate is representative of the polar monoesters, and the data could not be "read-across" to address their safety; therefore, the monoesters are not included in this amended safety assessment.

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl

The Panel issued a tentative safety assessment for public comment with the conclusion that this ingredient is safe in the present practices of use and concentration in hair dyes.

Hydroxypropyl bis(N-hydroxyethyl-p-phenylenediamine) HCl was reported to be used in 75 hair dyes and colors at a maximum concentration of 0.28%. Extensive data developed to support the safety of this oxidative hair dye ingredient in Europe was reviewed by the Panel. The Panel noted that UV absorption was seen in the UVC region of the spectrum, but because UVC is not present in sunlight, no photochemical interaction would be seen in routine use. There was a small absorption peak in the UVB range, but the available phototoxicity data demonstrated no adverse reactions.

While the safety of individual hair dye ingredients are not addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information. Currently available epidemiology studies provided insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers. A detailed summary of the available hair dye epidemiology data is available at http://www.cir-safety.org/cir-findings.

Isethionate Salts

The Panel issued a tentative amended safety assessment on isethionate salts with the conclusion that the 12 ingredients listed below are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

sodium cocoyl isethionate
ammonium cocoyl isethionate
sodium hydrogenated cocoyl methyl isethionate*
sodium isethionate
sodium lauroyl isethionate
sodium lauroyl methyl isethionate
sodium methyl isethionate
sodium myristoyl isethionate*
sodium oleoyl isethionate*
sodium oleyl methyl isethionate*
sodium palm kerneloyl isethionate*
sodium stearoyl methyl isethionate*

**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 considered that the available single dose and repeated dose animal studies, including reproductive and developmental toxicity studies, supported the safety of sodium cocoyl isethionate and sodium isethionate. The Panel noted the absence of carcinogenicity data, but considered the data demonstrating that sodium cocoyl isethionate and sodium isethionate were not mutagenic or clastogenic in in vitro genotoxicity studies adequate to support the safety of these ingredients. Although there are data gaps, the similar chemical structures, physicochemical properties, and functions (all are used as surfactants) and concentrations of use in cosmetics allow grouping these ingredients together and extending the available toxicological data to support the safety of the entire group. The Panel noted that most surfactants exhibit some irritancy.

The Panel looked at changes in the pattern and concentration of use since the original safety assessment of sodium cocoyl isethionate. They noted that the most recently reported concentration of use of sodium cocoyl isethionate in rinse-off products is 53%, which is essentially the level previously considered safe.

Methyl Glucose Polyethers and Esters

The Panel issued a revised tentative safety assessment with the conclusion that the 25 methyl glucose polyethers and esters listed below are safe in the present practices of use and concentration in cosmetics.

Esters:
methyl glucose caprylate/caprate*
methyl glucose dioleate
methyl glucose isostearate*
methyl glucose laurate*
methyl glucose sesquicaprylate/ sesquicaprate*
methyl glucose sesquicocoate*
methyl glucose sesquiisostearate
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*
PPG-20 methyl glucose ether acetate*
PPG-20 methyl glucose ether distearate
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

**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.*

Ingredients classified as polyethers function as skin and hair conditioning agents, whereas, the methyl glucose esters function only as skin conditioning agents in cosmetic products. This conclusion was previously issued for all but 3 ingredients in this group, for which the available data were insufficient because of inadequate data to support use in lipsticks. Those three ingredients were: methyl glucose sesquistearate, PEG-20 methyl glucose sesquistearate, and PEG-20 methyl glucose distearate.

Lipstick use concentration data were clarified and newly available toxicity data were obtained from the European Chemicals Agency's (ECHA) website and used with permission. Accordingly, the Panel considered that repeated dose toxicity/reproductive and developmental toxicity data on isostearic acid, esters with methyl α-D-glucoside, from the ECHA website, support the safety of the three ingredients as used in lipsticks. While no use concentrations were available on PEG-20 methyl glucose sesquistearate in lipsticks, it was assumed that this ingredient is being used at concentrations no greater than the 1% maximum reported for methyl glucose sesquistearate.

Polyquaternium-22 and Polyquaternium-39

The CIR Expert Panel issued a tentative safety assessment for public comment with the conclusion that Polyquaternium-22 and polyquaternium-39 are safe in the present practices of use and concentration in cosmetics.

Both ingredients function as antistatic agents, film formers, and hair fixatives in cosmetic products, and polyquaternium-22 and polyquaternium-39 are used at concentrations up to 2% and 3%, respectively. Relevant residual monomer data on polyquaternium,-22 and polyquaternium-39 were provided, and the unreacted monomers content was considered to be below the levels of toxicological concern. For example, acrylic acid (< 50 ppm or < 1000 ppm) and dimethyldiallyl ammonium chloride (<1% or < 2%) monomers used to manufacture both polymers were detected at low levels. For polyquaternium-39, where acrylamide monomer is used in the manufacturing, residual levels of acrylamide were below the level of detection (< 1 ppm).

The Panel acknowledged that there were data gaps for both ingredients, including no available skin sensitization data on polyquaternium-22. However, it was agreed that these polymers are large, highly polar molecules that would not penetrate the skin. Furthermore, though dermal absorption is not likely, the Panel noted that concern over skin irritation/sensitization potential is not warranted based on the negative skin irritation data on polyquaternium -22 and polyquaternium-39, and the negative skin sensitization data on polyquaternium-39.

Tromethamine

The CIR Expert Panel issued a tentative safety assessment for public comment with the conclusion that tromethamine, aminomethyl propanediol (AMPD) and aminoethyl propanediol (AEPD) are safe in the present practices of use and concentration in cosmetics.

These ingredients are aliphatic or substituted aliphatic compounds. They function in cosmetics as fragrance ingredients and pH adjusters. The Panel reviewed relevant animal and human safety test data related to these ingredients. In particular, impurities in these ingredients are below the levels of toxicological concern. The similar structure, properties, functions and uses of these ingredients enabled grouping them and using the available toxicological data to assess the safety of the entire group. Tromethamine is used in 488 leave-on products and 70 rinse-off products at concentrations up to 3.7%. AMPD was reported by the VCRP to be used in 131 leave-on products and 2 rinse-off products at concentrations up to 7%. There were no reported uses for AEPD. Were AEPD to be used in the future, it is expected that it would be used in product categories and at concentrations comparable to others in this group.

Since these ingredients are primary amines, not secondary amines, formation of nitrosating compounds was not a concern.

Insufficient Data Announcements

Amino Acid Alkyl Amides

The Expert Panel requested additional data to support the safety of 115 amino acid alkyl amides.

The additional data needed are: (1) dermal irritation and sensitization data for lauroyl lysine at the highest use concentration reported (45%) and (2) dermal irritation and sensitization data for sodium lauroyl glutamate at the highest use concentration reported (40%). These data, if made available, will span the chemistry space for this group. It was also noted that any available data on disodium malyl tyrosinate would be useful.

The 115 ingredients in this safety assessment are listed below.

acetyl arginine
acetyl cysteine
acetyl glutamic acid
acetyl glutamine
acetyl histidine
acetyl methionine
acetyl proline
acetyl tyrosine
disodium lauroyl glutamate
disodium malyl tyrosinate
disodium stearoyl glutamate
disodium undecylenoyl glutamate
lauroyl arginine
lauroyl collagen amino acids
lauroyl glutamic acid
lauroyl lysine
lauroyl proline
lauroyl silk amino acids
magnesium palmitoyl glutamate
myristoyl glutamic acid
oleoyl tyrosine
palmitoyl alanine
palmitoyl arginine
palmitoyl collagen amino acids
palmitoyl glutamic acid
palmitoyl glycine
palmitoyl gold of pleasure amino acids
palmitoyl isoleucine
palmitoyl keratin amino acids
palmitoyl millet amino acids
palmitoyl oat amino acids
palmitoyl pea amino acids
palmitoyl proline
palmitoyl quinoa amino acids
palmitoyl silk amino acids
potassium caproyl tyrosine
potassium capryloyl glutamate
potassium cocoyl glutamate
potassium cocoyl glycinate
potassium cocoyl rice amino acids
potassium lauroyl collagen amino acids
capryloyl collagen amino acids
capryloyl glycine
capryloyl gold of pleasure amino acids
capryloyl keratin amino acids
capryloyl pea amino acids
capryloyl quinoa amino acids
capryloyl silk amino acids
cocoyl glutamic acid
potassium lauroyl glutamate
potassium lauroyl oat amino acids
potassium lauroyl pea amino acids
potassium lauroyl silk amino acids
potassium lauroyl wheat amino acids
potassium myristoyl glutamate
potassium olivoyl/lauroyl wheat amino acids
potassium stearoyl glutamate
potassium undecylenoyl glutamate
propionyl collagen amino acids
sodium caproyl prolineate
sodium capryloyl glutamate
sodium cocoyl alaninate
sodium cocoyl amino acids
sodium cocoyl apple amino acids
sodium cocoyl barley amino acids
sodium cocoyl collagen amino acids
sodium cocoyl glutamate
sodium cocoyl glutaminate
sodium cocoyl glycinate
sodium cocoyl/hydrogenated tallow glutamate
sodium cocoyl oat amino acids
sodium cocoyl/palmoyl/sunfloweroyl glutamate
sodium cocoyl proline
sodium cocoyl threoninate
sodium cocoyl wheat amino acids
sodium hydrogenated tallowoyl glutamate
sodium lauroyl aspartate
sodium lauroyl collagen amino acids
sodium lauroyl glutamate
dipalmitoyl cystine
dipotassium capryloyl glutamate
dipotassium undecylenoyl glutamate
disodium capryloyl glutamate
disodium cocoyl glutamate
disodium hydrogenated tallow glutamate
disodium N-lauroyl aspartate
sodium lauroyl millet amino acids
sodium lauroyl/myristoyl aspartate
sodium lauroyl oat amino acids
sodium lauroyl silk amino acids
sodium lauroyl wheat amino acids
sodium myristoyl glutamate
sodium olivoyl glutamate
sodium palmitoyl proline
sodium palmoyl glutamate
sodium stearoyl glutamate
sodium/TEA-lauroyl collagen amino acids
sodium/TEA-lauroyl keratin amino acids
sodium/TEA-undecylenoyl collagen amino acids
sodium undecylenoyl glutamate
stearoyl glutamic acid
stearoyl leucine
TEA-cocoyl alaninate
TEA-cocoyl glutamate
TEA-cocoyl glutaminate
TEA-hydrogenated tallowoyl glutamate
TEA-lauroyl collagen amino acids
TEA-lauroyl glutamate
TEA-lauroyl keratin amino acids
TEA-lauroyl/myristoyl aspartate
undecylenoyl collagen amino acids
undecylenoyl glycine
undecylenoyl phenylalanine
undecylenoyl wheat amino acids
zinc lauroyl aspartate

Chamomile Ingredients

The Panel determined that there are sufficient differences in composition between chamomile ingredients from *Chamomilla recutita* (so-called German Chamomile) and *Anthemis nobilis*, (so-called Roman Chamomile) to split these into two reports.

One report will address *Chamomilla recutita*-derived ingredients and the other will address *Anthemis nobilis*-derived ingredients. These are presented separately below.

Chamomilla recutita-Derived Ingredients

The available data are insufficient for evaluating the safety of this group of ingredients in cosmetic products. The following data are needed:

(1) Skin irritation and sensitization data on chamomilla recutita (matricaria) flower extract at current use concentrations.

The group includes:

chamomilla recutita (matricaria) extract,
chamomilla recutita (matricaria) flower,
chamomilla recutita (matricaria) flower extract,*
chamomilla recutita (matricaria) flower/leaf extract,
chamomilla recutita (matricaria) flower/leaf/stem extract,
chamomilla recutita (matricaria) flower/leaf/stem water,
chamomilla recutita (matricaria) flower powder,
chamomilla recutita (matricaria) flower water,
chamomilla recutita (matricaria) leaf extract, and
chamomilla recutita (matricaria) oil.

The Panel also agreed that data from the final CIR safety assessments on bisabolol and azulene, which are both components constituents of chamomilla recutita (matricaria) flower oil, might be useful for assessing the safety of chamomilla recutita (matricaria) flower oil and should be incorporated into this safety assessment. Additionally, β-farnesene, linalool and quercetin, are constituents of *Chamomilla recutita*, and the safety assessment should address these constituents. The Panel noted that the pesticides and heavy metals content should be below levels of toxicological concern, independent of species.

***Anthemis nobilis*-derived ingredients**

The available data are insufficient for evaluating the safety of this group of ingredients in cosmetic products. The following data are needed:

(1) Composition data on all anthemis nobilis ingredients, except anthemis nobilis flower oil, and
(2) Skin irritation and sensitization data on all anthemis nobilis ingredients, except anthemis nobilis flower oil, at current use concentrations.

The group includes:

anthemis nobilis flower extract,*
anthemis nobilis flower oil,
anthemis nobilis flower powder,* and
anthemis nobilis flower water.*

The Panel noted that the pesticides and heavy metals content should be below levels of toxicological concern, independent of species.

Re-review and New Data

Formaldehyde and Methylene Glycol

The Panel reaffirmed that formaldehyde and methylene glycol are safe for use in cosmetics when formulated to ensure use at the minimal effective concentration, but in no case should the formalin† concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol. Additionally, formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail hardening products. However, formaldehyde and methylene glycol are unsafe in the present practices of use and concentration in hair smoothing products (a.k.a. hair straightening products).

†*Formalin is an aqueous solution wherein formaldehyde (gas) has been added to water to a saturation point, which is typically 37% formaldehyde (w/w). Because of the equilibrium between formaldehyde and methylene glycol in aqueous solution, formalin is composed of both formaldehyde and methylene glycol.*

Dr. Robert Golden, President, ToxLogic, briefed the Panel on behalf of the Professional Keratin Smoothing Council (PKSC) **(Slide presentation at end of minutes)**. Dr. Golden explained the PKSC position that methylene glycol is not chemically or toxicologically equivalent to formaldehyde and that the term "formaldehyde equivalents" is not appropriate. Additionally, they proposed establishing a limit of 3% methylene glycol in keratin smoothing products. Further, they recommended attaching a warning label, and restricting use to licensed professionals with additional training and certification on the safe use of such products and the ventilation issues. They asserted that proper product application and drying procedures (e.g., using a fine-tooth comb to remove excess product before heating the hair, and using cooler blow-dryer temperature settings), ventilation, and attention to avoiding sensory irritation can ensure that exposures do not exceed OSHA standards and American Conference of Government Industrial Hygienists (ACGIH) recommendations for occupational exposures to formaldehyde.

The Panel did not accept the rationale that Dr. Golden and the PKSC offered against using the term "formaldehyde equivalents," as defined in CIR's safety assessment report. The Panel remains convinced that this term best captures the idea that methylene glycol is rapidly, reversibly and continuously converted to formaldehyde, and vice versa, even at equilibrium, which can be easily shifted by heating, drying, and other conditions to increase the amount of formaldehyde. The concept of "formaldehyde equivalents," as defined, is also consistent with what is known about the interactions of exogenous formaldehyde with the tissues of the nasal passages and elsewhere in the respiratory tract. Further, this concept conforms to the analytical methods used by OSHA and other regulatory

agencies to monitor formaldehyde concentrations in the air, the results of which are directly and meaningfully comparable to the pertinent regulatory standards and guidelines.

The Panel reiterated its position that, in principle, measures such as limiting the concentrations of formaldehyde and methylene glycol in hair smoothing products, controlling the amount of product applied, using lower drying temperatures, and specifying approaches for adequate ventilation could help ensure that these products would be used safely in the future. However, the information provided by Dr. Golden and the PKSC did not include new exposure data with products at the proposed lower use concentration of 3% methylene glycol. Further, the information provided did not explain how the distribution and use of hair smoothing products could be effectively restricted or controlled, how the recommended training program would be implemented, or how the recommended measures, overall, would affect release of gaseous formaldehyde and exposures to salon workers and their customers.

The Panel is amenable to receiving new data characterizing exposures that would result from using keratin smoothing products containing methylene glycol and formaldehyde in accordance with the proposed measures. However, the Panel emphasized that any new information should focus specifically on addressing use and exposure issues, including both the elaboration of exposure-reduction/prevention strategies and the characterization of likely exposures. The Panel also emphasized that their concerns are not limited to the potential for eye and respiratory tract exposures to formaldehyde; the potential for adverse effects from direct dermal exposures during the use of keratin hair smoothing products needs to be addressed as well.

PVP

The Panel reaffirmed the original conclusion that PVP (polyvinylpyrrolidone) is safe in the present practices of use and concentration in cosmetics.

The Panel did note that the original report included extensive data for PVP-iodine and that PVP-iodine is listed in the International Cosmetic Ingredient Dictionary and Handbook as a cosmetic ingredient. There are currently no reported uses of PVP-iodine in cosmetics and, while listed as a cosmetic ingredient, PVP-iodine is actually an approved drug used as an active ingredient in such antiseptics as Betadine. Therefore, the Panel determined to not add PVP-iodine to this safety assessment.

Retinol, Retinoic Acid, and Retinyl Esters

The Expert Panel decided that the published CIR final safety assessment on retinol and retinyl palmitate should not be reopened at this time, but that the progress of a new, ongoing National Toxicology Program (NTP) photococarcinogenesis study on retinyl palmitate and retinoic acid should be monitored.

This decision was made after reviewing the original NTP photococarcinogenesis study on retinol and retinyl palmitate, including the summary of peer review comments and the conclusions presented in the NTP report that was finalized in 2012. The CIR Expert Panel concluded that the results of the original study are ambiguous and very difficult to interpret. The Panel was informed that the NTP has initiated a second photococarcinogenesis study to attempt to address the flaws of the original study, and that a 90-day range-finding study using a vehicle formulation different from that used in the original study has been completed.

In addition, the Panel reviewed toxicity data on retinol and retinyl palmitate published since the final CIR safety assessment was issued, and additional data on retinoic acid, retinyl acetate, and retinyl propionate. However, toxicity data on the following retinyl esters that were of interest were not found in the published literature: retinyl linoleate, retinyl oleate, retinyl rice branate, retinyl soyate, and retinyl tallate. The Panel noted that if a decision is made to reopen the CIR final safety assessment in the future, based on the results of the new NTP photococarcinogenesis study or other new data, retinoic acid should not be included because it is widely used as an FDA-approved drug. However, the Panel indicated that pertinent data on retinoic acid may be retained in the safety assessment, as appropriate. The possibility of adding other retinyl esters to this group remains open. The Panel also expressed interest in reviewing data on residual levels of retinyl palmitate and retinol in the epidermis following the application of these ingredients in the presence of UV light.

Re-review Summaries

The Panel approved the summaries of their actions at the March meeting to not reopen the safety assessments of HC yellow no. 4 and HC orange no. 1, with the addition to the latter of a reference to the Scientific Committee on Consumer Safety (SCCS) Opinion on HC orange no. 1.

2014 Ingredient Review Priorities

The Panel approved a list of 4 individual ingredients and 11 ingredient groups for review in 2014. The number of ingredients that potentially would be included in each group is given following the title that CIR intends to use to describe the group. The group size can be modified based on available data and the decisions by the Panel.

1. Glycerin
2. Inorganic Hydroxides – 6 ingredients
3. Alga-derived ingredients – 174 ingredients*
4. Ginkgo-derived ingredients – 9 ingredients
5. Phosphoglycerides – 5 ingredients
6. Sodium benzotriazolyl butylphenol sulfonate
7. Styrene and Vinyl-type Styrene Copolymers – 35 ingredients
8. PEGylated Alkyl Glycerides – 53 ingredients
9. *Avena sativa*-derived ingredients – 19 ingredients
10. Centella Asiatica-derived ingredients – 9 ingredients
11. PEG-150 pentaerythrityl tetrastearate
12. Alkoxy Polysiloxanes – 112 ingredients
13. Pyrus malus-derived ingredients – 19 ingredients
14. Potassium Alkyl Phosphates – 21 ingredients
15. 2-Amino-3hydroxypyridine

> **The Panel agreed this group was a 2014 review priority, but suggested that initial efforts be put toward better understanding the constituents of the different alga species.*

The Panel also discussed upcoming re-reviews of CIR safety assessments and whether it would be appropriate to modify the time interval at which a re-review is triggered. Currently that interval is 15 years and the possibility of extending that to 20 years was considered. The Panel did not support such an extension of the time interval because such an approach would only move the workload further into the future. Noting that many re-reviews are performed before the 15-year interval based on the need to consider new data that are highly public, the Panel suggested that CIR develop a targeted approach that would identify previous safety assessments that need to be re-reviewed based on information in the scientific literature and other relevant sites.

Formaldehyde/Methylene Glycol: Potential Chemical & Toxicological Equivalence: Implications for Recommended Maximum Safe Use Levels & Best Salon Practices

Robert Golden, PhD
ToxLogic LLC
CIR Meeting
June 10, 2013

Recent Authoritative Positions Regarding Chemical Equivalence

Recent Authoritative Positions Regarding Chemical Equivalence

- *"formation of MG or release of gaseous FA occurs extremely quickly. Via this dynamic equilibrium in aqueous solution, FA & MG mutually converted & hence inherently linked with each other due to low energy barriers of formation and degradation of methylene glycol"* (SCCS 2012)
- FA & MG treated as "equivalent" due to equilibrium, e.g. any concentration of MG essentially equivalent to FA, i.e., "formaldehyde equivalents" (CIR 2011)

Recent Authoritative Positions Regarding Chemical Equivalence

- *"It is proposed that 'free FA' could be defined as 'all hydrated or non-hydrated FA present in aqueous solution, including MG"* (ACCC 2012)
- Above statements based on:
  - precautionary principles with no supporting empirical data
  - concerns that upon heating MG-based keratin hair smoothing products convert to 100% FA emissions

Implications of FA/MG "Equivalence" Assumption

Implications of FA/MG "Equivalence" Assumption

- Chemical equivalence requires:
  - 100% of any MG solution converted to 100% FA under expected conditions of use
- Toxicological equivalence requires:
  - FA & MG to have similar toxicological properties

What is Chemical Equivalence?

- By definition, an equilibrium exists only between two different chemical species and an equilibrium shift changes their concentrations.
- Ionic equilibriums exists between HCl, H^+ & Cl^- however, it is incorrect to claim that H^+ or Cl^- ions are equivalent to HCl, nor does the reversibility of the reaction establish these as chemical equivalents.

What is Chemical Equivalence?

- The claim that MG is equivalent to FA does not fulfill the simplest chemical definition of "equivalent" as *"having the same combining or reacting value"*
- Based on IUPAC *Compendium of Analytical Nomenclature* the concept of "*chemical equivalence*" does NOT include equilibrium reactions between two species rendering this terminology inappropriate from a chemical point of view for FA & MG.

Determining the Relationship Between FA & MG

Determining the Relationship Between FA & MG

- Heating MG-containing products or formalin to 400^{0}F, releases some FA gas, but the air mostly contains MG, its oligomers and water vapors which can be captured, derivitized & measured by GCMS using BSTFA*
- Confirmed using two MG-containing keratin smoothing products & 37% formalin (Analytical Sciences 2011).

*N,O-bis-(trimethylsilyl) trifluoroacetamide

Determining the Relationship Between FA & MG

- Standardized commercial 37% formalin determined by 13C-NMR to contain 36.26% total releasable FA; i.e., as MG & oligomers or polymers (Analytical Sciences 2013)
- Precise amounts of formalin vaporized at 400^0F within two different containers with known volumes
- Duplicate air sampling tubes containing DNPH* derivatizing agent (used by OSHA & NIOSH) sampled air for 15 minutes and tested via HPLC for total FA.

*Dinitrophenyl hydrazine

Measured Conversion Rates of MG into FA

Test Method	Container/ Collection distance	Container Volume	% Conversation MG to FA gas & MG vapor
DNPH/HPLC	Dry box @ 6 inches	0.2724 m^3	44.3
DNPH/HPLC	Dry box @ 18 inches	0.2724 m^3	47.3
DNPH/HPLC	Small room @ 6 inches	15.15 m^3	46.5
DNPH/HPLC	Small room @ 36 inches	15.15 m^3	47.3

Above results represent conversion of MG into FA gas & MG vapor

Results show when formalin is heated only ≈ 47% of expected FA gas measured; this is because MG vapors produce artifactual FA

Measured Conversion Rates of MG into FA

- Not yet known is what portion of the 47% comes from MG vapors or from FA gas.
- Equilibrium calculations predicts when 37% formalin is heated to 400-425^{0}F, only about 12% of available MG should convert to FA.
- Accordingly, the contribution of MG to the reported values is ≈ 36%; which reduces FA ≈ 65%).

Measured Conversion Rates of MG into FA

- Further studies underway to better understand the process, but results demonstrate that MG is NOT 100% converted to FA.
- These studies confirm it is factually incorrect to assume that MG is equivalent to FA, even when heating to 400^{0}F.

How Artifactual FA Is Created

- When MG vapors drawn into air monitoring tubes, derivatizing agent such as DNPH artificially "force" conversion of MG → FA to maintain the equilibrium as DNPH removes FA.
- MG is consumed and misreported as "FA" even though it did NOT exist as FA in the air.
- Additional testing underway using 37% formalin to document this phenomenon.

Additional Testing

- Test vaporization of keratin smoothing products to determine what % of MG converted into airborne FA.
  - Initial evaluations suggest presence of ingredients, such as keratin extracts & botanicals, can hinder FA formation upon vaporization
- Quantify FA & MG formation from 37% formalin at 400^0F to determine FA/MG ratio & account for all potentially releasable FA & MG.

Toxicological Equivalence of FA & MG

Toxicological Equivalence of FA & MG

- Health effects of FA well understood & extensively characterized; those of MG are not
- FA alone can be readily studied with no confounding from MG
- Cannot study MG alone; always in equilibrium with traces (biological systems) to larger concentrations (formalin) of FA
- Formalin suicide case reports provide basis for inferring potential effects from FA & MG.

Toxicological Equivalence of FA & MG

- Formalin animal studies provide corroborating data.
- Formic acid (direct FA metabolite) suicide case reports provide further data not confounded by MG.
- Need to separate potential adverse effects from MG from those attributable to FA.
- Depending on ingested dose of formalin, all reports describe varying degrees of severe corrosive injuries of the esophagus & stomach similar to strong acids.

Toxicological Equivalence of FA & MG

- FA readily absorbed into circulation & rapidly metabolized to formic acid in liver & RBCs producing severe metabolic acidosis in all cases with life-threatening signs/symptoms:
  - chest pain, heart palpitations, arrhythmias, low blood pressure
  - nausea, vomiting, abdominal pain, breathing abnormalities
  - neurological symptoms (e.g., lethargy, stupor, coma, seizures) and death

Toxicological Equivalence of FA & MG

- Numerous case studies of suicide from formic acid ingestion
- Symptoms reported included adverse effects on:
  - respiratory system due to inhalation pneumonitis
  - CV system (e.g., ↑ &↓ heart rate, arrhythmia, vascular hypotension
  - renal system (e.g., hematuria, tubular necrosis and renal failure)
  - Severe corrosive injuries of esophagus & stomach
- All systemic symptoms due to severe metabolic acidosis identical with those reported from formalin

Conclusions About MG Toxicity

- Following ingestion of formalin or formic acid, all adverse effects due solely to FA with none attributable to MG.
- The data demonstrate that MG has no inherent toxicity.
- In biological systems MG is a reservoir for metabolically-produced FA for later use in protein synthesis.
- Consequently it can be reliably concluded that FA & MG are not toxicologically equivalent.

Recommended Practices & Safe Levels of MG in Keratin Smoothing Products

Recommended Safe Use Practices

- When properly used keratin smoothing products should NOT cause eye irritation to cosmetologist or clients.
- Use of fine tooth comb to ensure removal of excess product to decrease potential FA emissions.
- Setting blow dryers to cooler temperatures to reduce potential FA emissions.
- No application closer than ¼" from scalp to avoid skin irritation or allergic reactions.

Recommended Safe Use Practices

- Proper care taken to avoid skin/scalp contact with keratin smoothing products.
- Query clients about prior FA experiences & avoid services on those with any known sensitivity.
- Use of adequate salon ventilation to help prevent cosmetologist/client eye irritation.
- Use of local source ventilation as necessary to prevent cosmetologist/client eye irritation.

Recommended Safe Levels of MG in Keratin Smoothing Products

- Based on previously reported salon air monitoring results (Oregon OSHA, Exponent, etc.) when products properly applied in appropriate conditions, FA air levels well below OSHA & ACGIH standards.
- Sufficient evidence demonstrates safety of keratin smoothing products containing < 3.0% MG & < 0.2% dissolved FA gas (in equilibrium).

Cosmetic Ingredient Review

Commitment & Credibility since 1976

August 16, 2013

MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Subject: Draft Boiler Plate for Botanical Ingredients

Attached, please find the current version of the botanical boiler plate. In the process of the transition of our Directors, the draft boiler plate language was not posted for public comment in June with the rest of the reports. It was posted for public comment on July 30.

The Panel had requested another chance to examine the boilerplate language. Therefore, it is being presented to the Panel so that their comments may be incorporated into the language for further posting after the September, 2013 meeting.

The CIR staff anticipates finalizing the language at the December, 2013 meeting.

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BOTANICAL ABSTRACT/DISCUSSION FRAMEWORK

SENTENCES for ABSTRACT

Because formulations may contain more than one botanical ingredient in a formulation, caution was urged to avoid reaching [levels or thresholds] of toxicological concern for constituents. Industry should use the procedures needed to limit impurities.

Keep in mind the 150 word limit of the Abstract.

GUIDANCE for DISCUSSION

THE HEAVY METAL/PESTICIDE BOILER PLATE

The Expert Panel expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use procedures necessary to limit these impurities in ingredients before blending the ingredients into cosmetic formulations.

THE AFLATOXIN BOILER PLATE *{IF APPLICABLE}*

Aflatoxins have been detected in [*plant (part) where aflatoxins were found*]. The Panel believes that aflatoxins will not be present at levels of toxicological concern in [*botanical ingredient group*]; the Panel adopted the USDA designation of ≤ 15 ppb as corresponding to "negative" aflatoxin content.

CONSTITUENT FRAMEWORK

The basic framework for the constituent Discussion has three parts:

1) **Opening Paragraph.** An overview of the general issue that multiple botanical ingredients in a single formulation or in multiple formulations used simultaneously or sequentially can contribute, cumulatively, to total exposures to constituents of concern in the formulation (e.g., pulegone). *{This paragraph is boiler plate/static}*

2) **Description of Constituents [Constructed by the Writer].** One or more paragraphs describing the constituent(s) of concern for the botanical ingredient(s); include potential adverse health endpoints, amounts in the plant/extract, previous CIR report conclusions, limits or other restrictions specified by the Panel or regulatory agencies or other organizations, as appropriate. *{This/These paragraph(s) are written to support the choice of the third paragraph}*

3) **Wrap Up Paragraph.** Three paragraphs to choose from that provide a framework for discussion language, as appropriate.

Opening Paragraph

A cosmetic formulation may contain multiple botanical ingredients, each of which can contribute to the total concentration of constituents of concern in the formulation. This may include the combined use of multiple ingredients derived from a single plant species or plant group. Cumulative exposure may also occur when more than one product containing one or more constituents of concern are used simultaneously (e.g., multiple make up products) or sequentially (e.g., shampoo and conditioner).

Then Use One of the Following:

1) ***If no concentration limit has been specified for the constituent(s) of concern, and the threshold of toxicological concern (TTC) approach <u>was not</u> applied:***

{Example Discussion Paragraph}

The Panel noted that a constituent of these ingredients is hypericin. Hypericin has been shown to be a photosensitizer in visible light and to be potentially teratogenic based on the results of a study using rat embryos. Hypericin was reported to be present in samples of various parts of the plant at 5 – 18,000 ppm. Another constituent is quercetin. Quercetin may be genotoxic, and is reported to be in *H. perforatum* plant parts at 1000 – 20000 ppm. However, the maximum concentration of use of *H. perforatum* extracts in cosmetics was reported to be 0.07%. This indicates that exposures to hypericin, quercetin and other minor constituents of these ingredients in cosmetics would be clearly below levels of toxicological concern.

Followed by:

{Framework}

The Panel noted that the use of other botanical ingredients that may contain [*constituent(s)*], in combination with [*botanical name*] ingredients in a single formulation, could result in exposures that exceed levels of toxicological concern. Other constituents that may be of concern are potential sensitizers that may be present. Thus, cosmetic products containing one or more botanical ingredient(s) should be formulated to ensure that total exposures to such constituents remain below levels of toxicological concern when the products are used as intended, whether these products typically are used singly, simultaneously, or sequentially. The Panel recognized that every extract would likely be somewhat different and that the characterization of the composition of the plant-derived ingredients addressed in this safety assessment is broad. Nonetheless, the available composition data represent what would be found commonly in ingredients prepared in the manner described. The conclusion regarding safety, therefore, is valid only for ingredients prepared in a manner that produces a chemical profile similar to that described in this report. Extracts not prepared in a manner that produces similar chemical profiles could be considered safe only if they have similar safety test profiles.

2) ***If no concentration limit has been specified for the constituent(s) of concern, and the TTC approach <u>was</u> applied:***

{Example Discussion Paragraphs}

Other safety test data of individual constituents of calendula (e.g., lutein), did not suggest any adverse effects. There are no dermal reproductive or developmental toxicity data on calendula extracts, but data on coriander oil, high in linalool and other terpenes, demonstrated that adverse effects occurred only at maternally toxic doses.

Previous CIR safety assessments of fatty acids, plant sterols, paraffin, p-hydroxybenzoic acid, salicylic acid, and tocopherol, all of which are constituents of calendula extracts, supported that these constituents would be safe at the levels found in calendula extracts and at the use concentrations of these extracts. In previous CIR safety assessments of other constituents of calendula extracts, including pyrogallol, pyrocatechol, and t-butylhydroquinone, adverse effects were

identified. These concerns were considered relevant to this safety assessment because, for example, tannins comprise 6% - 10% of material derived from calendula. Analysis of calendula extracts, however, demonstrated that catechol, pyrogallol, coumarins (esculetin, scopoletin, and umbelliferon), and α-tocopherolquinone were not present at detectable concentrations. Given the low use concentrations of the extracts, and concentrations of constituents in these extracts, which represent only a small percentage of the total ingredient (below the level of detection in some cases), the Panel concluded that these extracts, as described, did not present a concern as used in cosmetics.

Followed by:

{Framework}

The Panel also noted that the use of other botanical ingredients that may contain [*constituent(s)*], in combination with [*botanical name*] ingredients in a single formulation, could result in exposures that exceed the threshold of toxicological concern. Other constituents that may be of concern are potential sensitizers that may be present. Thus, cosmetic products containing one or more botanical ingredient(s) should be formulated to ensure that total exposures to such constituents remain below the threshold of toxicological concern, whether these products typically are used singly, simultaneously, or sequentially. The Panel recognized that every extract would likely be somewhat different and that the characterization of the composition of the plant-derived ingredients addressed in this safety assessment is broad. Nonetheless, the available composition data represent what would be found commonly in ingredients prepared in the manner described. The conclusion regarding safety, therefore, is valid only for ingredients prepared in a manner that produces a chemical profile similar to that described in this report. Extracts not prepared in a manner that produces similar chemical profiles, could be considered safe only if they have similar safety test profiles.

3) If there is a limit on the constituent(s) of concern:

{Example Discussion Paragraph}

Because pulegone is toxic, the Panel limited it to ≤1% in cosmetic grade peppermint (mentha piperita) oil, peppermint (mentha piperita) extract, peppermint (mentha piperita) leaves, and peppermint (mentha piperita) water. The Panel was confident that this concentration was achievable both by controlling the time of harvest and through the patented technique described in this report. Recent data reported that peppermint (mentha piperita) oil is used at ≤ 3% in rinse-off formulations and ≤ 0.2% in leave-on formulations. This concentration of use data, coupled with the Panel's ≤ 1% restriction on pulegone, suggested to the Panel that pulegone toxicity would not occur with cosmetic use.

Or:

{Example Discussion Paragraph}

Pulegone is listed as a constituent of *P. quinquefolius.* The Panel recalled that pulegone toxicity was a concern for peppermint oil used as a cosmetic ingredient, for which the Panel adopted a concentration limit of ≤ 1% pulegone. Because of the low use concentrations of ginseng-derived ingredients, the Panel was confident that a toxic concentration of pulegone could not be reached in cosmetics. For example, recent data indicate that *P. quinquefolius*-derived ingredients were used at a maximum of 0.002%.

Followed by:

{Framework}

The Panel noted that the use of other botanical ingredients that may contain [constituent(s)], in combination with [botanical name] ingredients in a single formulation, or in formulations that are used at the same time or in close time proximity, could result in exposures that exceed levels of toxicological concern. Other constituents that may be of concern are potential sensitizers that may be present. Thus, cosmetic products containing one or more botanical ingredient(s)

should be formulated to ensure concentrations of [constituent(s)] do not exceed the limit set by the Panel [*or other source (FDA, USDA, etc.) if appropriate*], and that total exposures to such constituents remain below the levels of toxicological concern, whether these products typically are used simultaneously or sequentially. In setting the concentration limits for such constituents, the Panel takes into consideration the total exposure from the use of multiple products containing the same constituents.

The Panel recognized that every extract would likely be somewhat different and that the characterization of the composition of the plant-derived ingredients addressed in this safety assessment is broad. Nonetheless, the available composition data represent what would be found commonly in ingredients prepared in the manner described. The conclusion regarding safety, therefore, is valid only for ingredients prepared in a manner that produces a chemical profile similar to that described in this report. Extracts not prepared in a manner that produces similar chemical profiles, could be considered safe only if they have similar safety test profiles.

Cosmetic Ingredient Review
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CIR

Memorandum

To: CIR Expert Panel Members and Liaisons

From: Lillian Gill, Director, CIR

Date: August 16, 2013

Subject: Re-Review Summaries

At the June 2013 meeting, the Panel determined to not re-open the safety assessments of Polyvinylpyrrolidone and, Retinol and Retinyl palmitate.

The attached re-review summaries are included for your review and approval.

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PVP (Polyvinylpyrrolidone)

CONCLUSION: In the 1998 safety assessment of PVP (polyvinylpyrrolidone), the Cosmetic Ingredient Review (CIR) Expert Panel concluded that this ingredient was safe as used in cosmetic products.[1] The Expert Panel reviewed newly available studies since that assessment, along with updated frequency and concentration of use information.[2-26] The Expert Panel reaffirmed the original conclusion that PVP is safe as a cosmetic ingredient in the practices of use and concentration as given in Table 1.

DISCUSSION: Newly available data, including data related to PVP-iodine, did not raise any issues regarding the safety of PVP. The Panel did note that the original report included extensive supporting safety data for PVP-iodine and that PVP-iodine is listed in *the International Cosmetic Ingredient Dictionary and Handbook* as a cosmetic ingredient. There are currently no reported uses of PVP-iodine in cosmetics and, while listed as a cosmetic ingredient, PVP-iodine is actually an approved drug used as an active ingredient in such antiseptics as Betadine. Therefore, the Panel determined to not add PVP-iodine to this safety assessment.

Table 1. Historical and current use and concentration of use data for PVP.[1,6,20,21]

	# of Uses		*Max Conc of Use (%)*	
			PVP	
Data Year	**1998**	**2013**	**1998**	**2013**
Totals*	**395**	**799**	**0.15-35**	**0.0005-12**
Duration of Use				
Leave-On	283	675	0.15-35	0.002-12
Rinse-Off	112	123	0.5-2	0.0005-10.5
Diluted for (Bath) Use	NR	1	NR	NR
Exposure Type				
Eye Area	129	222	2-10	0.05-12
Incidental Ingestion	2	35	0.5-7.5	0.1-10.5
Incidental Inhalation-Spray	23	22	0.15-5	0.002-5[a]
Incidental Inhalation-Powder	NR	NR	NR	NR
Dermal Contact	87	186	1-35	0.0005-12
Deodorant (underarm)	NR	NR	NR	0.5
Hair - Non-Coloring	205	423	0.15-5	0.0005-10.5
Hair-Coloring	5	7	NR	1.6-3.3
Nail	NR	1	NR	0.3-5
Mucous Membrane	7	37	0.5-7.5	0.1-10.5
Baby Products	1	1	0.5	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
NR = Not reported
[a]0.1-3.5% reported in aerosol hair sprays; 0.02-5% reported in pump hair sprays; 3% reported in an aerosol hair tonic, dressing or other hair grooming aid; 0.5-3% reported in a pump hair tonic, dressing or other hair grooming aid; 0.42% reported in a body spray.

References

1. Andersen FA (ed.). Final Report on the Safety Assessment of Polyvinylpyrrolidone (PVP). *IJT*. 1998;17(Suppl. 4):95-130.

2. Adachi A, Fukunaga A, Hayashi K, Kunisada M, and Horikawa T. Anaphylaxis to polyvinylpyrrolidone after vaginal application of povidone-iodine. *Contact Dermatitis*. 2003;48:133-136.

3. Alp BN, Elibol O, Sargon MF, Aslan OS, Yanyali A, Karabas L, Talu H, and Caglar Y. The effect of povidone iodine on the corneal endothelium. *Cornea*. 2000;19(4):546-550.

4. Cheong SH, Yang YI, Choi MY, Kim MH, Cho KR, Lim SH, Lee JH, Lee KM, and Moon SH. Lung injury induced by the pulmonary instillation of povidone-iodine in rats. *J Anesth*. 2012;26:70-79.

5. European Union. 1976, Council Directive 1976/768/EEC of 27 July 1976 on the Approximation of the Laws of the Member States Relating to Cosmetic Products, as amended through Commission Directive 2008/42/EC. 2008. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1976L0768:20080424:en:PDF.

6. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* 2013. Washington, DC: FDA.

7. Food and Drug Administration (FDA). Drugs @ FDA: FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Date Accessed 5-2-2013.

8. Gottschalck TE and Breslawec HP. International Cosmetic Ingredient Dictionary and Handbook. 14 *ed*. Washington, DC: Personal Care Products Council, 2012.

9. Iijima S and Kuramochi M. Investigation of irritant skin reaction by 10% povidone-iodine solution after surgery. *Dermatology*. 2002;204(Suppl. 1):103-108.

10. Jiang J, Wu M, and Shen T. The toxic effect of different concentrations of povidone iodine on the rabbit's cornea. *Cutan Ocul Toxicol*. 2009;28(3):119-124.

11. Lachapelle JM. Allergic contact dermatitis from povidone-iodine: A re-evaluation study. *Contact Dermatitis*. 2005;52:9-10.

12. Lakhal K, Faidherbe J, Choukhi R, Boissier E, and Capdevila X. Povidone iodine: Features of critical systemic absorption. *Ann Fr Anesth.Réanim*. 2011;30:e1-e3.

13. Lee SK, Zhai H, and Maibach HI. Allergic contact dermatitis from iodine preparations: A conundrum. *Contact Dermatitis*. 2005;52:184-187.

14. Masse M, Falanga V, and Zhou LH. Use of topical povidone-iodine resulting in an iododerma-like eruption. *J Dermatol*. 2008;35:744-747.

15. Muller G, Hai DN, and Kramer A. Lack of in vitro genotoxicity of povidone-iodine in solution, in ointment or in a lipsomal formulation (Repithel). *Dermatology*. 2006;212(Suppl. 1):94-97.

16. Murthy MB and Krishnamurthy B. Severe irritant contact dermatitis induced by povidone iodine solution. *Indian J Pharmacol*. 2009;41(4):199-200.

17. Naor J, Savion N, Blumenthal M, and Assia EI. Corneal endothelial cytotoxicity of diluted povidone-iodine. *J Cataract Refract Surg*. 2001;27:941-947.

18. Nishioka K, Seguchi T, Yasuno H, Yamamoto T, and Tominaga K. The results of ingredient patch testing in contact dermatitis elicited by povidone-iodine preparations. *Contact Dermatitis.* 2000;42:90-94.

19. Pastor N, Silvestre JF, Mataix J, Lucas A, and Perez M. Contact cheilitis from bisabolol and polyvinylpyrrolidone/hexadecene copolymer in lipstick. *Contact Dermatitis*. 2008;58:178-179.

20. Personal Care Products Council. 1-23-2013. Concentration of use by FDA Product Category: PVP. 3 pages.

21. Personal Care Products Council. 5-22-2013. Concentration of Use by Product Category: Updated information on PVP. 1 pages.

22. Ronnau AC, Wulferink M, Gleichmann E, Unver E, Ruzicka T, Krutmann J, and Grewe M. Anaphylaxis to polyvinylpyrrolidone in an analgesic preparation. *Br J Dermatol*. 2000;143:1055-1058.

23. Vandergriff TW, Wasko CA, Schwartz MR, and Hsu S. Irritant contact dermatitis from exposure to povidone-iodine may resemble toxic epidermal necrolysis. *Dermatol Online J*. 2006;12(7):12.

24. Velazquez D, Zamberk P, Suarez R, and Lazaro P. Allergic contact dermatitis to povidone-iodine. *Contact Dermatitis*. 2009;60:348-349.

25. Wormser U, Brodsky B, Green BS, Arad-Yellin R, and Nyska A. Protective effect of povidone iodine ointment against skin lesions induced by chemical and thermal stimuli. *J Appl Toxicol*. 2000;20:S183-S185.

26. Yoshida K, Sakurai Y, Kawahara S, Takeda T, Ishikawa T, Murakami T, and Yoshioka A. Anaphylaxis to polyvinylpyrrolidone in povidone-iodine for impetigo contagiosm in a boy with atopic dermatitis. *Int Arch Allergy Immunol*. 2008;146:169-173.

Retinol and Retinyl Palmitate

CONCLUSION: In the 1987 safety assessment of retinyl palmitate and retinol, the Cosmetic Ingredient Review (CIR) Expert Panel stated that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration.[1] Since that assessment, the Panel reviewed additional studies along with updated frequency and concentration of use information.[2-152] The Expert Panel determined that this safety assessment should not be re-opened, but that the progress of a new, ongoing National Toxicology Program (NTP) photococarcinogenesis study on retinyl palmitate and retinoic acid should be monitored.

DISCUSSION: For retinol and retinyl palmitate, the Panel recognized the high public/media visibility of concerns raised by new studies, including the photococarcinogenesis study completed by the NTP in 2012. That study, in particular, had methodological flaws and could not be interpreted to suggest that there are additional risks associated with these ingredients. NTP has initiated a second photococarcinogenesis study to attempt to address the flaws of the original study, and the Panel may again consider this safety assessment when the new study is completed. In addition to the NTP study, the Panel reviewed toxicity data on retinol and retinyl palmitate that entered the published literature since the final safety assessment was issued, as well as data on retinoic acid, retinyl acetate, and retinyl propionate. Toxicity data on the following other retinyl esters that were of interest were not identified in the published literature: retinyl linoleate, retinyl oleate, retinyl rice branate, retinyl soyate, and retinyl tallate. The Panel noted that if a decision to reopen the CIR final safety assessment in the future is made after completion of the new NTP study, retinoic acid should not be included because it is an FDA-approved drug. The possibility of including other retinyl esters remains open. The Panel also expressed interest in reviewing data on residual levels of retinyl palmitate and retinol that remain in the epidermis following ingredient application in the presence of UV light.

Table 1. Historic and Current Uses and Concentrations.[17-18]

	# of Uses		*Max. Conc. of Use (%)*	
	Retinyl Palmitate and Retinol*			
data year	*1981*	*2013*	*1981*	*2013*
Totals	**131(R) 101(P)**	**188(R) 2161(P)**	**0.1-5(R) 0.1-5 (P)**	**0.0005-1(R) 0.0000002-1.97(P)**
Duration of Use				
Leave-On	*107(R) 93(P)*	*173(R) 1763(P)*	*0.1-5(R) 0.1-5(P)*	*0.0005-1(R) 0.0001-1.97(P)*
Rinse Off	*25(R) 6(P)*	*11(R) 383(P)*	*0.1-1(R) 0.1-1(P)*	*0.0005-0.1(R) 0.00001-1(P)*
Diluted for(bath) use	*NR(R) 2(P)*	*4(R) 15(P)*	*NR(R) 0.1(P)*	*NR(R) 0.0000001(P)*
Exposure Type				
Eye Area	1(R) 4(P)	18(R) 182(P)	0.1(R) 1(P)	0.0005-0.1(R) 0.01-0.5(P)
Incidental Ingestion	5(R) 14(P)	12(R) 232(P)	NR(R) 1(P)	0.15(R) 0.006-0.28(P)
Incidental Inhalation - Sprays	1(R) 1(P)	NR(R) 85(P)	0.1(R) 1(P)	NR(R) 0.0006-0.18(P)
Incidental Inhalation – Powders	2(R) 1(P)	1(R) 53(P)	1(R) 0.1(P)	NR(R) 0.01-1(P)
Dermal Contact	70(R) 81(P)	169(R) 1609(P)	5(R) 0.1-5(P)	0.0005-1(R) 0.0000002-1.97 (P)
Deodorant (underarm)	NR	1(P)	NR	NR
Hair - Non-Coloring	15(R) 4(P)	3(R) 264(P)	0.1-1(R) 0.1-1(P)	0.1(R) 0.0001-0.5(P)
Hair-Coloring	NR	NR(R) 6(P)	NR	NR(R) 0.0011-0.02(P)
Nail	2(R) 2(P)	4(R) 32(P)	0.1(R) 0.1(P)	0.01(R) 0.01-0.1(P)
Mucous Membrane	6(R) 16(P)	22(R) 351(P)	NR(R) 0.1-1(P)	0.15(R) 0.0000002-0.28(P)
Baby Products	1(R)	1(R) 4(P)	1(R)	NR

*(P) = Retinyl Palmitate; (R) = Retinol; NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

References

1. Elder, R. L. Final report on the safety assessment of retinyl palmitate and retinol. *JACT*. 1987;6(3):279-320.

2. Bergfeld, W. F. Belsito D. V. Klaassen C. D. Marks J. G. Jr. Shank R. C. Slaga T. J. Snyder P. W. and Andersen F. A. Annual review of cosmetic ingredient safety assessments: 2005/2006. Retinol and retinyl palmitate. *IJT*. 2008;27(1):120-127.

3. Environmental Working Group. http://www.ewg.org/2010sunscreen/. Date Accessed 7-28-2010.

4. Wang, S. Q., Dusza, S. W., and Lim, H. W. Safety of retinyl palmitate in sunscreens: a critical analysis. *J Am Acad.Dermatol.* 2010;63(5):903-906.

5. Fu, P. P., Xia, Q., Boudreau, M. D., Howard, P. C., Tolleson, W. H., and Wamer, W. G. Physiological role of retinyl palmitate in the skin. *Vitam.Horm.* 2007;75:223-256.

6. Al Tanoury, Z. Aleksandr P. and Rochette-Egly C. Vitamin A and retinoid signaling: genomic and non-genomic effects. *Journal of Lipid Research*. 2013;1-46.

7. Fu, P. P., Xia, Q., Yin, J. J., Cherng, S. H., Yan, J., Mei, N., Chen, T., Boudreau, M. D., Howard, P. C., and Wamer, W. G. Photodecomposition of vitamin A and photobiological implications for the skin. *Photochem.Photobiol.* 2007;83(2):409-424.

8. Crank, G. and Pardijanto M. S. Photooxidations and photosensitized oxidations of vitamin A and its palmitate ester. *J.Photochem.Photobiol.* 1995;85:93-100.

9. Lamb, L. E. Zaeba M. Plakoudas S. N. Sarna T. and Simon J. D. Retinyl palmitate and the blue-light-induced phototoxicity of human ocular lipofusacin. *Arch.Biochem.Biophys.* 2001;393:316-320.

10. Tatariunas, A. and Matsumoto S. A. A retinyl palmitate model of the phenomenon of the intrinsic fluorescence increase in ceroid-lipofuscin cytosomes. *Exp.Gerontol.* 2000;35:1327-1341.

11. Mei, N., Xia, Q., Chen, L., Moore, M. M., Chen, T., and Fu, P. P. Photomutagenicity of anhydroretinol and 5,6-epoxyretinyl palmitate in mouse lymphoma cells. *Chem.Res.Toxicol.* 2006;19(11):1435-1440.

12. Xia, Q., Yin, J. J., Wamer, W. G., Cherng, S. H., Boudreau, M. D., Howard, P. C., Yu, H., and Fu, P. P. Photoirradiation of retinyl palmitate in ethanol with ultraviolet light--formation of photodecomposition products, reactive oxygen species, and lipid peroxides. *Int.J Environ.Res.Public Health.* 2006;3(2):185-190.

13. Bempong, D. K. Honigberg I. L. and Meltzer N. M. Normal phase LC-MS determination of retinoic acid degradation products. *J.Pharm.Biomed.Anal.* 1995;13:285-291.

14. Murayama, A. Suzuki T. and Matsui M. Photoisomerization of retinoic acids under room light: a warning for cell biological study of geometrical isomers of retinoids. *J.Nutr.Sci.Vitaminol.* 1997;43:167-176.

15. Cahnman, H. J. A fast photoisomerization method for the preparation of tritium-labeled 9-cis-retinoic acid of high specific activity. *Anal.Biochem.* 1995;227:49-53.

16. Gottschalck, T. E. and Breslawec, H. P. International Cosmetic Ingredient Dictionary and Handbook. 14 *ed.* Washington, DC: Personal Care Products Council, 2012.

17. Food and Drug Administration (FDA). Information supplied to FDA by industry as part of the VCRP FDA database. 2013. Washington, D.C.: FDA.

18. Personal Care Products Council. Concentration of use by FDA product category. Retinol and retinyl esters. Unpublished data submitted by the Personal Care Products Council on 1-23-2013. 2013. pp.1-4.

19. Hubinger, J. C. Determination of retinol, retinyl palmitate, and retinoic acid in consumer cosmetic products. *J.Cosmet.Sci.* 2009;60(5):485-500.

20. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104.

21. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4.
2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

22. Rothe H. Special aspects of cosmetic spray evaluation. 2011.

23. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;24-27.

24. Food and Drug Administration (FDA). Direct food additives. 21 CFR 184.1930; 582.5933; 582.5936. 2012.

25. Food and Drug Administration (FDA). Over-the-Counter (OTC) Drug Ingredients. 21 CFR 310.545. 2012.

26. Aquilina, G. Bach A. Bampidis V. et al. Scientific opinion on the safety and efficacy of vitamin A (retinyl acetate, retinyl palmitate, and retinyl propionate) as a feed additive for all animal species and categories. *EFSA Journal*. 2013;11(1):3037.

27. Food and Drug Administration (FDA). News & Events. Concerns regarding Accutane (isotretinoin). www.fda.gov. Date Accessed 5-14-2013.

28. Food and Drug Administration (FDA). Drugs. Inormation for healthcare professionals: Isotretinoin (marketed as Accutane). www.fda.gov. Date Accessed 5-14-2013.

29. Yourick, J. J. Jung C. t. and Bronaugh R. L. Percutaneous absorption of retinol in fuzzy rat (in vivo and in vitro) and human skin (in vitro) from cosmetic vehicles. *The Toxicologist*. 2006;90(S1):164.

30. Yourick, J. J. Jung C. t. and Bronaugh R. L. *In vitro* and *in vivo* percutaneous absorption of retinol from cosmetic formulations: Significance of the skin reservoir and prediction of systemic absorption. *Toxicol.Appl.Pharmacol.* 2008;231:117-121.

31. Jenning, V. Gysler A. Schafer-Korting M. et al. Vitamin A loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. *Eur.J.Pharm.Biopharm.* 2000;49:211-218.

32. Yan, J., Xia, Q., Wamer, W. G., Boudreau, M. D., Warbritton, A., Howard, P. C., and Fu, P. P. Levels of retinyl palmitate and retinol in the skin of SKH-1 mice topically treated with retinyl palmitate and concomitant exposure to simulated solar light for thirteen weeks. *Toxicol Ind.Health.* 2007;23(10):581-589.

33. Yan, J., Wamer, W. G., Howard, P. C., Boudreau, M. D., and Fu, P. P. Levels of retinyl palmitate and retinol in the stratum corneum, epidermis, and dermis of female SKH-1 mice topically treated with retinyl palmitate. *Toxicol Ind.Health.* 2006;22(4):181-191.

34. Yan, J., Xia, Q., Webb, P., Warbritton, A. R., Wamer, W. G., Howard, P. C., Boudreau, M., and Fu, P. P. Levels of retinyl palmitate and retinol in stratum corneum, epidermis and dermis of SKH-1 mice. *Toxicol Ind.Health.* 2006;22.(3):103-112.

35. Willhite, C. C. Sharma R. P. Allen P. V. and Berry D. L. Percutaneous retinoid absorption and embryotoxicity. *J.Invest.Dermatol.* 1990;95(5):523-529.

36. Chou, R. Bürgin H. Schmitt G. and Eggers H. Absorption of tretinoin in rats and rabbits following oral and dermal application. *Arzneimittelforschung*. 1997;47(4):401-405.

37. Howard, W. B. Willhite C. C. Omaye S. T. and Sharma R. P. Comparative distribution, pharmacokinetics, and placental permeabilities of all-trans-retinoic acid, 13-cis-retinoic acid, all-trans-4-oxo-retinoic acid, retinyl acetate, and 9-cis-retinal in hamsters. *Arch.Toxicol.* 1989;63(2):112-120.

38. Mills, J. P. and Tanumihardjo S. A. Vitamin A toxicity in wild-caught African green vervet monkeys (*Chlorocebus aethiops)* after 2 years in captivity. *Comparative Medicine*. 2006;56(5):421-425.

39. Nohynek, G. J. Meuling W. J. A. Vaes W. H. J. Lawrence R. S. Shapiro S. Schulte S. Steiling W. Bausch J. Gerber E. Sasa H. and Nau H. Repeated topical treatment, in contrast to single oral doses, with vitamin A-containing preparations does not affect plasma concentrations of retinol, retinyl esters, or retinoic acids in female subjects of child-bearing age. *Toxicology Letters*. 2006;163(1):65-76.

40. Duitsman, P. K. and Olson J. A. Comparative embryolethality and teratogenicity of the all-trans isomers of retinoic acid, 3,4-didehydroretinyl acetate, and retinyl acetate in pegnant rats. *Teratology*. 1996;53(4):237-244.

41. Schäffer, M. W. Roy S. S. Mukhedrjee S. Ong D. E. and Das S. K. Uptake of all-trans retinoic acid-containing aerosol by inhalation to lungs in a guinea pig model system - A pilot study. *Exp.Lung Res.* 2010;36(10):593-601.

42. Lind, P. M. Johansson S. Rönn M. and Melhus H. Subclinical hypervitaminosis A in rat: Measurements of bone mineral density (BMD) do not reveal adverse skeletal changes. *Chemico-Biological Interactions*. 2006;159(1):73-80.

43. de Oliveira, M. R. and Moreira J. C. F. Acute and chronic vitamin A suplementation at therapeutic doses induces oxidative stress in submitochondrial particles isolated from cerebral cortex and cerebellum of adult rats. *Toxicology Letters*. 2007;173(3):145-150.

44. de Oliveira, M. R. Oliveira M. W. S. Lorenzi R. da Rocha R. F. and Moreira J. C. F. A Short-term vitamin A supplementation at therapeutic doses induces a pro-oxidative state in the hepatic environment and facilitates calcium-ion-induced oxidative stress in rat liver mitochondria independently from permeability transition pore formation. *Cell Biol.Toxicol.* 2009;25(6):545-560.

45. da Rocha, R. F., De Oliveira, M. R., Schonhofen, P., Schnorr, C. E., Dal, Pizzol F., and Moreira, J. C. Long-term vitamin A supplementation at therapeutic doses induces mitochondrial electrons transfer chain (METC) impairment and increased mitochondrial membrane-enriched fraction (MMEF) 3-nitrotyrosine on rat heart. *Free Radic.Res.* 2010;44(5):505-512.

46. McCormick, D. L. Hultin T. A. and Detrisac C. J. Potentiation of vitamin A hepatotoxicity by butylated hydroxytoluene. *Toxicol.Appl.Pharmacol.* 1987;90(1):1-9.

47. Takahashi, O. Hemorrhaic toxicity of a large dose of a-, b-, g-, and d-tocopherols, ubiquinone, b-carotene, retinol acetate, and L-ascorbic acid in the rat. *Fd.Chem.Toxic.* 1995;33(2):121-128.

48. Alberts, D. Ranger-Moore J. Einspahr J. Saboda K. Bozzo P. Liu Y. Xu X. C. Lotan R. Warneke J. Salasche S. Stratton S. Levine N. Goldman R. Islas M. Duckett L. Thompson D. Bartels P. and Foote J. Safety and efficacy of dose-intensive oral vitamin A in subjects with sun-damaged skin. *Clinical Cancer Research*. 2004;10(6):1875-1880.

49. North Cliff Consultants, Inc. A 28-day ophthalmologic and dermatologic safety evaluation of a moisturizer product containing 0.3% retinyl propionate. Unpublished data submitted by the Personal Care Products Council on 1-10-2013. 2013. pp.1-17.

50. Institute for in Vitro Sciences, Inc. Tissue equivalent assay with Epiocular™ cultures (face ceam containing 0.3% retinyl propionate). Unpublished data submitted by the Personal Care Products Council on 1-10-2013. 2008. pp.1-13.

51. Schiltz, J. R. Lanigan J. Nabial W. Petty B. and Birnbaum J. E. Retinoic acid induces cyclical changes in epidermal thickness and dermal collagen and glycosaminoglycan biosynthesis rates. *J.Invest.Dermatol.* 1986;87:663-667.

52. Gunning, D. B. Barua A. B. Myers R. K. Ueltschy A. Romans D. and Olson J. A. Comparative histologic effects of dialy topical application of creams containing all-trans-retinoic acid or all-trans-retinoyl ß-glucuronide on pig skin. *Skin.Pharmacol.Appl.Skin Physiol.* 2002;15(4):205-212.

53. Kang, S. Duell E. A. Fisher GJ et al. Application of retinol to human skin in vivo induces epidermal hyperplasia and cellular retinoid binding proteins characteristic of retinoic acid but without measurable retinoic acid levels of irritation. *J.Invest.Dermatol.* 1995;105:549-556.

54. Kang, S. Bergfeld W. Gottlieb et al. Long-term efficacy and safety of tretinoin emollient cream 0.05% in the treatment of photodamaged facial skin. *Am.J.Clin.Dermatol.* 2005;6(4):245-253.

55. Brelsford, M. and Beute T. C. Preventing and managing the side effects of isotretinoin. *Semin.Cutan.Med.Surg.* 2008;27(3):197-206.

56. Green, C. Orchard G. Cerio R. and Hawk J. L. M. A clinicopathological study of the effects of topical retinyl propionate cream in skin photoaging. *Clin.Exp.Dermatol.* 1998;23(4):162-167.

57. TKL Research, Inc. 21-day cumulative human irritation patch study (facial moisturizer containing 0.5% retinyl propionate). Unpublished data submitted by the Personal Care Products Council on 1-10-2013. 2005. pp.1-29.

58. Slade, H. B. Shroot B. Feldman S. R. Cargill D. I. and Stanfield J. Reappraising the phototoxicity of tretinoin: a report of four controlled clinical trials. *Photodermatol.Photoimmunol.Photomed.* 2009;25(3):146-152.

59. KGL, Inc. Human phototoxicity test of a topical product (face cream containing 0.4% retinyl propionate). Unpublished data submitted by the Personal Care Products Council on 1-10-2013. 2001. pp.1-15.

60. KGL, Inc. Human photoallergy test of a topical product (face cream containing 0.4% retinyl propionate). Unpublished data submitted by the Personal Care Products Council on 1-10-2013. 2001. pp.1-18.

61. Schilling, K. Extract on phototoxicity of the dossier on retinol and retinyl ester to hand over to the Cosmetic Ingredient Review (CIR). Unpublished data submitted by the Personal Care Products Council on 5-31-2013. 2013. pp.1-8.

62. TKL Research, Inc. Human repeated insult patch study (facial cream containing 0.4% retinyl propionate). Unpublished data submitted by the Personal Care Products on 1-10-2013. 2001. pp.1-27.

63. Rühl, R. Hänel A. Garcia A. L. Dahten A. Herz U. Schweigert F. J. and Worm M. Role of vitamin A elimination or supplementation diets during postnatal development on the allergic sensitization in mice. *Mol.Nutr.Food Res.* 2007;51:1173-1181.

64. Mastro, A. M. and Pepin K. G. The effects of retinoic acid and a tumor promoter, 12-O-tetradecanoylphorbol-13-acetate, on lymphocyte proliferation. *Carcinogenesis*. 1982;3(4):409-413.

65. Nikawa, T. Ikemoto M. Kano M. Tokuoka K. Hirasaka K. Uehara S. Takatsu K. Rokutan K. and Kishi K. Impaired vitamin A-mediated mucosal IgA response in IL-5 receptor-knockout mice. *Biochem.Biophys.Res.Commun.* 2001;285(2):546-549.

66. Bessler, H. Wyshelesky G. Osovsky M. Prober V. and Sirota L. A comparison of the effect of vitamin A on cytokine secretion by mononuclear cells of preterm newborns and adults. *Neonatology*. 2007;91(3):196-202.

67. Long, K. Z. Santos I. S. Rosado J. L. Estrada-Gardia T. Haas M. Al Mamun A. Dupont H. L. and Nanthakumar N. N. Vitamin A supplementation modifies the association between mucosal innate and adaptive immune responses and resolution of enteric pathogen infections. *Am.J.Clin.Nutr*. 2011;93(3):578-585.

68. Boden, S. D. Labropoulos P. A. Ragsdale B. D. Gullino P. M. and Gerber L. H. Retinyl actate-induced arthritis in C3H-A^{vy} mice. *Arthritis Rheum.* 1989;32(5):625-633.

69. Yoon, H. S. Kim Y. K. and Chung J. H. High-concentration all-trans retinoic acid induces dermal inflammation and reduces the accumulation of type I procollagen in human skin in vivo. *Br.J.Dermatol.* 2011;165(3):669-672.

70. Castaño, G. Etchart C. and Sookoian S. Vitamin A toxicity in a physical culturist patient: A case report and review of the literature. *Annals of Hepatology*. 2006;5(4):293-295.

71. Cheruvattath, R. Orrego M. Gautam M. Byrne T. Alam S. Voltchenok M. Edwin M. Wilkens J. Williams J. W. and Vargas H. E. Vitamin A toxicity: When one a day doesn't keep the doctor away. *Liver Transplantation*. 2006;12(12):1888-1891.

72. Clemmensen, A., Thormann, J., and Andersen, K. E. Allergic contact dermatitis from retinyl palmitate in polycaprolactone. *Contact Dermatitis*. 2007;56(5):288-289.

73. Ramanathan, V. s. hensley G. French S. Eysselein V. Chung D. Reicher S. and Pham B. Hypervitaminosis A inducing intra-hepatic cholestasis - a rare case report. *Experimental and Molecular Pathology*. 2010;88(2):324-325.

74. Khasru, M. R. Yasmin R. Salek A. K. Khan K. H. Nath S. D. and Selim S. Acute hypervitaminosis A in a young lady. *Mymensingh Med.J.* 2010;19(2):294-298.

75. Lindgren, S. Groth O. and Molin L. Allergic contact response ro vitamin A acid. *Contact Dermatitis*. 1976;2(4):212-217.

76. Tanaka, M. Fukushima N. Itamura H. Urata C. Yokoo M. Ide M. Hisatomi T. Tomimasu R. Sueoka E. and Kimura S. Gangrenous cheilitis associated with all-trans rertinoic acid thexrapy for acute promyelocytic leukemia. *Int.J.Hematol.* 2010;91(1):132-135.

77. Heidenheim, M. and Jemec G. B. E. Occupational allergic contact dermatitis from vitamin A acetate. *Contact Dermatitis*. 1995;33:49.

78. Biesalski, H. K. Hemmes C. El Hanafy M. Weiser H. Zschaebitz H. and Stofft E. Long-term administration of high dose vitamin A to rats does not cause fetal malformations: macroscopic, skeletal and physicochmical findings. *J.Nutr*. 1996;126(4):973-983.

79. McDaniel, S. M., O'Neill, C., Metz, R. P., Tarbutton, E., Stacewicz-Sapuntzakis, M., Heimendinger, J., Wolfe, P., Thompson, H., and Schedin, P. Whole-food sources of vitamin A more effectively inhibit female rat sexual maturation, mammary gland development, and mammary carcinogenesis than retinyl palmitate. *J Nutr*. 2007;137(6):1415-1422.

80. Rezaei, N., Hashemi Soteh, M. B., and Rahimi, F. Effects of limited doses of retinyl palmitate at the critical time of limb morphogenesis in mouse embryos. *Indian J Exp Biol*.. 2009;47(12):949-954.

81. Schnorr, C. E. Morrone M. D. S. Weber M. H. Lorenzi R. Behr G. A. and Moreira J. C. F. The effects of vitamin A supplementation to rats during gestation and lactation upon redox parameters: Increased oxidative stress and redox modulation in mothers and their offspring. *Food and Chemical Toxicology*. 2011;49(10):2645-2654.

82. Schnorr, C. E., da Silva, Morrone M., Simäes-Pires, A., da Rocha, R. F., Behr, G. A., and Moreira, J. C. Vitamin A supplementation in rats under pregnancy and nursing induces behavioral changes and oxidative stress upon striatum and hippocampus of dams and their offspring. *Brain Res.* 2011;1369:60-73.

83. Tember, E. A. Honeywell R. Buss N. E. and Renwick A. G. All-trans-retinoic acid in maternal plasma and teratogenicity in rats and rabbits. *Toxicol.Appl.Pharmacol.* 1996;141(2):456-472.

84. Juneja, H. S. Murthy S. K. and Ganguly J. Effect of retinoic acid on the reproductive performances of male and female rats. *Indian J.Exp.Biol.* 1964;2:153-154.

85. Kutz, S. A. Troise N. J. Cimprich R. E. Yearsley S. M. and Rugen P. J. Vitamin A acetate: A behavioral teratology study in rats. *Drug Chem.Toxicol.* 1989;12(3-4):259-275.

86. Kochhar, D. M. Teratogenic activity of retinoic acid. *Acta Pathol.Microbiol.Scand.* 1967;70:398-404.

87. Sadek, I. A. and Abdul-Mohsen M. H. Long-term admnistration of vitamin A and the process of spermatogenesis. *East.Mediterr.Health Journal*. 1999;5(1):123-129.

88. Seegmiller, R. E. Carter M. W. Ford W. H. and White R. D. Induction of maternal toxcity in the rat by dermal application of retinoic acid and its effect on fetal outcome. *Reprod.Toxicol.* 1990;4(4):277-281.

89. Eckhoff, C. Chari S. Kromka M. Staudner and H., Juhasz L. Rudiger H. and Agnish N. Teratogenicity and transplacental pharmacokinetics of 13-cis-retinoic acid in rabbits. *Toxicol.Appl.Pharmacol.* 1994;125(1):34-41.

90. Tzimas, G. Burgin H. Collins M. D. Hummler H. and Nau H. *Arch.Toxicol.* 1994;68(2):119-128.

91. Horie, S. and Yasuda M. Alterations in palatal ruga patterns in Jcl:ICR mouse fetuses from dams treated with all-*trans* retinoic acid. *Hiroshima J.Med.Sci.* 2001;50(1):17-25.

92. Mulder, g. b. Manley N. Grant J. Schmidt K. Zeng W. Eckhoff C. and Maggio-Price L. Effects of excess Vitamin A on development of cranial neural crest-derived structures: A neonatal and embryologic study. *Teratology*. 2000;62(4):214-226.

93. Freytag, T. L. Liu S. M. Rogers Q. R. and Morris J. G. Teratogenic effects of chronic ingestion of high levels of vitamin A in cats. *J.Anim.Physiol.Anim.Nutr.* 2003;87(1-2):42-51.

94. Lee, M. Potentiation of chemically induced cleft palate by ethanol ingestion during gestation in the mouse. *Teratog.Carcinog.Mutagen.* 1985;5(6):433-440.

95. Martínez-Angoa, A. Parra-Hernández E. Madrigal-Bujaidar E. Chamorro-Cevallos G. Carvajal-Sandoval G. and Zamudio-Cortes P. Reduction of all-trans retinoic acid-induced teratogenesis in the rat by glycine administration. *Birth Defects Res.A.* 2006;76(10):731-738.

96. West, K. P. Jr. Christian P. Labrique A. B. Rashid M. Shamim A. A. Klemm R. D. W. Massie A. B. Mehra S. Schulze K. J. Ali HY. Ullah B. Wu L. S. F. Katz J. Banu H. Akhter H. H. and Sommer A. Effects of vitamin A or beta carotene supplementation on pregnancy-related mortality and infant mortality in rural Bangladesh. *JAMA.* 2011;305(19):1986-1995.

97. Sladden, M. J. and Harman K. E. What is the chance of a normal pregnancy in a woman whose fetus has been exposed to isotretinoin? *Arch.Derm.* 2007;143:1187-1188.

98. Berard, A. Azoulay L. Koren G. et al. Isotretinoin, pregnancies, abortions, and birth defects. *Br.J.Clin.Pharm.* 2007;63:196-205.

99. Dai, W. S. LaBraico J. M. and Stern R. S. Epidemiology of isotretinoin exposure during pregnancy. *J.Am.Acad.Dermatol.* 1993;26:599-606.

100. Inoue, Y. Hasegawa S. Yamada T. Date Y. Mizutani H. Nakata S. Matsunaga K. and Akamatsu H. Bimodal effect of retinoic aciud on melanocyte differentiation identified by time-depoendent analysis. *Pigment Cell Melanoma Res.* 2012;25(3):299-311.

101. Nau, H. Embryotoxicity and teratogenicity of topical retinoic acid. *Skin Pharmacol.* 1993;6(1):35-44.

102. Hummler, H. Korte R. and Hendrickx A. G. Induction of malformations in the cynomolgus monkey with 13-cis retinoic acid. *Teratology*. 1990;42:263-272.

103. Hendrickx, A. G. and Hummler H. Teatogenicity of all-trans retinoic acid during early embryonic development in the cynomolgus monkey (*macaca fascicularis*). *Teratology*. 1992;45:65-74.

104. Louisse, J. Gönen S. Rietjens I. M. C. M. and Verwei M. Relative developmental toxicity potencies of retinoids in the embryonic stem cell test compared with their relative potencies in vivo and two other in vitro assays for developmental toxicity. *Toxicology Letters*. 2011;203(1):1-8.

105. Qin, S. and Huang C. C. Effect of retinoids on carcinogen-induced mutagenesis in Salmonella tester strains. *Mutation Research*. 1985;142(3):115-120.

106. Mei, N., Xia, Q., Chen, L., Moore, M. M., Fu, P. P., and Chen, T. Photomutagenicity of retinyl palmitate by ultraviolet a irradiation in mouse lymphoma cells. *Toxicol Sci.* 2005;88(1):142-149.

107. Fu, P. P. Cheng S. H. Coop L. Xia Q. Culp S. J. Tolleson W. H. Wamer W. G. and Howard P. C. Photoreaction, phototoxicity, and photocarcinogenicity of retinoids. *Journal of Environmental Science and Health*. 2003;C21(2):165-197.

108. Cherng, S. H., Xia, Q., Blankenship, L. R., Freeman, J. P., Wamer, W. G., Howard, P. C., and Fu, P. P. Photodecomposition of retinyl palmitate in ethanol by UVA light-formation of photodecomposition products, reactive oxygen species, and lipid peroxides. *Chem.Res.Toxicol.* 2005;18(2):129-138.

109. Yin, J. J. Xia Q. and Fu P. P. UVA photoirradiation of anhydroretinol-formation of singlet oxygen and superoxide. *Toxicol.Ind.Health*. 2007;23:625-631.

110. Xia, Q., Yin, J. J., Cherng, S. H., Wamer, W. G., Boudreau, M., Howard, P. C., and Fu, P. P. UVA photoirradiation of retinyl palmitate--formation of singlet oxygen and superoxide, and their role in induction of lipid peroxidation. *Toxicol Lett.* 2006;163(1):30-43.

111. Yan, J., Xia, Q., Cherng, S. H., Wamer, W. G., Howard, P. C., Yu, H., and Fu, P. P. Photo-induced DNA damage and photocytotoxicity of retinyl palmitate and its photodecomposition products. *Toxicol Ind.Health*. 2005;21(7-8):167-175.

112. Dufour, E. K. Whitwell J. Nohynek G. J. Kirkland D. and Toutain H. Retinyl palmitate is non-genotoxic in Chinese hanster ovary cells in the dark after pre-irradiation or simultaneous irradiation with UV light. *Mutation Research*. 2009;672(1):21-26.

113. Mei, N., Chen, T., Godar, D. E., and Moore, M. M. Letter to the editor. UVA-induced photomutagenicity of retinyl palmitate. *Mutat.Res.* 2009;677(1-2):105-108.

114. Dufour, E. K. Whitwell J. Nohynek G. J. Kirkland D. and Toutain H. Reply to the letter to the editor. *Mutat.Res.* 2009;677:107-108.

115. Mei, N. Hu J. Xia Q. Fu P. P. Moore M. M. and Chen T. Cytotoxicity and mutagenicity of retinol with ultraviolet A irradiation in mouse lymphoma cells. *Toxicology in Vitro*. 2010;24:439-444.

116. Sasaki, M. Sugimura K. Yoshida M. A. and Abe S. Cytogenetic effects of 60 chemicals on cultured human and Chinese hamster cells. *Senshokutai (Kromosoma)*. 1980;20:574-584.

117. Sirianni, S. R. Chen H. H. and Huang C. C. Effect of retinoids on plating efficiency, sister-chromatid exchange (SCE) and mitomycin-C induced SCE in cultured Chinese hamster cells. *Mutat.Res.* 1981;90:175-182.

118. Sorg, O. Tran C. Carraux P. Grand D. Hügin A. Didierjean L. and Saurat J. H. Spectral properties of topical retinoids prevent DNA damage and apoptosis after acute UV-B exposure in hairless mice. *Photochemistry and Photobiology*. 2005;81(4):830-836.

119. Kontek, R. Drozda R. Sliwinski M. and Grzegorczyk K. Genotoxicity of irinotecan and its modulation by vitamins A, C, and E in human lymphocytes from healthy individuals and cancer patients. *Toxicology in Vitro*. 2010;24(2):417-424.

120. Mehta, R. G. and Moon R. C. Inhibition of DNA synthesis by retinyl acetate during chemically induced mammary carcinogenesis. *Cancer Res.* 1980;40(4):1109-1111.

121. Welsch, C. W. Goodrich-Smith M. Brown C. K. and Crowe N. Enhancement by retinyl acetate of hormone-induced mammary tumorigenesis in female GR/A mice. *J.Natl.Cancder Inst.* 1981;67(4):935-938.

122. Kurokawa, Y. Hayashi Y. Maekawa A. takahashi M. and Kukubo T. High incidences of pheochomocyomas after long-term administration of retinol acetate to F344/DuCrj rats. *J.Natl.Cancer Inst.* 1985;74(3):715-723.

123. Grubbs, C. J. Eto I. Juliaa M. M. Hardin J. M. and Whitaker L. M. Effect of retinyl acetate and 4-hydroxyphenylretinamide on onitiation of chemically-induced mammary tumors. *Anticancer Res.* 1990;10(3):661-666.

124. Epstein, J. H. Chemicals and photocarcinogenesis. *Aust.J.Dermatol.* 1977;18:57-61.

125. Epstein, J. H. Effects of beta-carotene on ultraviolet-induced cancer formation in the hairless mouse skin. *Photochem.Photobiol.* 1977;25:211-213.

126. Kligman, L. H. Retinoic acid and photocarcinogenesis - a controversy. *Photodermatology*. 1981;4:88-101.

127. Forbes, P. D. Urbach F. and Davies R. E. Enhancement of experimental photocarcinogenesis by topical retinoic acid. *Cancer Lett.* 1979;7:85-90.

128. Forbes, P. D. Photocarcinogenesis: an overview. *J.Invest.Derm.* 1981;77:139-143.

129. Kligman, L. H. and Kligman A. M. Lack of enhancemernt of experimental photocarcinogenesis by topical retinoic acid. *Arch.Dermatol.Res.* 1981;270:453-462.

130. Hartmann, H. R. and Teelmann K. The influence of topical and oral retinoid treatment on photocarcinogenicity in hairless albino mice. Orfanos, C. E.Springer-Verlag; 1981:447-451.

131. Kligman, L. H. and Kligman A. M. Lack of enhancement of experimental photocarcinogenesis by retinoic acid. Orfanos, C. E. Braun-Falco O. Farber E. M. Grupper C. L. Polano M. K. and Schuppli R.Berlin: Springer-Verlag; 1981:411-415.

132. Davies, R. E. and Forbes P. D. Retinoids and photocarcinogenesis: a review. *J.Toxicol.-Cut.& Ocular Toxicology*. 1988;7:241-253.

133. Halliday, G. M. Robertson B. O. and Barnetson R. S. Topical retinoic acid enhances, and a dark tan protects, from subedemal solar-stimulated photocarcinogenesis. *J.Invest.Dermatol.* 2000;114:923-927.

134. Fu, P. P. Howard P. C. Culp S. G. Xia Q. Webb P. J. Blankenship L. R. Wamer W. G. and Bucher J. R. Do topically applied skin creams containing retinyl palmitate affect the photocarcinogenicity of simulated solar light? *J.Food Drug Anal.* 2002;10:262-268.

135. National Toxicology Program. NTP technical report of the photocarcinogenesis study of retinoic acid and retinyl palmitate in SKH-1 mice (simulated solar light and topical application study). http://ntp.niehs.gov. Date Accessed 4-26-2013.

136. Burnett, M. E. and Wang, S. Q. Current sunscreen controversies: a critical review. *Photodermatol.Photoimmunol.Photomed.* 2011;27(2):58-67.

137. Department of health and Human Services.National Toxicology Program (NTP). TR-568: technical report pathology tables and curves. http://ntp.niehs.nih.gov/index.cfm?objectid=555571BB-F1F6-975E-76F2BC5E369EB6F7. Date Accessed 8-17-2010.

138. Kraemer, K. H. et al. Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. *New Engl.J.Med.* 1988;318:1633-1637.

139. McKenna, D. B. and Murphy G. M. Skin cancer chemoprophylaxis in renal transplant recipients: 5 years of experience using low-dose acitretin. *Br.J.Dermatol.* 1999;140:656-660.

140. Smith, D. M. Rogers A. E. herndon B. J. and Newberne P. M. Vitamin A (retinyl acetae) and benzo(a)pyrene-induced respiratory tract carcinogenesis in hanmsters fed a commercial diet. *Cancer Res.* 1975;35(1):11-16.

141. Smith, D. M. Rogers A. E. and Newberne P. M. Vitamin A and benzo(a)pyrene carcinogenesis in the respiratory tract of hamsters fed a semisynthetic diet. *Cancer Research*. 1975;35:1485-1488.

142. Thompson, H. J. Meeker L. D. and Becci P. J. Effect of combined selenium and retinyl acetate treatment on mammary carcinogenesis. *Cancer Res.* 1981;41(4):1413-1416.

143. McCormick, D. L. Burns F. J. and Albert R. E. Inhibition of rat mammary carcinogenesis by short dietary exposure to retinyl acetate. *Cancer Res.* 1980;40(4):1140-1143.

144. Dawson, W. D. Miller W. W. and Liles W. B. Retinyl acetate prophylaxis in cancer of the uinary bladder. *Invest.Urol.* 1979;16(5):376-377.

145. Maiorana, A. and Gullino P. M. Effect of retinyl acetate on the incidence of mammary carcinomas and hepatomas in mice. *J Natl.Cancer Inst.* 1980;64:655-663.

146. Kandarkar, S. V. Potdar P. D. and Sirsat S. M. Dose response effect of retinyl acetate on DMBA induced carcinogenesis in the hamster cheek pouch. *Neoplasma*. 1984;31(4):415-421.

147. Welsch, C. W. DeHoog J. V. and Moon R. C. Lack of an effect of dietary retinoids in chemical carcinogenesis of the mouse mammary gland: inverse relationship between mamary tumor cell anaplasia and retinoid efficacy. *Carcinogenesis*. 1984;5(10):1301-1304.

148. Stenbäck, F. Mu B. and Williams G. Retinyl acetate effects the life span and the incidence of cryptogenic neoplasms in C3H mice. *Nutr.Cancer*. 1987;10(3):119-128.

149. Slaga, T. J. Fischer S. M. Weeks C. E. and Klein-Szanto A. J. P. Multistage chemical carcinogenesis in mouse skin. *Curr.probl.Dermatol.* 1980;10:193-218.

150. Connor, M. J. Lowe N. J. Breeding J. H. and Chalet M. Inhibition of ultraviolet-B skin carcinogenesis by all trans-retinoic acid regimens that inhibit ornithine decarboxylase induction. *Cancer Res.* 1983;43:171-174.

151. Papadimitrakopoulou, V. A., Lee, J. J., William, W. N., Jr., Martin, J. W., Thomas, M., Kim, E. S., Khuri, F. R., Shin, D. M., Feng, L., Hong, W. K., and Lippman, S. M. Randomized trial of 13-cis retinoic acid compared with retinyl palmitate with or without beta-carotene in oral premalignancy. *J Clin.Oncol.* 2009;27(4):599-604.

152. Yuspa, S. H. Elgjo K. Morse M. A. and Wiebel F. J. Retinyl acetate modulation of cell growth kinetics and carcinogen-cellular interaction in mouse epidermal cell cultures. *Chem.-Biol.Interactions*. 1977;16(3):251-264.