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CIR EXPERT PANEL MEETING

SEPTEMBER 8-9, 2014

Commitment & Credibility since 1976

MEMORANDUM

To: CIR Expert Panel Members and Liaisons
From: Director, CIR
Subject: 132nd Meeting of the CIR Expert Panel — Monday and Tuesday, September 8-9, 2014
Date: August 18, 2014

Enclosed are the agenda and accompanying materials for the 132nd CIR Expert Panel Meeting to be held on September 8-9, 2014. The meeting will be held at the Washington Court Hotel, 525 New Jersey Avenue, NW, Washington, DC 20001. Phone: (202) 628-2100. Fax: (202) 879-7993. The meeting agenda includes consideration of 13 ingredient groups advancing in the process and 3 re-reviews.

At the June meeting, CIR provided boilerplates and guidance language documents for Panel review and comment. The changes made to several of the documents, based on the comments received from the Council, are included for your review. Additionally, in our continuing effort to investigate ways to improve our review process, CIR is providing a number of strategy documents for your review and comment. These include a proposal for initiating the review of the algae family of ingredients, and documents describing our plan for assessing previously-reviewed ingredients that will reach the 15-yr mark in 2015.

Schedule and hotel accommodations

We have reserved rooms for the nights of Sunday September 7 and Monday September 8, at the Washington Court Hotel. If you encounter any travel problems, please contact me on my cell phone at 410-299-0777.

Team meetings

Re-review – there are 3 safety assessments to re-review and re-open to revise the conclusion, re-open to add additional ingredients, or reaffirm the original conclusion and not reopen.

1. PCA and Its Salts (agenda and flash drive name – PCA) – PCA (more commonly known as pyroglutamic acid and sodium pyroglutamate) and sodium PCA were reviewed previously (published in 1999) with the conclusion that these skin conditioning agents-humectants are safe as used and that these ingredients should not be used in cosmetic products containing *N*-nitrosating agents. Both frequency of use and concentration of use have increased; however, the concentration of use has only increased slightly. The new data are summary data found on the European Chemicals Agency (ECHA) website. Three additional salts (simple; inorganic; non-transitional metal) are being suggested for addition to this family. If the Panel agrees that the data in the existing report and the new data support the safety of these ingredients, the Panel should re-open this assessment to add these ingredients.

2. Propylene Glycol Esters (agenda and flash drive name – PGesters) – PGesters were reviewed previously in several safety assessments (1983 and reaffirmed in 2005; 1999; 2010; and 2011) with the conclusion that these skin conditioning agents are safe as used. Uses of propylene glycol

dicaprylate increased substantially; most other PGesters have decreased in use. Eleven additional PGesters are being suggested for addition to this family. If the Panel agrees that the data in the existing report and the new data support the safety of these ingredients, the Panel should re-open this assessment to add these ingredients.

3. Sorbitan Esters (agenda and flash drive name – sorbitan esters) – Sorbitan esters were reviewed previously (published in 1985 and 2002) with the conclusion that these ingredients were safe. (Seven sorbitan esters included in the 1985 assessment, and in 2002, the Panel reviewed the safety of an additional 10 esters). Much of the new data are found on the ECHA website. Four additional sorbitan esters are being suggested for addition to this family. If the Panel agrees that the data in the existing reports, as well as the new data presented in this re-review document, support the safety of these proposed ingredients, the Panel should re-open this assessment and add these ingredients, thereby creating a family of 21 sorbitan esters.

Draft reports - there are 3 draft reports for review.

1. Glycerin (agenda and flash drive name – glycerin) – This is the first time that the Panel is seeing this report on this ingredient. The Scientific Literature Review was issued on May 29, 2014. Glycerin (also referred to as glycerol) is reported to function in cosmetics as a denaturant; fragrance ingredient; hair conditioning agent; humectant; oral care agent; oral health care drug; skin protectant; skin-conditioning agent - humectant; and viscosity decreasing agent. Glycerin occurs naturally in all animals and plants. Limited data and concentration of use data received from the Council are included. Do we need more data or can we proceed to issue a tentative report?

2. PEGylated Alkyl Glycerides (agenda and flash drive name – PEG glycerides) – This is the first time the Panel is seeing this report on 60 ingredients that mostly function as skin conditioning agents or surfactants. The Scientific Literature Review was issued on June 5, 2014. This report includes the PEG glyceryl cocoates that were reviewed (published in 1999) and found safe in rinse-off products and safe at up to 10% in leave-on products, as well as PEG-3 glyceryl cocoate. Data received from the Council have been incorporated into the report. Do we need more data or can we proceed to issue a tentative report?

3. Plant Polysaccharide Gums (agenda and flash drive name – polysaccharide gums) – This is the first time that the Panel is seeing this report on 114 ingredients. The Scientific Literature Review was announced for public comment on May 29, 2014. Plant polysaccharide gums are used in rinse-off cosmetic products at maximum use concentrations up to 50%, and in leave-on cosmetic products at maximum use concentrations up to 45.7%. Unpublished data and concentration of use data received from the Council have been incorporated into the report. Are these data sufficient or are more data needed to issue a tentative report?

Tentative reports – there are 2 draft tentative reports.

1. *Avena sativa* -Derived Ingredients (agenda and flash drive name – *avena sativa*) – At the June meeting, the Panel issued an insufficient data announcement for *Avena sativa* (oat)-derived ingredients. The 21 ingredients in this package include three hydrolyzed oat ingredients (hydrolyzed oats, hydrolyzed oat protein and hydrolyzed oat flour) that were added based on comments from the Council. Data submitted by industry that addresses most of the data needs including method of manufacture, irritation and sensitization studies, and characterization of hydrolyzed oat protein, are included in the report. Some additional published information is also added to the report. Are the data sufficient to issue a tentative report with a safe or safe with qualifications conclusion, or a tentative report with an insufficient conclusion?

2. Polyoxalkylene Siloxane Copolymers, Alkyl-Polyoxyalkylene Siloxane Copolymers, and Related Ingredients (agenda and flash drive name – polysiloxanes) – At the June meeting, the Panel issued an insufficient data announcement for 111 polyoxyalkylene siloxane copolymers, alkyl-polyoxyalkylene siloxane copolymers, and related ingredients (alkyl polysiloxanes). The data

needed included molecular weight ranges of all of the ingredients, impurities data, and dermal penetration, irritation, and sensitization data for the smallest ingredient(s). Data submitted, including an HRIPT and some impurities data and molecular weight data, are included. Are the data sufficient to issue a tentative report with a safe or safe with qualifications conclusion, or a tentative report with an insufficient conclusion?

Final reports - there are 8 draft final reports for consideration. After reviewing these drafts, especially the rationales provided in the Discussion sections, the Panel should issue them as final reports.

1. Alkyl Phosphates (agenda and flash drive name – alkyl phosphates) – At the June meeting, the Panel issued a Tentative Report with the conclusion that these 28 ingredients are safe when formulated to be non-irritating. Summary data from an irritation and sensitization study on dimyristyl phosphate was submitted and are included in the report. Comments from the Council have been addressed.

2. Citrus-Derived Ingredients (agenda and flash drive name – citrus) – At the June meeting, the Panel concluded that the 14 citrus-derived peel oils are safe for use in cosmetic products when finished products that are applied to the skin, excluding rinse-off products, do not contain more than 0.0015% or 15 ppm 5-methoxysporalen (5-MOP), and when formulated to be non-sensitizing and non-irritating. The Science and Support Committee (SSC) proposes deleting the phrase "that are applied to skin" from the conclusion as it may be misinterpreted to mean that citrus peel oils should not be used in products that are applied to hair and/or nails. The Council also commented that citrus aurantifolia (lime) peel oil should be removed from the report because fragrance is the only function listed in the Dictionary and there is an IFRA standard for lime oil. CIR is asking the Council for clarification because it is not clear that the lime oil referred to by RIFM is the peel oil.

3. 2-Amino-3-Hydroxypyridine (agenda and flash drive name – hydroxypyridine) – At the June meeting, the Panel concluded that 2-amino-3-hydroxypyridine is safe for use in oxidative hair dye formulations. In response to the Panel statement that hair dyes with 2-amino-3-hydroxypyridine should be formulated to avoid the formation of *N*-nitrosopyridinium compounds, Industry commented that nitrosation at the nitrogen atom of the heterocycle, especially for the 2,3-substituted pyridine derivative, would be very unlikely. Updated concentration of use data indicating that the maximum undiluted concentration has not changed, but that the actual "on-head" use concentration is 1%, not 0.6% as previously reported, is included in the report. Technical comments have been considered.

4. *Camellia sinensis*-Derived Ingredients (agenda and flash drive name – *camellia*) – At the June meeting, the Panel concluded all *Camellia sinensis* leaf-derived ingredients and the catechins are safe as used when formulated to be non-sensitizing. The Panel upheld the insufficient data conclusion for camellia sinensis flower extract, camellia sinensis flower/leaf/stem juice, camellia sinensis root extract, camellia sinensis seed coat powder, camellia sinensis seed extract, camellia sinensis seed powder, and hydrolyzed camellia sinensis seed extract. No new data has been submitted. Comments from the Council have been addressed.

5. Hydroquinone (agenda and flash drive name – hydroquinone) – At the June meeting, the Panel concluded that hydroquinone is safe at concentrations of ≤ 1% for cosmetic formulations designed for discontinuous, brief use followed by rinsing from the skin and hair. Hydroquinone is safe for use in nail adhesives and as a polymerization inhibitor in artificial nail coatings that are cured by UV light when photo-protective materials (e.g., gloves, sunscreen) are used in professional settings but unsafe for home use when used with UVA light. Hydroquinone should not be used in other leave-on cosmetic products. Comments submitted from Industry suggest that the conclusion reached by the Panel should address only the ingredient and not bulb replacement. Additionally, they state that the wavelength required for curing nail gel products sold for home use was given (at the last Panel meeting) as 400-420 nm, which is visible light. Additional comments are submitted in Wave 2 by Dr. Steinberg regarding LED bulbs that are currently produced for home-use nail gel curing lamps.

6. *p*-Hydroxyanisole (agenda and flash drive name – hydroxyanisole) – At the June meeting, the Panel concluded that *p*-hydroxyanisole is safe for use as a polymerization inhibitor in artificial nail coatings when photo-protective materials for the skin (e.g., gloves, sunscreen) are used in a professional setting and unsafe for the new in-home products when used with UVA light sources. The Panel reiterated that *p*-hydroxyanisole is unsafe for use in all other cosmetics because of dermal depigmentation potential. Comments submitted from Industry suggest that the conclusion reached by the Panel should address only the ingredient and not bulb replacement. Additionally, they state that the wavelength required for curing nail gel products sold for home use was given (at the last Panel meeting) as 400-420 nm, which is visible light. Additional comments are submitted in Wave 2 by Dr. Steinberg regarding LED bulbs that are currently produced for home-use nail gel curing lamps. Comments from industry were addressed. No new data on this ingredient or UV nail lamps have been submitted.

7. Styrene and Vinyl-type Styrene Copolymers (agenda and flash drive name – styrene) – At the June 2014 meeting, The Panel concluded the 35 styrene and vinyl-type styrene copolymers are safe. The results of the uterotrophic assay on polystyrene received from the National Technical Information Service (NTIS) are included in the report. Comments from the Council have been addressed.

8. Methylisothiazolinone (agenda and flash drive name – MI) – At the June meeting, the Panel issued a tentative amended safety assessment for public comment with the conclusion that methylisothiazolinone (MI) is safe for use in rinse-off cosmetic products at concentrations up to 100 ppm and safe in leave-on cosmetic products when they are formulated to be non-sensitizing, which may be determined based on a QRA. Additional QRA estimates were received from the CIR SCC and were added to the report, including QRA estimates predicting maximum safe use concentrations in hair products and leave-on products in which MI has been reported to be used, based on data from the VCRP. Comments from the Council have been considered and are included in this report package.

Full Panel Meeting

Remember, the breakfast buffet will open at 8:00 am and the meeting starts at 8:30 am on day 1 and on day 2.

The Panel will consider the 8 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 infant skin resource document, boilerplate and guidance documents, the strategies for the review of algae ingredients and the strategies for assessing the 2015 re-reviews.

The bulk of the agenda is the final reports. We also have three re-reviews. It is likely that the full Panel session will conclude before lunch on day 2, so plan your travel accordingly.

Have a safe journey.

Agenda
132nd Cosmetic Ingredient Review Expert Panel Meeting
September 8-9, 2014

Monday, September 8

8:00 am **CONTINENTAL BREAKFAST**

8:30 am **WELCOME TO THE 132st EXPERT PANEL TEAM MEETINGS** **Drs. Bergfeld/Gill**

8:40 am **TEAM MEETINGS** **Drs. Marks/Belsito**

	Dr. Marks' Team		**Dr. Belsito's Team***
FAR (IB)	MI	FR (WJ)	styrene
Admin (IB/MF)	infant skin/bp	DR (WJ)	polysaccharide gums
Admin (BH)	2015 RR strategies	TR (LB)	*avena sativa*
FR (MF)	alkyl phosphates	FR (LB)	*camellia*
FR (MF)	citrus	FAR (LB)	hydroquinone
FR (MF)	hydroxypyridine	FAR (LB)	hydroxyanisole
DR (MF)	PEG glycerides	TR (LB)	polysiloxanes
RR (MF)	PCA	DR (LB)	glycerin
RR (MF)	sorbitan esters	RR (LB)	PGesters
FR (WJ)	styrene	FAR (IB)	MI
DR (WJ)	polysaccharide gums	Admin (IB/MF)	infant skin/bp
TR (LB)	*avena sativa*	Admin (BH)	2015 RR strategies
FR (LB)	*camellia*	FR (MF)	alkyl phosphates
FAR (LB)	hydroquinone	FR (MF)	citrus
FAR (LB)	hydroxyanisole	FR (MF)	hydroxypyridine
TR (LB)	polysiloxanes	DR (MF)	PEG glycerides
DR (LB)	glycerin	RR (MF)	PCA
RR (LB)	PGesters	RR (MF)	sorbitan esters

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

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

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

FR: Final report
FAR: Final amended report
TR: Tentative 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 9

8:00 am	**CONTINENTAL BREAKFAST**		
8:30 am	**WELCOME TO THE 132nd FULL CIR EXPERT PANEL MEETING**		
8:45 am	Admin	**MINUTES OF THE JUNE 2014 EXPERT PANEL MEETING**	**Dr. Bergfeld**
9:00 am	**DIRECTOR'S REPORT**		**Dr. Gill**
9:15 am	**FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, RE-REVIEWS, and OTHER DISCUSSION ITEMS**		

Final Reports

FR (MF)	Alkyl Phosphates - Dr. Marks reports
FR (MF)	Citrus - Dr. Belsito reports
FR (MF)	Hydroxypyridine - Dr. Marks reports
FAR (IB)	MI – Dr. Belsito reports
FR (WJ)	Styrene – Dr. Marks reports
FR (LB)	*Camellia* - Dr. Belsito reports
FAR (LB)	Hydroquinone - Dr. Marks reports
FAR (LB)	Hydroxyanisole - Dr. Belsito reports

Reports Advancing

TR (LB)	*Avena sativa* – Dr. Marks reports
TR (LB)	Polysiloxanes – Dr. Belsito reports
DR (LB)	Glycerin – Dr. Marks reports
DR (WJ)	Polysaccharide gums – Dr. Belsito reports
DR (MF)	PEG glycerides – Dr. Marks reports

Re-reviews

RR (MF)	Sorbitan esters – Dr. Belsito reports
RR (MF)	PCA – Dr. Marks reports
RR (LB)	PGesters – Dr. Belsito reports

New Information

Admin (IB/MF)	Infant Skin/BP – Dr. Marks reports
Admin (BH)	2015 RR strategies – Dr. Belsito reports

ADJOURN - Next meeting *Monday and Tuesday, December 8-9, 2014*

FR: Final report
FAR: Final amended report
TR: Tentative 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.

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ONE HUNDRED THIRTY-FIRST MEETING

OF THE

EXPERT PANEL

June 9-10, 2014

Washington Court 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

Jay Ansell, 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

Louise Aust	Henkel
Robene Azn	FDA
Jay Ansell	PCPC
Yutaka Aoki	Kanebo
Lillian Becker	CIR
Don Bjerke	Procter & Gamble
Ivan Boyer	CIR
Christina Burnett	CIR
Sheila Daniels	Henriquez
Kapal Dewan	FDA
Carol Eisenmann	Council
Monice Fiume	CIR
Kevin Fries	CIR
Lillian Gill	CIR
Tracy Guerrero	SEHSC
Bart Heldreth	CIR
Sandra Hong	Exponent
Carla Jackson	CIR
Wilbur Johnson, Jr.	CIR
Akihiro Kinoshita	Shiseido
Wendy Koch	SEHSC
Lois Kotkoske	Croda
Dennis Laba	Presperse
Rex Lowe	
Jason Magby	Colgate Polmolive
Ann-Marie Materi	Coty
Stanley Milstein	FDA-CFSCAN
Joanne Nikitakis	PCPC
Damani Parran	Akzo Nobel
Diego Rua	FDA
Anthony Schatz	Ashkind
Noriko Shibuya	Shiseido
Nakira Sodirle	FDA
David Steinberg	Steinberg & Associates
Victoria Tu	Revlon
Ian Watt	Dow Chemicals
Jeremy Wong	Estee Lauder

MINUTES FROM THE 131st CIR EXPERT PANEL MEETING

CHAIRMAN'S OPENING REMARKS

The 131st meeting of the Cosmetic Ingredient Review (CIR) Expert Panel was called to order by Dr. Wilma Bergfeld at 8:28 a.m. on Tuesday, June 10, 2014. All attendees were welcomed. Dr. Bergfeld stated that 18 ingredients reports were reviewed in Teams on the preceding day, 10 of which are final reports. Furthermore, the Panel heard a presentation on infant skin (absorption and other considerations) by Dr. Peter Elias and a presentation on algae by Dr. Richard Lowe. Dr. Bergfeld noted that CIR's Dr. Ivan Boyer developed a guidance document on infant skin, for use in addressing issues relating to the use of cosmetic ingredients on infant skin that may arise during the CIR review process. This document will be revised to include input from Dr. Elias. Information from the presentation on algae will be captured for use in the safety assessment on algae and related ingredients that will be developed in the future.

CIR boilerplates, which include guidelines for certain groups of ingredients (e.g., in the areas of pesticides and other contaminants, formaldehyde/formaldehyde releasers, and hair dye epidemiology), were also reviewed in Teams on the preceding day. Dr. Bergfeld noted that the revised boilerplates are well done and complimented the CIR staff for this effort as well as efforts in the area of report development.

APPROVAL OF MINUTES

The minutes of the March 17-18, 2014 CIR Expert Panel meeting were unanimously approved.

DIRECTOR'S REPORT

Dr. Gill expressed appreciation on behalf of CIR for the presentations on Algae and on the Dermal Diffusion Barrier in Neonates and Infants. The information on Algae will be particularly helpful as CIR develops a strategy for grouping this large family of ingredients.

Dr. Gill mentioned that Beth Lange has been appointed as the new Executive Vice President and Chief Scientist of the Personal Care Products Council. The Council's Chief Scientist serves as the Industry Liaison to the CIR Expert Panel. Dr. Gill reminded the Panel that Dr. Lange is no stranger to the CIR process; she attended previous Panel meetings as the Chair of the CIR Science and Support Committee. Dr. Lange is expected to begin her new position in early July 2014 and attend the September Panel meeting.

Finally, Dr. Gill acknowledged the efforts of the Panel since the beginning of the year. In addition to hosting 4 presentations from subject matter experts, the Panel completed more than 38 safety assessments and reviewed 3 administrative documents.

Final Safety Assessments

Barium Sulfate

The Panel issued a final safety assessment with the conclusion that barium sulfate is safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

The Panel noted that the history of safe medical use of barium sulfate indicates no significant toxicity concerns associated with systemic exposure to this ingredient in cosmetics. Furthermore, the extensive clinical experience of the Panel, and the results of numerous clinical patch tests, indicates that barium salts do not have the potential to induce sensitization. The Panel noted that salts of sulfuric acid, such as sodium sulfate, can be irritating to the skin. Thus, given the absence of skin irritation data specifically for barium sulfate, cosmetic products containing barium sulfate should be formulated to be non-irritating.

Barium sulfate is used in leave-on products at concentrations up to 37%. Among leave-on product categories that include powders, barium sulfate is used at concentrations up to 15.8%. The Panel discussed the potential for incidental inhalation exposures to this ingredient in products that are powders and agreed that, based on likely airborne particle size distributions and concentrations in the breathing zone, ingredient use concentrations, and negative results in acute oral toxicity studies, incidental inhalation would not lead to local respiratory effects (e.g., baritosis) or systemic effects.

Fatty Acid Amidopropyl Dimethylamines

The Panel issued a final safety assessment with the conclusion that the following 24 fatty acid amidopropyl dimethylamine ingredients are safe for use in cosmetics when formulated to be non-sensitizing, which may be based on a quantitative risk assessment (QRA).

almondamidopropyl dimethylamine* avocadamidopropyl dimethylamine*

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

*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 CIR Expert Panel had expressed concern in the previous Cocamidopropyl Betaine and Related Fatty Acid Amidopropyl Betaines (CAPB) safety assessment about the impurities that have sensitizing potential. These impurities of CAPB include the ingredients discussed in this safety assessment. The Panel noted that, for stearamidopropyl dimethylamine, the highest reported maximum use concentration in leave-on products may result in DMAPA concentrations that exceed the limit for this impurity recommended by the Panel for CAPB. Eleven HRIPT studies of normal human subjects indicated that no sensitization was induced by stearamidopropyl dimethylamine applied to the skin at concentrations of use; 2 rodent sensitization studies were also negative. However, a LLNA yielded an EC3 of 1.4% (350 μg/cm2), indicating that stearamidopropyl dimethylamine is a potential sensitizer. A QRA based on the HRIPTs and rodent studies resulted in a conservative weight of evidence no-expected sensitization induction level (WoE NESIL) of 1000 μg/cm2 for stearamidopropyl dimethylamine, and confirmed that this ingredient has the potential to induce sensitization at reported use concentrations in many categories of finished cosmetic products. The Panel concluded that non-sensitizing concentrations of fatty acid amidopropyl dimethylamine ingredients in finished products can be determined by formulators based on QRAs for these ingredients with fatty acid groups with carbon-chain lengths less than C18 and for DMAPA using appropriate NESILs for these substances. The Panel advised industry to continue minimizing the concentrations of the sensitizing impurity DMAPA.

The Panel expressed concern about the possible ability of amidopropyl dimethylamines with fatty acids chain lengths <C18 to be absorbed through the skin and into the systemic circulation. However, the high no-observed-adverse-effect-levels (NOAELs) in toxicity tests of amidopropyl dimethylamines with longer fatty acids alleviated this concern. The Panel felt that the overall toxicological data supported the safety of the amidopropyl dimethylamines ingredients.

Hydrolyzed Wheat Gluten and Hydrolyzed Wheat Protein

The Panel issued a final safety assessment with the conclusion that hydrolyzed wheat protein and hydrolyzed wheat gluten are safe for use in cosmetics when formulated to restrict peptides to a weight-average molecular weight (MW) of 3,500 daltons (Da) or less.

The Panel reviewed data from industry and information presented by experts on the potential for exposures to hydrolyzed wheat protein in cosmetic products to cause type 1 immediate hypersensitivity reactions. Production processes that involve high-heat acid hydrolysis of wheat protein/gluten may yield deamidated high-MW polypeptides with substantial potential to sensitize individuals through percutaneous and mucous-membrane exposures, especially in formulations that contain surfactants. Studies have shown that hydrolysates with weight-average MWs < 3,000 exhibit no potential to elicit hypersensitivity reactions in sensitized individuals, in contrast to hydrolysates with weight-average MWs >30,000 Da. The experimental results support the theory that a polypeptide must be at least 30 amino acids long to have the two IgE-binding epitopes needed to elicit type 1 hypersensitivity reactions. Thus, polypeptides with MW less than 3500 Da do not have the potency required to induce type 1 hypersensitivity.

Magnesium Sulfate

The Panel issued a final safety assessment with the conclusion that magnesium sulfate is safe in the present practices of use and concentration in cosmetics.

The Panel noted that the history of safe medical use of magnesium sulfate indicates no significant toxicity concerns associated with systemic exposure to this ingredient in cosmetics. Magnesium sulfate (50%) did not induce skin irritation or sensitization in tests using guinea pigs. Furthermore, the extensive clinical experience of the Panel, and the results of numerous clinical patch tests, indicates that magnesium salts do not have the potential to induce sensitization.

Magnesium sulfate is used at concentrations up to 11% in pump hair sprays and up to 1% in foot powders and sprays. The Panel discussed the issue of incidental inhalation exposure from pump sprays and powders, and considered pertinent data indicating that incidental inhalation exposures to this ingredient in such products would not cause adverse health effects.

PEG-150 Pentaerythrityl Tetrastearate

The Panel issued a final safety assessment with the conclusion that PEG-150 pentaerythrityl tetrastearate is safe in the present practices of use and concentration in cosmetics.

Current use concentration data indicate that the maximum reported use concentrations of PEG-150 pentaerythrityl tetrastearate in rinse-off and leave-on products were 5% and 1.8%, respectively. Data provided during the Panel meeting indicate that the method of manufacture ensures minimal formation of free PEG, and that the specifications for impurities limit ethylene oxide and 1, 4-dioxane to 1 ppm and 5 ppm, respectively. The Panel agreed that concerns about these impurities are not warranted for this ingredient.

Furthermore, after considering the large size of this molecule and its chemical structure, the Panel agreed that percutaneous absorption is not expected. The absence of the potential for percutaneous absorption and the negative results of genotoxicity and skin irritation and sensitization studies provided the Panel with a sufficient basis to assess the safety of PEG-150 pentaerythrityl tetrastearate used as a viscosity increasing agent in cosmetic products.

It is possible that PEG-150 pentaerythrityl tetrastearate may be used in products that are sprayed (highest maximum use concentration = 1.8% in tonics, dressings, and other hair grooming aids) and in face and neck powders (highest maximum use concentration = 1.4%). Though the use of this ingredient in these types of products has not been confirmed, the Panel discussed the issue of potential incidental inhalation exposures from propellant and pump sprays and powders. The Panel considered pertinent data indicating that incidental inhalation exposures to this ingredient in such products would not cause adverse health effects.

Rosmarinus officinalis (Rosemary)-Derived Ingredients

The Panel issued a final safety assessment with the conclusion that the following 10 Rosmarinus officinalis-derived ingredients are safe as used in cosmetics when formulated to be non-sensitizing:

rosmarinus officinalis (rosemary) extract
rosmarinus officinalis (rosemary) flower extract
rosmarinus officinalis (rosemary) flower/leaf stem extract
rosmarinus officinalis (rosemary) flower/leaf/stem water*
rosmarinus officinalis (rosemary) leaf
rosmarinus officinalis (rosemary) leaf extract
rosmarinus officinalis (rosemary) leaf oil
rosmarinus officinalis (rosemary) leaf powder
rosmarinus officinalis (rosemary) leaf water
rosmarinus officinalis (rosemary) water

*Not reported to be in current use. If this ingredient were to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in this group.

The Panel had concluded at the March meeting that rosmarinus officinalis (rosemary) flower extract and rosmarinus officinalis (rosemary) leaf extract were safe at concentrations ≤0.2% in leave-on products, and safe as used in rinse-off products, when formulated to be non-sensitizing.

At the current meeting, the Panel emphasized that the conclusion includes the statement that products containing these botanical ingredients must be formulated to be non-sensitizing. The Panel noted that specifying a concentration limit of <0.2% in the conclusion is not necessary if products are to be formulated to be non-sensitizing.

Tripeptide-1, Hexapeptide-12, their Metal Salts and Fatty Acyl Derivatives, and Palmitoyl Tetrapeptide-7

The Panel issued a final safety assessment with the conclusion that the following 10 ingredients, identified as tripeptide-1, hexapapeptide-12, their metal salts and fatty acyl derivatives, and palmitoyl tetrapeptide-7, are safe in the present practices of use and concentration in cosmetics.

tripeptide-1
palmitoyl tripeptide-1
myristoyl tripeptide-1*
hexapeptide-12*
palmitoyl hexapeptide-12
myristoyl hexapeptide-12*
copper tripeptide-1
bis(tripeptide-1) copper acetate*
manganese tripeptide-1*
palmitoyl tetrapeptide-7

*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.

This conclusion is applicable only to ingredients with peptide sequences that are defined as follows: tripeptide-1 (glycine-histidine-lysine), hexapeptide-12 (valine-glycine-valine-alanine-proline-glycine only), and tetrapeptide-7 (glycine-glutamine-proline-arginine). This assessment does not apply to the hexapeptide-12 (i.e., ala-pro-gly-val-gly-val) sequence listed in the INCI dictionary, because of the potential for major differences in chemistry and biological activity of some of the more complex groups attached to the peptide compared to those of the ingredients included in this safety assessment.

The peptides are used in cosmetic products at concentrations between 1 ppm and 30 ppm, and use at concentrations < 10 ppm is customary. However, data on the use concentrations of palmitoyl tetrapeptide-7 were not provided for this safety assessment. Given the high use frequency of use of palmitoyl tetrapeptide-7 reported to FDA, industry was urged to complete a use concentration survey for this ingredient.
Palmitoyl hexapeptide-12 is reported to function as an antioxidant in cosmetic products; the remaining 9 ingredients reportedly function as skin conditioning agents.

Tentative Safety Assessments

Alkyl Phosphates

The Panel issued a tentative safety assessment for public comment with the conclusion that the following 28 alkyl phosphates are safe as used in cosmetics when formulated to be non-irritating:

potassium cetyl phosphate
potassium C9-15 alkyl phosphate
potassium C11-15 alkyl phosphate*
potassium C12-13 alkyl phosphate
potassium C12-14 alkyl phosphate*
potassium lauryl phosphate
C8-10 alkyl ethyl phosphate*
C9-15 alkyl phosphate
C20-22 alkyl phosphate
castor oil phosphate
cetearyl phosphate*
cetyl phosphate
disodium lauryl phosphate*
disodium oleyl phosphate*
lauryl phosphate
myristyl phosphate*
octyldecyl phosphate*
oleyl ethyl phosphate*
oleyl phosphate*
sodium lauryl phosphate*
stearyl phosphate
dicetyl phosphate
dimyristyl phosphate*
dioleyl phosphate
tricetyl phosphate*
trilauryl phosphate*
trioleyl phosphate
tristearyl phosphate*

*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 included the phrase “when formulated to be non-irritating” in the conclusion because test data indicated that there was some potential for ocular irritation, and potassium cetyl phosphate is used at up to 8.3% in mascara products. Additionally, some of the alkyl phosphates were irritating to the skin in animal tests; however, these studies were conducted with concentrations that were much greater than the concentrations reported to be used in cosmetics.

The Panel also noted that there were no impurities data. Based on the method of manufacture and the absence of adverse effects in repeat oral toxicity studies, the Panel was not concerned about the absence of impurities data.

Lastly, the Panel commented that, although there were no safety-test data available specifically for the triesters, these ingredients are not expected to penetrate the skin. Therefore, the Panel determined that it was appropriate to include the triesters among the ingredients in this safety assessment.

2-Amino-3-Hydroxypyridine

The CIR Expert Panel issued a tentative safety assessment for public comment with a conclusion that 2-amino-3-hydroxypyridine is safe in the present practices of use and concentration.

The CIR Expert Panel expressed concern about in vitro genotoxicity studies that indicated the potential for mutagenicity. However, the Panel noted that, in general, the cytotoxicity of test materials tends to confound results in the types of studies conducted. Additionally, the Panel noted that skeletal effects were observed in fetal rodents at high doses of 2-amino-3-hydroxypyridine in a teratogenicity study. Given that other genotoxicity studies (including an in vivo study) were negative for mutagenicity, dams in the teratogenicity study exhibited signs of toxicity at the high doses associated with the skeletal effects in the fetal rats, and the NOAELs for both dams and fetuses were much greater than the concentrations reported to be used in hair dyes, the Panel determined that no adverse effects would be likely at the highest reported maximum concentration of 0.6% that is applied to hair.

In considering hair dye epidemiology data, the CIR Expert Panel concluded that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer or other toxicological endpoints, based on lack of strength of the associations and inconsistency of findings.

Camellia sinensis-Derived Ingredients

The Panel issued a revised tentative safety assessment for public comment with the conclusion that the following 7 Camellia sinensis leaf-derived ingredients are safe in cosmetic products when formulated to be non-sensitizing:

camellia sinensis leaf
camellia sinensis leaf extract
camellia sinensis leaf oil
camellia sinensis leaf powder
camellia sinensis leaf water
camellia sinensis catechins
hydrolyzed camellia sinensis leaf

The Panel also concluded that the available data are insufficient to assess the safety of the following 7 camellia sinensis ingredients:

camellia sinensis flower extract
camellia sinensis flower/leaf/stem juice
camellia sinensis root extract
camellia sinensis seedcoat powder
camellia sinensis seed extract
camellia sinensis seed powder
hydrolyzed camellia sinensis seed extract

The additional data needed are (1) methods of manufacturing; (2) chemical characterization of the constituents of these ingredients; (3) human sensitization data; and (4) concentrations of use in cosmetics.

These ingredients reportedly function as antioxidants, and skin-conditioning agents – humectant and miscellaneous in cosmetics. The C. sinensis-derived ingredients in this safety assessment are from plants that are used extensively in the human diet. The Panel agreed that exposures to these ingredients in beverages result in much larger systemic exposures than from cosmetic uses; thus, potential toxicity from oral exposures is not a primary concern. Reproductive toxicity, genotoxicity, and carcinogenicity data are presented in the safety assessment; but the primary focus of the assessment is on the potential for irritation and sensitization.

The Panel acknowledged the on-going evaluation of C. sinensis-derived green tea.by the National Toxicology Program (NTP). The Panel decided that the current data are sufficient for determining the safety of these ingredients. Should a final NTP report become available before the safety assessment report for these ingredients is finalized, the additional data will be incorporated into the assessment.

Citrus-Derived Peel Oils

The Panel issued a tentative safety assessment for public comment with the conclusion that the 14 citrus-derived peel oils listed below are safe for use in cosmetic products when finished products that are applied to the skin, excluding rinse-off products, do not contain more than 0.0015% (15 ppm) 5-methoxysporalen (5-MOP), and when formulated to be non-sensitizing. Based on the findings of a rodent carcinogenicity study, the Panel concluded that citrus-derived peel oils could be irritants; therefore, these botanicals must be formulated to be non-irritating.

citrus aurantifolia (lime) peel oil*
citrus aurantium amara (bitter orange) peel oil
citrus aurantium currassuviensis peel oil*
citrus aurantium dulcis (orange) peel oil
citrus clementina peel oil*
citrus grandis (grapefruit) peel oil
citrus iyo peel oil*
citrus junos peel oil
citrus limon (lemon) peel oil
citrus medica vulgaris peel oil*
citrus nobilis (mandarin orange) peel oil
citrus reticulata (tangerine) peel oil*
citrus tachibana/reticulata peel oil*
citrus tangerina (tangerine) peel oil

*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 Research Institute for Fragrance Materials (RIFM) confirmed that citrus aurantium bergamia (bergamot) peel oil and citrus paradise (grapefruit) peel oil are used as fragrance ingredients and, thus, do not fall with CIR's purview for review. These ingredients were deleted from the report.

The Panel expressed concern about the potential for constituents, such as the fucocoumarin 5-MOP, in citrus-derived peel oils to cause photo toxicity. They agreed that application of the standards set by the International Fragrance Association (IFRA) for such constituents will prevent phototoxicity.

Additionally, the Panel addressed the concern that multiple botanical ingredients may each contribute to the final concentration of a single constituent, stating that, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse effects.

Ingredients in this report represent a subset of a larger report, presented to the Panel in March 2014, which included all citrus species currently listed as cosmetic ingredients in the International Cosmetic Ingredient Dictionary and Handbook.

Hydroquinone

The Panel issued a revised tentative amended assessment of hydroquinone for public comment with a conclusion of safe for use as a polymerization inhibitor in artificial nail coatings when photo-protective materials for the skin are used in a professional setting; these products are unsafe for home use when used with UVA light sources. The previous conclusion that hydroquinone is safe at concentrations of ≤1% in cosmetic formulations designed for discontinuous, brief use followed by rinsing from the skin and hair, safe for use in nail adhesives in the present practices of use and concentration, and unsafe for use in other leave-on cosmetic products, was reaffirmed.

The Panel remained concerned about the potential risk of squamous cell carcinoma in individuals who expose their hands to the UVA light sources used to cure artificial nail coatings containing this ingredient. Further, the UVA bulbs used in nail lamps emanate UVA light (320-400 nm), but can be easily replaced with UVB and UVC bulbs. Thus, the Panel discussed the possibility that, in a home-use setting, an individual could look into the lamp and incur eye damage from UVC light. Additionally, the Panel was concerned that these lamps might be used at the eye level of small children. There was also concern that home users may be exposed to additional UV light exposures to the hands if they increase the exposure duration when the nail gel does not set properly because the wrong bulb is used.

The Panel noted that there is substantial research demonstrating the general public's inattention to product warning labels and operating instructions, and discussed the possibility that an improper replacement bulb could be inserted into the UV lamp. The Panel stated that industry should manufacture lamps in which the bulbs cannot be replaced; so that the lamps will be disposed when the bulbs no longer function, or develop unique sockets for the lamps to ensure that only use the appropriate UVA-only bulbs are used.

p-Hydroxyanisole

The Panel issued a revised tentative amended safety assessment of p-hydroxyanisole for public comment with a conclusion of safe for use as a polymerization inhibitor in artificial nail coatings when photo protective materials for the skin are used in a professional setting; these products are unsafe for home use when used with UVA light sources. This ingredient is unsafe for use in all other cosmetic products because of the potential for dermal depigmentation, irritation and sensitization.

The Panel remained concerned about the potential risk of squamous cell carcinoma in individuals who expose their hands to the UVA light sources used to cure artificial nail coatings containing this ingredient. Further, the UVA bulbs used in nail lamps emanate UVA light (320-400 nm), but can be easily replaced with UVB and UVC bulbs. Thus, the Panel discussed the possibility that, in a home-use setting, an individual could look into the lamp and incur eye damage from UVC light. Additionally the Panel was concerned that these lamps might be used at the eye level of small children. There was also concern that home users may incur additional UV light exposures to the hands if they increase the exposure duration when the nail gel does not set properly because the wrong bulb is used.

The Panel noted that there is substantial research demonstrating the general public's inattention to product warning labels and operating instructions, and discussed the possibility that an improper replacement bulb could be inserted into the UV lamp. The Panel stated that industry should manufacture lamps in which the bulbs cannot be replaced; so that the lamps will be disposed when the bulbs no longer function, or develop unique sockets for the lamps to ensure that only use the appropriate UVA-only bulbs are used.

Methylisothiazolinone

The Panel issued a tentative amended safety assessment for public comment with the conclusion that methylisothiazolinone (MI) is safe for use in rinse-off cosmetic products at concentrations up to 100 ppm and safe in leave-on cosmetic products when they are formulated to be non-sensitizing, which may be determined based on a QRA.

The Panel reviewed the results of QRAs performed by Cosmetics Europe and the CIR Science and Support Committee using.EC3 values (the effective concentrations of the test substance required to produce a three-fold increase in the stimulation index, compared to vehicle-treated controls) from local lymph node assays (LLNAs) corrected in the literature since the Panel previously considered this ingredient in 2008 and the results of HRIPTs on which to base the WoE analysis. The results supported the safety of the use of MI in rinse-off product categories at concentrations up to 100 ppm; however, the QRA indicated that MI use in many leave-on product categories would be safe only at substantially lower concentrations.

Styrene and Vinyl-type Styrene Copolymers

The Panel issued a tentative safety assessment for public comment with the conclusion that the following 35 ingredients are safe in the present practices of use and concentration in cosmetics.

ethylene/propylene/styrene copolymer
butylene/ethylene/styrene copolymer
acrylates/ethylhexyl acrylate/styrene copolymer*
butyl acrylate/styrene copolymer
C4-6 olefin/styrene copolymer*
C5-6 olefin/styrene copolymer*
hydrogenated butadiene/isoprene/styrene copolymer*
hydrogenated butylene/ethylene/styrene copolymer
hydrogenated ethylene/ propylene/styrene copolymer
hydrogenated styrene/butadiene copolymer
hydrogenated styrene/isoprene copolymer
isobutylene/styrene copolymer
methacrylic acid/styrene/vp copolymer*
methylstyrene/vinyltoluene copolymer
polystyrene
polystyrene/hydrogenated polyisopentene copolymer
sodium methacrylate/styrene copolymer*
sodium styrene/acrylates copolymer
sodium styrene/acrylates/ethylhexyl acrylate/lauryl acrylate copolymer*
styrene/acrylates copolymer
styrene/acrylates/ethylhexyl acrylate/lauryl acrylate copolymer*
styrene/butadiene copolymer
styrene/isoprene copolymer*
styrene/methylstyrene copolymer*
styrene/stearyl methacrylate crosspolymer*
styrene/va copolymer*
styrene/vp copolymer
polyacrylate-2*
polyacrylate-5
polyacrylate-12*
polyacrylate-15
polyacrylate-16
polyacrylate-18*
polyacrylate-21
polyacrylate-30*

*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.

These ingredients function mostly as viscosity increasing agents, opacifying agents, and film formers in cosmetic products. The highest maximum use concentrations for rinse-off and leave-on products have been reported as 36.5% (polystyrene) and 35% (styrene/acrylates copolymer), respectively.

The Panel agreed that percutaneous absorption is not expected because of the large sizes of these molecules and their chemical structures.

Styrene monomer, a component of all of the copolymers reviewed in this safety assessment, and 1,3-butadiene monomer are classified as carcinogenic in animals and in humans. Data provided by industry suggest that the residual monomer content of styrene and vinyl-type styrene copolymer trade name materials is < 500 ppm. The Panel agreed that any detectable levels of residual styrene or 1,3-butadiene in cosmetic products would be substantially below levels of concern because of the low use concentrations and the low level of residual monomers.

The Panel also discussed the potential for incidental inhalation exposures to these ingredients in products that are sprayed or are in powder form and agreed that, based on likely airborne particle size distributions and concentrations in the breathing zone, ingredient use concentrations, and negative results in toxicity tests, incidental inhalation would not lead to local respiratory effects or systemic effects.

Insufficient Data Announcements

Avena Sativa–Derived Ingredients

The Expert Panel requested additional data to support the safety of 21 Avena sativa-derived ingredients.

The additional information needed are (1) UV absorption and/or photo toxicity; (2) irritation and sensitization, including the results of HRIPTs; (3) methods of manufacture; (4) identification of the ingredients included in this safety assessment that are also used in human food and/or animal feeds; (5) molecular weight of the hydrolyzed ingredients; and (6) peptide lengths of the proteins.

The 21 ingredients in this safety assessment are listed below.

avena sativa (oat) bran
avena sativa (oat) bran extract
avena sativa (oat) flower/leaf/stem juice
avena sativa (oat) kernel extract
avena sativa (oat) kernel flour
avena sativa (oat) kernel meal
avena sativa (oat) kernel protein
avena sativa (oat) leaf extract
avena sativa (oat) leaf/stalk extract
avena sativa (oat) leaf/stem extract
avena sativa (oat) meal extract
avena sativa (oat) meristem cell extract
avena sativa (oat) peptide
avena sativa (oat) protein extract
avena sativa (oat) seed extract
avena sativa (oat) seed water
avena sativa (oat) sprout oil
avena sativa (oat) straw extract
hydrolyzed oat protein
hydrolyzed oat flour
hydrolyzed oats

Polyoxyalkylene Siloxane Copolymers, Alkyl-Polyoxyalkylene Siloxane Copolymers, and Related Ingredients

The Expert Panel requested additional data to support the safety of 111 polyoxalkylene siloxane copolymers, alkyl-polyoxyalkylene siloxane copolymers, and related ingredients.

The additional information needed include: (1) molecular weight ranges of all of the ingredients; (2) impurities and explanation of how they are removed (especially for allyl alcohol ethoxylate and alkylated as impurities); and (3) dermal penetration, irritation, and sensitization data for the smallest ingredient(s) in this group (assumed to be PPG-2 dimethicone and PEG-3 dimethicone). If these smaller ingredients penetrate the skin or cause sensitization, then dermal penetration, irritation, and sensitization data for the next larger ingredients should be submitted, and data up to the ingredient size demonstrated to be non-penetrating and non-sensitizing.

The 111 ingredients in this safety assessment are listed below.

behenoxy dimethicone
behenoxy PEG-10 dimethicone
bis-cetyl/PEG-8 cetyl PEG-8 dimethicone
bis-hydroxyethoxypropyl dimethicone
bis-isobutyl PEG/PPG-10/7/dimethicone copolymer
bis-isobutyl PEG-13/dimethicone copolymer
bis-isobutyl PEG-24/PPG-7/dimethicone copolymer
bis-PEG-1 dimethicone
bis-PEG-4 dimethicone
bis-PEG-8 dimethicone
bis-PEG-10 dimethicone
bis-PEG-12 dimethicone
bis-PEG-12 dimethicone beeswax
bis-PEG-12 dimethicone candelillate
bis-PEG-15 methyl ether dimethicone
bis-PEG-20 dimethicone
bis-PEG-8 PEG-8 dimethicone
bis-PEG/PPG-14/14 dimethicone
bis-PEG/PPG-15/5 dimethicone
bis-PEG/PPG-16/16 PEG/PPG-16/16 dimethicone
bis-PEG/PPG-18/6 dimethicone
bis-PEG/PPG-20/20 dimethicone
bis-PEG/PPG-20/5 PEG/PPG-20/5 dimethicone
bis-stearoxy dimethicone
bis-stearoxyethyl dimethicone
cetyl PEG/PPG-10/1 dimethicone
cetyl PEG/PPG-15/15 butyl ether dimethicone
cetyl PEG/PPG-7/3 dimethicone
cetyl PEG-8 dimethicone
lauryl isopentyl-PEG/PPG-18/18 methicone
lauryl PEG/PPG-18/18 methicone
lauryl PEG-10 methyl ether dimethicone
lauryl PEG-10 tris(trimethylsiloxy)silylethyl dimethicone
lauryl PEG-8 dimethicone
lauryl PEG-8 PPG-8 dimethicone
lauryl PEG-9 polydimethylsiloxyethyl dimethicone
lauryl polyglyceryl-3 polydimethylsiloxyethyl dimethicone
methoxy PEG-11 methoxy PPG-24 dimethicone
methoxy PEG/PPG-25/4 dimethicone
methoxy PEG-13 ethyl polysilsesquioxane
PEG/PPG-10/2 dimethicone
PEG/PPG-10/3 oleyl ether dimethicone
PEG/PPG-12/16 dimethicone
PEG/PPG-12/18 dimethicone
PEG/PPG-14/4 dimethicone
PEG/PPG-15/15 dimethicone

PEG/PPG-15/5 dimethicone
PEG/PPG-16/2 dimethicone
PEG/PPG-16/8 dimethiconePEG/PPG-17/18 dimethicone
PEG/PPG-18/12 dimethicone
PEG/PPG-18/18 dimethicone
PEG/PPG-18/6 dimethicone
PEG/PPG-19/19 dimethicone
PEG/PPG-20/15 dimethicone
PEG/PPG-20/20 dimethicone
PEG/PPG-20/22 butyl ether dimethicone
PEG/PPG-20/22 methyl ether dimethicone
PEG/PPG-20/23 dimethicone
PEG/PPG-20/29 dimethicone
PEG/PPG-20/6 dimethicone
PEG/PPG-22/22 butyl ether dimethicone
PEG/PPG-22/23 dimethicone
PEG/PPG-22/24 dimethicone
PEG/PPG-23/23 butyl ether dimethicone
PEG/PPG-23/6 dimethicone
PEG/PPG-24/18 butyl ether dimethicone
PEG/PPG-25/25 dimethicone
PEG/PPG-27/27 dimethicone
PEG/PPG-27/9 butyl ether dimethicone
PEG/PPG-3/10 dimethicone
PEG/PPG-30/10 dimethicone
PEG/PPG-4/12 dimethicone
PEG/PPG-6/4 dimethicone
PEG/PPG-6/11 dimethicone
PEG/PPG-8/14 dimethicone
PEG/PPG-8/26 dimethicone
PEG-10 dimethicone
PEG-10 methyl ether dimethicone
PEG-10 polydimethylsiloxyethyl dimethicone/bis-vinyl dimethicone crosspolymer
PEG-11 methyl ether dimethicone
PEG-12 dimethicone
PEG-14 dimethicone
PEG-17 dimethicone
PEG-3 dimethicone
PEG-32 methyl ether dimethicone
PEG-4 PEG-12 dimethicone
PEG-6 dimethicone
PEG-6 methyl ether dimethicone
PEG-7 dimethicone
PEG-7 methyl ether dimethicone
PEG-8 cetyl dimethicone
PEG-8 dimethicone
PEG-8 dimethicone dimer dilinoleate
PEG-8 dimethicone/dimer dilinoleic acid copolymer
PEG-8 methicone
PEG-8 methyl ether dimethicone
PEG-8 PEG-4 dimethicone
PEG-8 PPG-8 dimethicone
PEG-9 dimethicone
PEG-9 methyl ether dimethicone
PPG-25 dimethicone
PPG-27 dimethicone
PPG-4 oleth-10 dimethicone
PEG-9 polydimethylsiloxyethyl dimethicone
polysilicone-13
PPG-12 butyl ether dimethicone
PPG-12 dimethicone
PPG-2 dimethicone
stearoxy dimethicone
stearoxymethicone/dimethicone copolymer

Ceramides

The Expert Panel requested additional data to support the safety of 14 ceramide ingredients.

The additional data needed are (1) methods of manufacture; (2) impurities; (3) concentrations of use of the ingredients added to this safety assessment; and (4) dermal absorption. If these ingredients exhibit appreciable dermal absorption, the additional data needed are (a) reproductive and developmental toxicity; (b) genotoxicity; and (c) dermal irritation and sensitization data at the highest maximum reported use concentration.

The initial 14 ingredients in this safety assessment are listed below.

ceramide 1
ceramide 1A
ceramide 2
ceramide 3
ceramide 4
ceramide 5
ceramide 6 II
ceramide AP
ceramide AS
ceramide EOP
ceramide EOS
ceramide NP
ceramide NS
ceramide NS dilaurate

The Panel added the following 8 ingredients because of their structural similarities to the ceramides and the promise that industry would provide safety test data that can be used to support read-across analysis for all of the above ingredients:

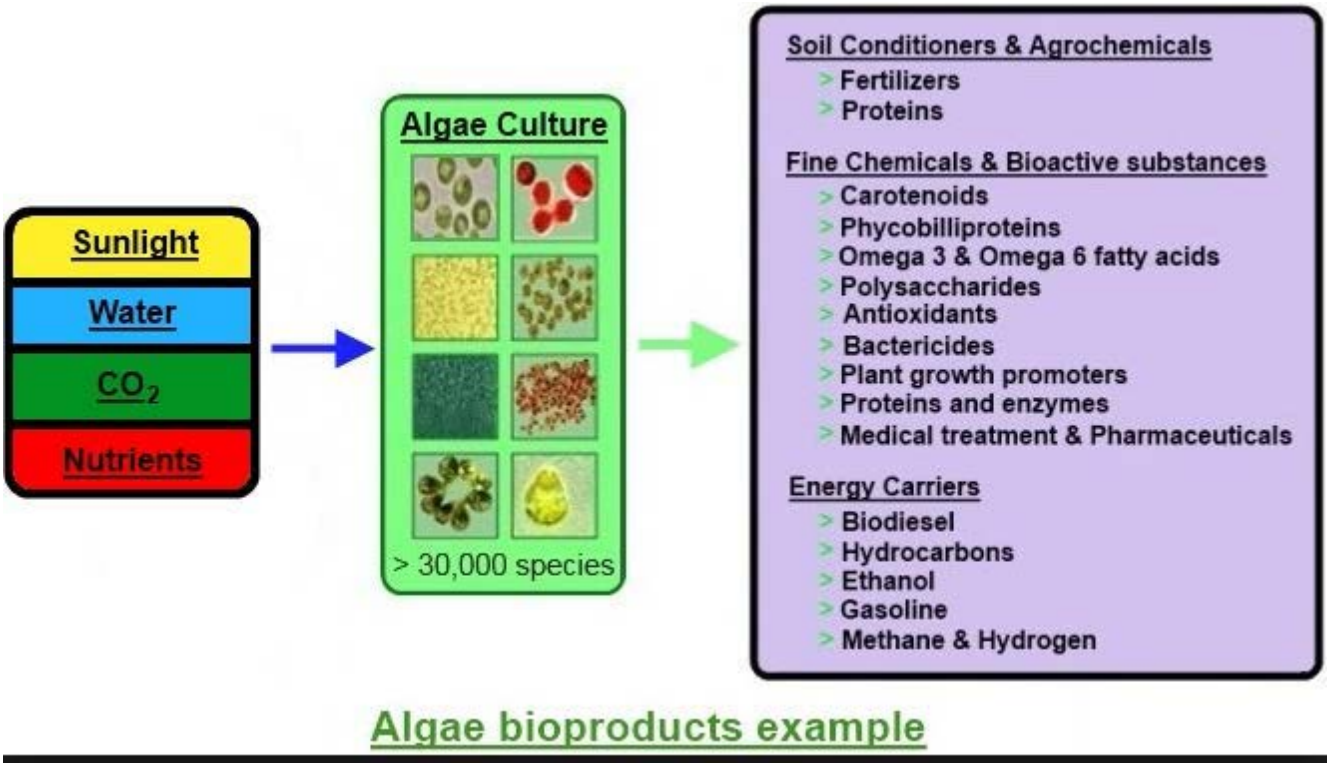
caprooyl phytosphingosine
caprooyl sphingosine
caproyl sphingosine
hydroxycaproyl phytosphingosine
hydroxycapryloyl phytosphingosine
hydroxylauroyl phytosphingosine
hydroxypalmitoyl sphinganine
2-oleamido-1,3-octadecanediol

Re-review Summaries

The Panel approved the summary of their actions at the December 2013 meeting during which they determined not to reopen the safety assessment of polyvinyl alcohol.

Presentation on Algae

Dr. Rex L. Lowe, Professor Emeritus of Biological Sciences at Bowling Green State University, reviewed the current classification, taxonomy, and common, non-cosmetic uses of algal. He explained the great diversity of the four Algal Phyla and classified each algae cosmetic ingredient based on its common name subclass (i.e., Blue Green, Brown, Red, Green, Euglenoid, Diatom or Haptophyte). Dr. Lowe cautioned the Panel about the potential toxicity of some species of Blue Green Algae. He also commented on the high volume, commercial use of many species of Brown, Red, and Green Algae, and the lack of adverse reports for such use. The Panel greatly appreciated Dr. Lowe's presentation and his clarification of the sources of these cosmetic ingredients.



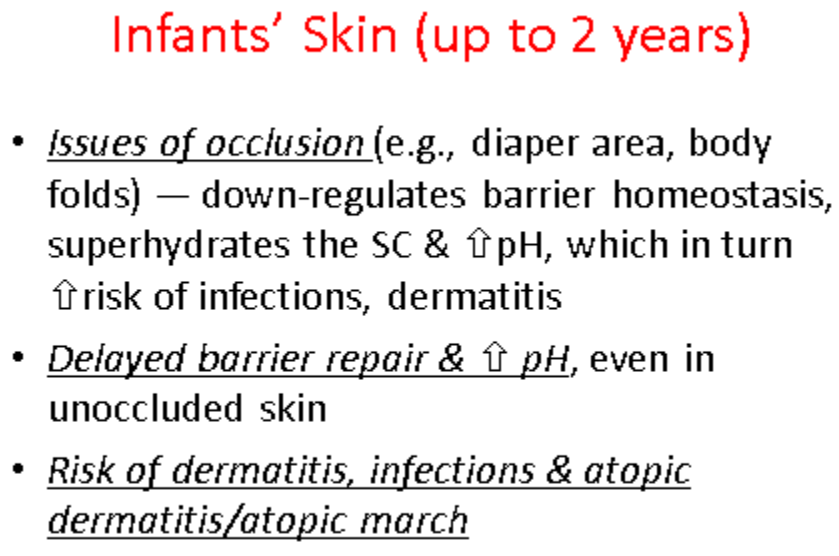
Algae bioproducts example

Using the 7 subclasses of Algae, Dr. Lowe classified the list of 173 ingredients provided to him by CIR as follows: 6 from Blue Green Algae, 65 from Brown Algae, 53 from Red Algae, 36 from Green Algae, 3 from Euglenoids, 3 from Diatoms, and 2 from Haptophytes. There were also 3 ingredients, Algae, Algae Extract, and Hydrolyzed Algae Extract, which were unclassifiable. Classification of these 3 vaguely defined ingredients is needed, especially because the ingredient algae extract has 805 reported cosmetic uses (per the FDA VCRP). Of the classifiable ingredients, fucus vesiculosus extract and laminara digita extract had the first and second highest reported frequencies of uses. Both of these ingredients are classified as Brown Algae.

Briefing on the Dermal Diffusion Barrier in Neonates and Infants

In March 2013, the CIR Expert Panel discussed the dermal penetration and percutaneous absorption of topically-applied ingredients in neonates and infants compared with adults. The Panel invited Dr. Peter Elias and Dr. Mary Williams to address the subject of the diffusion barrier of the skin, which is a principle function of the stratum corneum (SC). They are eminent physician/researchers, dermatologists, and professors at the University of California, and both contributed to Dr. Elias' presentation to the Panel at the current meeting. Dr. Williams is also a pediatrician, and Dr. Elias leads a research group focused on elucidating factors important for maintaining and restoring the cutaneous barrier.

Dr. Elias explained that, as defined by pediatric dermatologists, children from birth to 6 months of age are babies, and from 6 months to 2 years of age are infants. Full-term neonates are born after 37 weeks gestational age (GA), and premature neonates born between 34 and 37 weeks GA generally have dermal barrier functions similar to full-term neonates. He noted that the skin of infants is relatively mature, compared to the skin of babies, but does not yet function as a fully mature permeability barrier.



Dr. Elias explained that the immaturity of the barrier in babies and infants can be largely attributed to the elevated pH of the skin in these children, as well as to super-moisturization in the diaper area and body folds. The pH of the surface of the skin does not become similar to that of adults until about 6 months of age and older, and continues to be more readily perturbed than adult skin until about 2 years of age. He used the slide on the left to indicate that this factor helps to explain why babies and infants continue to have increased risk of dermatitis and infections and recover more slowly from damage by exposures to irritants, for example.

Dr. Elias noted that there are exogenous and endogenous dermal acidifying mechanisms in the skin, which are responsible for the development and maintenance of the skin's protective "acid mantle." The major acidifying mechanism that is immature in neonates is the endogenous secretory phospholipase A2 (sPLA2) mechanism, which breaks down phospholipids to release free fatty acids (FFAs) in the skin.

Dr. Elias noted that, when the barrier is compromised in babies, the pH of the skin increases, and this increase activates serine proteases (SPs) that release pro-inflammatory cytokines, which helps to explain the increased tendency for dermatitis and other types of inflammatory reactions.

Dr. Elias emphasized that the barrier function of the skin at about 34 weeks GA and thereafter is sufficient for life after birth. However, barrier repair is slower in babies than in adults, and continues to be delayed up to about 2 years of age. He noted that the immature barrier of babies and infants will be manifested both by the increased potential for evaporative water loss from the skin and by the increased potential for dermal penetration and percutaneous absorption of topically-applied ingredients.

2015 Priorities

The following 2015 Priority list was approved by the CIR Expert Panel. There are 22 ingredient/ingredient groups on the list, however, it is likely that not all of those listed will be chosen for work in 2015.

- hydrolyzed soy protein – 840 uses / glycine soja (soybean) protein [glycine max (soybean) protein] – 329 uses
- hydrolyzed silk – 694 uses
- hydrolyzed keratin – 540 uses
- polysilicone-2 – 515 uses
- phosphoric acid – 443 uses / dicalcium phosphate – 353 uses
- magnesium carbonate – 429 uses
- tridecyl trimellitate – 426 uses
- hydrofluorocarbon 152a – 422 uses
- stearalkonium bentonite – 403 uses
- butyrospermum parkii (shea) butter extract – 396 uses
- hdi/trimethylol hexyllactone crosspolymer – 388 uses
- ammonium acryloyldimethyltaurate/vp copolymer – 383 uses / ydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer – 383 uses
- panthenyl ethyl ether – 375 uses
- adipic acid/neopentyl glycol/trimellitic anhydride copolymer – 367 uses
- tetrahexyldecyl ascorbate – 365 uses
- polyglyceryl-3 diisostearate – 358 uses
- etidronic acid – 345 uses
- helianthus annuus (sunflower) seed extract – 344 uses
- rosa canina fruit extract – 343 uses
- sodium methyl cocoyl taurate – 335 uses
- tetradecene – 327 uses
- 1-hydroxyethyl-4,5-diamino pyrazole sulfate – 77 uses

These 2015 CIR priorities are based on those ingredients listed in the 2014 VCRP database that have not been reviewed by CIR and have the largest number of uses. Some ingredients are excluded from review by the CIR, as discussed in the CIR Procedures. This list only names the lead ingredients. Families of ingredients may be reviewed, as appropriate. Interested parties are encouraged to submit data pertinent to these ingredients to the CIR for use in the development of the Scientific Literature Review. Although the specific data needs vary for each safety assessment, the following are typical data that the Panel reviews for each safety assessment.

- chemistry, impurities, and method of manufacture
- toxicokinetics data, specifically dermal absorption and/or penetration
- repeated-dose toxicity data
- inhalation toxicity data, if the ingredient is used in a product that can be incidentally inhaled
- reproductive/developmental toxicity data
- genotoxicity data; and if positive, carcinogenicity data may be needed
- dermal irritation and sensitization data

For the review of botanical ingredients, the additional data needed include: species, plant part, extraction method, solvent, and data on component chemical characterization. It is important that these data are specific to the ingredient(s).

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume, Assistant Director/Senior Scientific Analyst
Bart Heldreth, Chemist
Ivan Boyer, Senior Toxicologist
Date: August 18, 2014
Subject: Follow-up on formaldehyde releasers, impurities, hair dyes, and infant skin boilerplate and guidance language documents

At the June meeting, several boilerplate and guidance language documents were presented to the Panel for review, per your request. Changes were made to several of these documents based on comments made at the June meeting or received after that meeting. Only the documents that had comments or changes are being re-presented at this meeting.

The CIR SSC submitted comments on formaldehyde releasers that suggest such a boilerplate is unwarranted and would likely be of little value (*forrel092014data_CIRSSC*). Accordingly, the Panel should decide if it agrees with that suggestion and if the formaldehyde releasers "boilerplate" should be discontinued.

Also in the CIR SSC memo, comments were provided on the benzene, 1,4-dioxane, ethylene oxide, and heavy metals boilerplates. The attached boilerplate and guidance document table reflects these changes (*BP092014table*). Please review each comment, consider whether you agree with them, and if the boilerplates as now written accurately reflect the changes. Feedback on each comment will be appreciated.

The updated hair dye epidemiology and the infant skin documents are also included for your review, and the language addressing both is also in the boilerplates table. The hair dye epidemiology background document and accompanying "boilerplate" have been revised to address the comments of the participants at the June meeting (*hdyepi092014min-final*). Please review the revised document and "boilerplate" (*hdyepi092014rep- final*) and decide whether they can be finalized and the revised document posted on the CIR Website in place of the older version.

Finally, please review the most current version of the infant skin resource document (*Infskn092014rep- final*). The current draft addresses all of the comments received to date from the CIR Expert Panel (Panel), Dr. Elias, and the Personal Care Products Council (Council). Dr. Boyer has prepared a separate memo addressing this document (*Infskn092014memo- final*).

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Contaminants, Residues, Impurities

updated 8/2014

Benzene, 1,4-Dioxane and/or Ethylene Oxide

Boilerplate and Guidance Language

Impurities (boilerplate)	**specific to PEG-containing ingredients** PEGs are the condensation products of ethylene oxide and water, with the chain length controlled by number of moles of ethylene oxide that are polymerized. PEGs may contain trace amounts of 1,4-dioxane, a by-product of ethoxylation; 1,4 Dioxane is reasonably anticipated to be a human carcinogen (IARC, 1999). The FDA has been periodically monitoring the levels of 1,4-dioxane in cosmetic products, and the cosmetic industry is aware that 1,4-dioxane may be an impurity in PEGs and, thus uses purification steps to limit the presence of 1,4-dioxane (Elder 1983; FDA 2007). ***Example: see PEGylated Oils***
	for ingredients that contain ethylene oxide, 1,4-dioxane, and/or benzene [*Ingredient*] may contain [*state amount, if known*] of [***as appropriate:*** ethylene oxide/1,4-dioxane/benzene]. [**as appropriate:** *Ethylene oxide* (IARC 2012)/*benzene* (IARC 2012)] is/are carcinogenic to humans, and [*1,4-dioxane* (IARC 1999)] is reasonably anticipated to be a human carcinogen. The cosmetic industry should remove this impurity/these impurities from [*ingredient*] before blending [*ingredient*] into cosmetic formulations.
Discussion (boilerplate)	**specific to PEG-containing ingredients** The Panel expressed concern regarding the possible presence of ethylene oxide and trace amounts of 1,4-dioxane as impurities in any cosmetic ingredient containing a PEG moiety. They stressed that the cosmetic industry should continue to use the necessary purification procedures to limit these impurities in the ingredient before blending it into cosmetic formulations.
	for ingredients that contain ethylene oxide, 1,4-dioxane, and/or benzene The Panel expressed concern regarding the possible presence of [ethylene oxide/1,4-dioxane/benzene] as an impurity/impurities. The Panel stressed that the cosmetic industry should continue to use the necessary purification procedures to limit these impurities in the ingredient before blending it into cosmetic formulations.
	if amounts of ethylene oxide or 1,4-dioxane need to be addressed specifically [*Ingredient*] can contain up to [*x*] ppm ethylene oxide and up to [*x*] ppm 1,4-dioxane (both are carcinogenic). However, the Panel was not concerned about the toxicity of ethylene oxide in cosmetics containing [*ingredient*] given that use of products containing [*ingredient*] only in excessive amounts could yield an average exposure of 0.1 mg ethylene oxide/day, which is the level of exposure established (using chronic toxicity and carcinogenicity data) by the International Organization for Standardization (ISO) as the average residue limit for patient exposure to ethylene oxide (30 days to life) from medical devices. Although the ISO limitation was mentioned in the CIR report discussion on lower molecular weight [*ingredient*], it does not appear in the report conclusion because the Panel recognized that it is very unlikely that use of a cosmetic product could result in this level of exposure (0.1 mg /day) to ethylene oxide. The latter part of the preceding statement would also be true in terms of exposure to 1,4-dioxane (ethylene oxide polymerization product) and polycyclic aromatic compounds, which are also known to be carcinogenic. **Question to Panel – should the ISO standard be included as part of the boiler plate?** ***Example: see Nonoxynols***

Pesticide and Heavy Metal Limits

Boilerplate and Guidance Language

Discussion (boilerplate)	The Panel expressed concern regarding pesticide residues and heavy metals that may be present in finished products that contain botanical ingredients. The Panel stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit these impurities in the ingredient before blending into cosmetic formulation.

Background

	Previously, the CIR Expert Panel had specified limits: • The CIR Expert Panel expressed concern about toxic metal residues that may be present in (ingredient name) and advised industry that finished products containing this ingredient should not contain more than: 3 mg/kg of arsenic (as As), 1 ppm mercury (as Hg), and 0.1 mg/kg of lead (as Pb). • In its safety assessment of Acid Violet 43 (Andersen 2001a), the CIR Expert Panel adopted limitations established by the Food and Drug Administration for certification of Ext. D & C No. 2 as a color additive (FDA 1976). In its safety assessment of the Lard Glycerides group of ingredients (Andersen 2001b), the CIR Expert Panel adopted the Food Chemicals Codex limit for lead in unhydrogenated lard (National Academy of Sciences 1996). However, the appropriate limit

should be examined on a case-to-case basis.

- The Panel recognizes that these limits were developed for uses other than cosmetics, but considers that such limits would assure that any cosmetic product with these ingredients can be used safely.
- In 2001, the Environmental Protection Agency established a limit of 10 ppb for arsenic in drinking water (40 CFR 141.6). The CIR Expert Panel considered this EPA determination as it might relate to cosmetics such as lipsticks that may be ingested. According to Loretz et al. (2005), the mean application per day of lipstick is 24 mg. Recognizing that not all of that application would be ingested and that not all ingredients in a lipstick product would contain arsenic up to 3 ppm, the Panel determined that the daily ingestion of arsenic from lipstick would be less than that received from the ingestion of 2 liters of drinking water per day at the 10 ppb level established by EPA.]

Formaldehyde Releasers and Formaldehyde as an Impurity – DELETE THIS BP??

updated 6/2014

Boilerplate and Guidance Language

Discussion (Guidance)

if the formaldehyde level is less than the limit established by the Panel

According to [*information cited in the report*], this ingredient may contain formaldehyde at a maximum level of [*x%*]. The Panel noted that this level is less than the 0.074% formaldehyde limit established by the Panel in its final safety assessment on this ingredient, and is well below the threshold for any toxicological concerns relating to this chemical. [***If applicable***: Furthermore, the effective formaldehyde concentration yielded by [*ingredient*] in formulation would be even lower, considering that this ingredient is being used at concentrations up to [*x%*] in leave-on products and at concentrations up to [*x%*] in rinse-off products. At the maximum use concentration of [*x%*], the formaldehyde concentration would be no more than [*x%*].] (***IF the ingredient may be aerosolized***: Additionally, where aerosolization is intended by use "it could not be concluded … that formaldehyde is safe in cosmetic products intended to be aerosolized." Since the potential exists for formaldehyde to be released from [*ingredient*], the Panel considers it inappropriate to use [*ingredient*] in aerosolized products.")]

Accordingly, formaldehyde released, or present as an impurity, should neither exceed these concentrations in final product formulations nor should ingredients that release or contain formaldehyde be used in certain product types, such as hair smoothing products or those products intended to be aerosolized. This, of course, is in addition to any safety limitation(s) presented by the ingredient(s) under investigation.

if the formaldehyde level in the ingredient, but not in formulation, would be more than the limit established by the Panel

According to [*information cited in the report*], this ingredient may contain formaldehyde at a maximum level of [*x%*]. The Panel noted that this level is greater than the 0.074% formaldehyde limit established by the Panel in its final safety assessment on this ingredient. However, based on the reported concentration of use of this ingredient in formulation, the effective formaldehyde concentration yielded by [*ingredient*] in formulation would be lower than the 0.074% formaldehyde limit, considering that this ingredient is being used at concentrations up to [*x%*] in leave-on products and at concentrations up to [*x%*] in rinse-off products; at the maximum use concentration of [*x%*], the formaldehyde concentration would be no more than [*x%*].] [***IF the ingredient may be aerosolized***: Additionally, where aerosolization is intended by use "it could not be concluded … that formaldehyde is safe in cosmetic products intended to be aerosolized." Since the potential exists for formaldehyde to be released from [*ingredient*], the Panel considers it inappropriate to use [*ingredient*] in aerosolized products.")]

Accordingly, formaldehyde released, or present as an impurity, should neither exceed these concentrations in final product formulations nor should ingredients that release or contain formaldehyde be used in certain product types, such as hair smoothing products or those products intended to be aerosolized. This, of course, is in addition to any safety limitation(s) presented by the ingredient(s) under investigation.

if the formaldehyde level in the ingredient and in formulation would be more than the limit established by the Panel

According to [*information cited in the report*], this ingredient may contain formaldehyde at a maximum level of [*x%*]. The Panel noted that this level is greater than the 0.074% formaldehyde limit established by the Panel in its final safety assessment on this ingredient. Additionally, based on the reported concentration of use of this ingredient in formulation, the effective formaldehyde concentration yielded by [*ingredient*] in formulation would be greater than the 0.074% formaldehyde limit, considering that this ingredient is being used at concentrations up to [*x%*] in leave-on products and at concentrations up to [*x%*] in rinse-off products; at the maximum use concentration of [*x%*], the formaldehyde concentration would be no more than [*x%*].] [***IF the ingredient may be aerosolized***: Furthermore, where aerosolization is intend-

	ed by use "it could not be concluded … that formaldehyde is safe in cosmetic products intended to be aerosolized." Since the potential exists for formaldehyde to be released from [*ingredient*], the Panel considers it inappropriate to use [*ingredient*] in aerosolized products.")] Accordingly, [*ingredient*] is limited to a maximum concentration of use of [*maximum concentration in formulation that would not exceed the 0.074% limit*] so that the formaldehyde released, or present as an impurity, would not exceed these maximum concentration of 0.074% formaldehyde in final product formulations. Also, ingredients that release or contain formaldehyde should not be used in certain product types, such as hair smoothing products or those products intended to be aerosolized. This, of course, is in addition to any safety limitation(s) presented by the ingredient(s) under investigation.
Conclusion (Boilerplate)	The CIR Expert Panel concluded [*ingredient*] is safe in the present practices of use and concentration described in this safety assessment when formulations containing [*ingredient*] are formulated to ensure that concentrations of free formaldehyde not exceed 0.074%. It cannot be concluded that [*ingredient*] is safe for use in cosmetic products intended to be aerosolized.
Background	
	Formaldehyde can function in cosmetics as a cosmetic biocide, denaturant, and preservative (Nikitakis and Breslawec, 2014). In 2013, the Panel published a report with the conclusion 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 (Boyer et al., 2013). 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. According to the EU Biocidal Products, Directive, formaldehyde releasing biocides or formaldehyde releasers or formaldehyde donators are biocides, which are intended to release formaldehyde under specific use conditions.[3] The biocidal activity of formaldehyde releasers can be, but is not solely, based on the released formaldehyde. Formaldehyde in a formaldehyde releaser is chemically and not physically bound, i.e. covalently bound to a carrier molecule. During the production process of a formaldehyde releaser, formaldehyde as an electrophilic substance reacts mainly with nucleophilic substances like amides, amines and alcohols to form methylol or methylene groups. The formaldehyde is then covalently bound to the nitrogen or oxygen atom of the molecule. Formaldehyde releasers when used in aqueous systems may release formaldehyde under specific conditions into the aqueous phase to form an equilibrium with the formaldehyde releaser or to be fragmented completely into the carrier molecule and formaldehyde. This reaction is significantly dependent on the structure of the chemical compound. *-from ANNEX 1, CEFIC Information on Formaldehyde Releasing Biocides in the context of the EU Biocidal Products Directive (98/8/EC)* Whether an ingredient is a true formaldehyde releaser, or simply contains formaldehyde as an impurity, the recommendation on use is the same: limit exposure of formaldehyde in the same manner as in the current Formaldehyde and Methylene Glycol Final Report. Specifically, the limitations outlined in the conclusion of that report should apply. While it is almost certainly an over estimate of exposure to assume 100% release of formaldehyde from a true formaldehyde releaser, this assumption is a safe starting point for each ingredient, that leaves the onus on those who would argue for a smaller maximum percentage of release to provide clear and convincing evidence to that point. Additionally, where aerosolization is intended by use "it could not be concluded … that formaldehyde is safe in cosmetic products intended to be aerosolized. Since the potential exists for formaldehyde to be released from [this ingredient], the Panel considers it inappropriate to use [this ingredient] in aerosolized products." Accordingly, formaldehyde released, or present as an impurity, should neither exceed these concentrations in final product formulations nor should ingredients that release or contain formaldehyde be used in certain product types, such as hair smoothing products or those products intended to be aerosolized. This, of course, is in addition to any safety limitation(s) presented by the ingredient(s) under investigation.

	Language Previously Used: The formaldehyde-releaser boiler plate has been used several times throughout the years, and the language has varied. Examples of some of that language are: **Diazolidinyl Urea:** The Expert Panel noted that Diazolidinyl Urea is a formaldehyde releaser. The Panel has previously concluded that the use of formaldehyde in cosmetic products is safe to the great majority of consumers. However, due to skin sensitivity of some individuals to formaldehyde it should be used at the minimum effective concentration (not to exceed 0.2 percent). There is no indication that the use of Diazolidinyl Urea as used in cosmetic products would release formaldehyde at concentrations which would exceed the limits recommended for formaldehyde. The Panel noted that the results of tests with Diazolidinyl Urea, at low concentrations, were indicative of a potential for sensitization. **DMDM Hydantoin:** Formaldehyde in cosmetic products is safe to the great majority of consumers. The Panel believes that because of skin sensitivity of some individuals to this agent, the formulation and manufacture of a cosmetic product should be such as to ensure use at the minimal effective concentration of formaldehyde, not to exceed 0.2 percent measured as free formaldehyde. It cannot be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized. Use of DMDM Hydantoin at its current concentration of use in cosmetic products would not expose the consumer to levels of formaldehyde above the limit previously stated. **Methenamine:** The CIR Expert Panel based their conclusion for Methenamine, in part, on the fact that Methenamine decomposes to ammonia and formaldehyde. Formaldehyde was previously reviewed by CIR (Elder, 1984) and it was concluded by the Panel that the maximum concentration of formaldehyde considered safe for cosmetic use was 0.2%. Methenamine was approved for cosmetic use at a concentration not to exceed 0.16% so that the released formaldehyde concentration would not exceed 0.2% in formulation. An additional restriction on Methenamine is that it should not be used in products intended to be aerosolized since it was not concluded that formaldehyde is safe in aerosolized products. **Polyoxymethylene Urea:** The Panel was concerned about the release of formaldehyde from Polyoxymethylene Urea. In their review of formaldehyde in 1984, the Panel determined that formaldehyde is an irritant at low concentrations, especially to the eyes and respiratory tract. Under experimental conditions it was teratogenic, mutagenic, and induced neoplasms. The Panel concluded in 1984 that the formulation and manufacture of cosmetic products should be such as to ensure use at the minimal effective concentration of formaldehyde, not to exceed 0.2% measured as free formaldehyde. That limitation was considered appropriate for Polyoxymethylene Urea as well. It could not be concluded in 1984 that formaldehyde is safe in cosmetic products intended to be aerosolized. Since the potential exists for formaldehyde to be released from Polyoxymethylene Urea, the Panel considers it inappropriate to use Polyoxymethylene Urea in aerosolized products. CONCLUSION: On the basis of the animal, clinical, and use data presented in this report, the CIR Expert Panel concludes that Polyoxymethylene Urea is safe for use as a cosmetic ingredient. Cosmetics containing Polyoxymethylene Urea should be formulated to ensure that concentrations of free formaldehyde not exceed 0.2%. It cannot be concluded that Polyoxymethylene Urea is safe for use in cosmetic products intended to be aerosolized. **Disodium Laureth Sulfosuccinate (*not a true formaldehyde releaser*, but may contain it as an impurity):** According to an MSDS on disodium laureth sulfosuccinate, this chemical may contain formaldehyde at a maximum level of 0.056%. The Panel noted that this level is less than the 0.076% formaldehyde limit established by the Panel in its final safety assessment on this ingredient, and is well below the threshold for any toxicological concerns relating to this chemical. Furthermore, the effective formaldehyde concentration yielded by disodium laureth sulfosuccinate in formulation would be even lower, considering that this ingredient is being used at concentrations up to 10% in rinse-off products and at concentrations up to 2% in leave-on products. At the maximum use concentration of 10%, the formaldehyde concentration would be no more than 0.006%.
REFERENCES	Boyer IJ, Heldreth BA, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW, Andersen FA. 2013. Amended safety assessment of formaldehyde and methylene glycol as used in cosmetics. *Int J Toxicol* 32 (Suppl 4): 5S-32S. Nikitakis J, Breslawec HP. 2014. *International Cosmetic Dictionary and Handbook*, 15th edn.

Hair Dye Epidemiology

updated 7/2014

Boilerplate and Guidance Language

Epidemiology (boilerplate)	Hair dyes may be broadly grouped into oxidative (permanent) and direct (semi-permanent) dyes. The oxidative dyes consist of precursors mixed with developers to produce color, while direct hair dyes are a preformed color. [INSERT INGREDIENT] is a/n [OXIDATIVE/DIRECT] hair dye ingredient. While the safety of individual hair dye ingredients is not addressed in epidemiology studies that seek to determine links, if any, between hair-dye use and disease, such studies do provide broad information. IARC (1993, 2010) and Rollison et al (2006) have completed comprehensive reviews of the available data. IARC (1993) concluded that there is inadequate evidence that personal use of hair colorants entails exposures that are carcinogenic. Rollison et al. (2006) concluded that the evidence is insufficient to support a causal association between personal hair dye use and cancer. IARC (2010) concluded that the epidemiological evidence for personal use of hair colorants is inadequate, and personal use of hair colorants is not classifiable as to its carcinogenicity to humans.
Summary (Boilerplate)	Currently available epidemiology studies do not provide sufficient evidence to support a causal association between personal hair dye use and cancer. A summary of the available hair dye epidemiology data is available at http://www.cir-safety.org/findings.shtml.
Discussion (Boilerplate)	The CIR Expert Panel considered the results of numerous hair dye epidemiology studies and determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer, based on lack of strength of the associations and inconsistency of the findings. Additionally, the Panel noted that there was no consistent pattern of genotype/phenotype influence on hair-dye epidemiology findings.
Background	
	See separate document
REFERENCES	International Agency for Research on Cancer (IARC). IARC Monographs on the evaluation of carcinogenic risks to humans. Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. IARC Monogr Eval Carcinog Risks Hum. 1993;57(1):43-118. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans. Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. IARC Monogr Eval Carcinog Risks Hum. 2010;99(1):499-646. Rollison DE, Helzlsouer KJ, and Pinney SM. Personal Hair Dye Use and Cancer: A Systematic Literature Review and Evaluation of Exposure Assessment in Studies Published Since 1992. J Toxicol Environ Health Part B. 2006;9(5):413-439.

Infant Skin

(developed 7/2014)

Boilerplate and Guidance Language

Discussion; Absorption (Boilerplate)	NOTE: The boilerplate would be used in reports assessing the safety of ingredients for which absorption or metabolism could be an issue in baby/infant skin but not necessarily in adult skin. The boilerplate should be tailored particularly to address ingredients for which absorption, but not metabolism, is a likely issue in baby/infant skin. The boilerplate is not appropriate for ingredients that neither penetrate nor are metabolized in the skin of babies and infants. The CIR Expert Panel noted that the potential dermal penetration and systemic absorption of ingredients in topically-applied cosmetic products in babies (0-6 mos) and infants (6 mos – 2 yrs) is governed by two major factors, including the development of the stratum corneum (SC) as a diffusion barrier, and the development of biotransformation-enzyme systems in the skin. The Panel concluded that the skin of babies and infants provides an effective diffusion barrier under basal conditions. However, susceptibility of the skin to external insults is greater, and recovery is slower, in babies than in adults. The increasing expression and activity of sPLA2 in the skin after birth yield free fatty acids that acidify the skin, which is critical for the maturation of the barrier. The barrier function becomes similar to that of adults sometime between 6 months to 2 years of age;

	the exact time of the maturation within this period varies considerably from individual to individual. However, the absence of capillary loops until about 2 weeks after birth, which develop only gradually until about 3 months of age, probably helps to reduce the rate of systemic absorption of ingredients that can penetrate the SC in babies. There is very little information on the development of biotransformation capacities in the skin. The Panel noted that information that may be available on known or likely biotransformation pathways of an ingredient in the liver and other internal organs can indicate whether there is reason to be concerned about potential metabolism and likely metabolites of the ingredient in the skin. The CIR Expert Panel recognizes that babies, infants and other children represent a distinct subpopulation in the assessment of potential exposures, and routinely considers the effect of greater skin-surface area to body-mass ratio on percutaneous absorption in children when performing cosmetic ingredient safety assessments. A detailed discussion and summary of the Panel's position on evaluating dermal penetration and systemic absorption of ingredients in cosmetic products on the skin of babies and infants is available at http://www.cir-safety.org/cir-findings
Discussion; Irritation (Boilerplate)	***NOTE:*** *The boilerplate below is for use in reports assessing the safety of ingredients for which irritation could be an issue particularly in babies and infants. The boilerplate should be tailored particularly to address ingredients for which dermal penetration and potentially dermal metabolism as well, could exacerbate the irritation of the skin of babies and infants, compared with adult skin. The boilerplate below should be combined in an integrated manner with the absorption boilerplate, above, when the potential for dermal irritation and systemic exposure/toxicity of topically applied ingredients are both increased in babies and infants, compared with adults. The boilerplate is not appropriate for ingredients that do not penetrate and, if relevant, are not metabolized in the skin of babies and infants, or otherwise have little or no potential to irritate the skin.* The CIR Expert Panel noted that the potential dermal penetration and absorption of topically-applied cosmetic ingredients in babies and infants is governed by two major factors, including the development of the stratum corneum (SC) as a diffusion barrier, and the development of biotransformation-enzyme systems in the skin. The Panel concluded that the skin of babies and infants provides an effective diffusion barrier under basal conditions. However, susceptibility of the skin to external insults is greater, and recovery is slower, in babies than in adults. The increasing expression and activity of sPLA2 in the skin after birth yield free fatty acids that acidify the skin, which is critical for the maturation of the barrier. The barrier function becomes similar to that of adults sometime between 6 months to 2 years of age; the exact time of the maturation within this period varies considerably from individual to individual. Additionally, there is very little information on the development of biotransformation capacities in the skin. The Panel noted that information that may be available on known or likely biotransformation pathways of an ingredient in the liver and other internal organs can indicate whether there is reason to be concerned about potential metabolism and likely metabolites of the ingredient in the skin. A detailed discussion and summary of the Panel's position on evaluating dermal penetration of ingredients in cosmetic products on the skin of babies and infants is available at http://www.cir-safety.org/cir-findings.
Background	
	See separate document.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: CIR Science Support Committee (CIR SSC) of the Personal Care Products Council

DATE: July 29, 2014

SUBJECT: Comments on the Draft Boilerplates and Guidance Language Prepared for the June 2014 CIR Expert Panel Meeting

The CIR SSC appreciates the opportunity to comment on the draft boilerplates and guidance language that was prepared for the June 2014 CIR Expert Panel meeting.

We are concerned with language regarding impurities that suggests that the CIR Expert Panel routinely sets specific limits for impurities in ingredients. Regarding impurities in ingredients, language such as that presented under pesticide and heavy metals is appropriate. "The Panel stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit these impurities in the ingredient before blending into cosmetic formulation."

Language related to impurities should focus on the level of impurities in the finished products rather than the level of impurities in ingredients

Benzene, 1,4-dioxane, ethylene oxide
Discussing benzene with 1,4-dioxane and ethylene oxide is misleading and suggests that PEG ingredients may be contaminated with benzene. Benzene should be discussed in a separate section, or in the section on residual solvents in polymers.

As analytical methods are capable of measuring lower and lower levels of contaminants it is misleading to state that 1,4-dioxane is "removed" from ingredients before blending into cosmetic products. Please change the language to "industry is aware that 1,4-dioxane may be an impurity in PEGs and, thus uses purification steps to limit it."

Although it may have been used in the report on Nonoxynols, the comparison with the ISO standard for exposure to ethylene oxide from medical devices sterilized with ethylene oxide is

not appropriate and should not be used. If left as part of the boilerplate, a reference for the ISO standard needs to be provided.

Heavy Metal Limits

Although 0.1 mg/kg is the Food Chemical Codex limit for lead in lard, this limit is not acceptable for all ingredients, and the boilerplate language should not suggest that it be applied to all ingredients. If specific limits for heavy metals are stated they should be for the finished product rather than the ingredient.

Formaldehyde Releasers

The actual levels of formaldehyde in products containing formaldehyde releasers is very low and difficult to measure. In formulation, the released formaldehyde is reactive and is used up once it is released, which contributes to the releasers' effectiveness as a preservative. Because of the difficulty in measuring formaldehyde in products, how will the level of formaldehyde in the product or ingredient be determined to select the appropriate boilerplate language under: "if the formaldehyde level is less than the limit established by the Panel", "if the formaldehyde level in the ingredient, but not the formulation, would be more than the limit established by the Panel", or "if the formaldehyde level in the ingredient and in formulation would be more than the limit established by the Panel"?

With the exception of a limit of formaldehyde in finished products of 0.074%, we do not recommend general boilerplate language for formaldehyde releasers. Limits on formaldehyde levels in the formaldehyde releaser ingredients are not needed. The safety of formaldehyde releasers must be assessed based on the safety of the ingredient, not based on the formaldehyde released. The inhalation safety of formaldehyde releasers also needs to be assessed based on the ingredient and its use in a finished product, not just the potential to release formaldehyde. Formaldehyde is a product of normal metabolism and is found in the air at low levels. Therefore, if the safety of inhalation exposure to the ingredient can be supported, use of the ingredient in aerosol products may be acceptable, if it does not significantly increase formaldehyde levels above ambient formaldehyde concentrations.

Although not about aerosol exposure, the following paper examines inhalation exposure to formaldehyde from the use of personal care products containing formaldehyde releasers (abstract attached) and may be helpful as background to the development of the guidance language.

Lefebvre MA, Meuling WJ, Engel R, et al. 2012. Consumer inhalation exposure to formaldehyde from the use of personal care products/cosmetics. *Regul Toxicol Pharmacol* 63(1): 171-176.

Regul Toxicol Pharmacol. 2012 Jun;63(1):171-6. doi: 10.1016/j.yrtph.2012.02.011. Epub 2012 Mar 3.

Consumer inhalation exposure to formaldehyde from the use of personal care products/cosmetics.

Lefebvre MA[1], Meuling WJ, Engel R, Coroama MC, Renner G, Pape W, Nohynek GJ.

Author information

Abstract

We measured consumer exposure to formaldehyde (FA) from personal care products (PCP) containing FA-releasing preservatives. Six study subjects applied facial moisturiser, foundation, shower gel, shampoo, deodorant, hair conditioner, hair styling gel or body lotion at the 90th percentile amount of EU PCP consumer use. FA air concentrations were measured in the empty room, in the presence of study subjects prior to PCP use, and for one hour (breathing zone, area monitoring) after PCP use. The mean FA air concentration in the empty bathroom was 1.32 ± 0.67 μg/m³, in the presence of subjects it was 2.33 ± 0.86 μg/m³). Except for body lotion and hair conditioner (6.2 ± 0.1.9 or 4.5 ± 0.1.5 μg/m³, respectively), mean 1-h FA air concentrations after PCP use were similar to background. Peak FA air concentrations, ranging from baseline values (2.2 μg/m³; shower gel) to 11.5 μg/m³ (body lotion), occurred during 0-5 to 5-10 min after PCP use. Despite of exaggerated exposure conditions, FA air levels were a fraction of those considered to be safe (120 μg/m³), occurring in indoor air (22-124 μg/m³) or expired human breath (1.4-87 μg/m³). Overall, our data yielded evidence that inhalation of FA from the use of PCP containing FA-releasers poses no risk to human health.

PMID: 22406137 [PubMed - indexed for MEDLINE]

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Ivan J. Boyer
Senior Toxicologist
Date: August 18, 2014
Subject: Hair Dye Epidemiology "Boilerplate" Paragraph

At the June 2014 meeting, the CIR Expert Panel reviewed an updated draft of the hair dye epidemiology background document, and accompanying "boilerplate." Both of these items have been revised to address the comments of the participants of that meeting. Please review the revised document and "boilerplate" and decide whether they can be finalized, and the revised document can be posted on the CIR Website in place of the older version.

Dr. Belsito's Team

DR. BERGFELD: Have we added non-sensitizing to the hair dye boilerplate conclusion?

DR. BELSITO: No, because it doesn't matter whether they sensitize or not. They're exempt. Right?

DR. BERGFELD: Well, that's true, but I was wondering --

DR. BELSITO: … The only issue that we've been discussing is whether, you know, as opposed -- the Europeans are vehemently -- increasingly vehemently against having that warning or notice or whatever you want to call it on the label about doing self-patch testing. So I think in terms of if we're going to change anything, we need to continue to monitor that issue...

… And then the caveat, well, we really don't know if the enzymes in the skin develop along the same time for us. We're sort of working on the assumption that they do, but we don't know, but there may be data on the development of pathways in the kidney or something that we could use as well. Otherwise, I had no comments on the boilerplates….

MS. FIUME: And I was talking the whole boilerplate document as well, if you have any specific comments…

DR. BELSITO: Yeah, I basically – the only thing I said here is see comment on infant skin, so I must have thought the other boilerplates were fine.

…boilerplates are great until you put them into a document, and then you see they don't work, so I would say we need to do some work on the baby. The others I think look okay. Let's see how they actually look when we put them into a document…

Dr. Marks' Team

DR. MARKS: Good. Okay. Next is hair dye, and Tom, I particularly asked your comments for this. There's revised epidemiology. Is that okay? Then meta-analysis was included, I think, for the first time. And then there was a comment, Rob, and so European update for self-testing. So let me see. Page 28, it has the boilerplate, and then 108, maybe we should go to 108, that's the memo. And Ivan -- oh, it's from you again.

So, revised hair dye epidemiology, and meta-analysis, and then briefing, update the Panel on the progress of the European Study on self-testing issue and we are fine. I know the Europeans are concerned that if self-testing becomes pandemic, that there may be increased sensitization; the practice in the United States, at least, because it's rarely done even though it's on the package label.

DR. BOYER: Right. And there is an -- ongoing study in Europe too, saying that.

DR. MARKS: Yeah. So, Tom, let's get back to the -- and in the meta analysis, was that correct? Ivan, is this the first time?

DR. BOYER: No -- what I did was to see whether or not there was any literature, new literature that came out since 2010 that ought to be included in the background paper for hair dye epidemiology. And I found one new epidemiological study, which I summarized and incorporated. It really doesn't change anything. And when I did

come across several meta analyses as well, which -- I mean, they've been done for the past decade or two, but historically they haven't been incorporated into this background document, so.

I did incorporate summaries of the meta analyses, the new ones, in each of the text of the background document, but I didn't include them in a table. And I guess the question simply, do you want to include meta analyses, or is there some reason why we don't necessarily, don't want to incorporate them?

DR. SLAGA: Well, the meta analysis well give you a greater picture of what's going on. I mean, to be comparing a bunch of them at one time. To have them in the document, I mean, in every document we are talking or --

DR. BOYER: As we go forward, and we continue to monitor the literature, and we update background documents, that according to what we find. And the question is, should we incorporate summaries of the meta analysis? And I guess what you're saying is that we should.

DR. SLAGA: Yeah. I think we should.

DR. SHANK: But we have two documents. One is the boilerplate, and then we have a website that has a whole lot more --

DR. BOYER: Yeah. That's what I'm talking about --

DR. SLAGA: And that's -- I would put it on the website, I wouldn't put it in the individual documents.

DR. BOYER: Right. And that's what we are talking about, yes.

DR. MARKS: So 29, page 29, that's -- now is this the revised hair dye epidemiology? You had the boilerplate, you had the summary, the discussion, you made changes. Did -- Ron -- Rons and Tom, are you fine with those?

DR. SHANK: With the boilerplate, page 29 --

DR. HILL: We are just looking at hair dyes now, right?

DR. MARKS: Yes.

DR. SHANK: Hair dye epidemiology it says, boilerplate. And in the discussion here we are adding that last line in red. And you have NAT1, NAT2, et cetera, and you need to give a little bit of (inaudible). That doesn’t -- won't mean anything to anybody unless you're familiar with that LE; Los Angeles Epidemiological Study. I can't remember the name of the author right now, but what do those mean? So just on more sense or something describing what those acronyms mean.

DR. BOYER: You see, actually the changes -- the changes that were made to the boilerplate make it conform to what is in the summary section of that background document, that's up on the website. But it's basically to indicate that there's been studies on the polymorphism -- they are out there, so we can -- we can work by that.

DR. SHANK: We know what it means, but if this is going to go into a report, standing alone, there would be a lot of people who won't know what the significance is of that statement.

DR. MARKS: So you would have one more sentence explaining what the NAT1, 2, GSTM1, and GST 21 is. Is that what you're saying?

DR. SHANK: Correct. Yes.

DR. MARKS: Yeah. So one more sentence, perhaps. I'm just surprised, Ron Shank, he likes the

(inaudible). The next paragraph, it "may depend on other safety test data for these substances." Whenever I -- my question was, what other data depend on other safety test data? That seems to be pretty vague in terms of, okay, I'm -- we have all this but, you know, this -- the safety may depend on other test data but, I wasn't -- you know, that really left me a little bit wondering, okay, what other data do we need to feel safe about this? Or, do we not feel safe because we don't have this other data?

DR. BOYER: Because these are generalizations, you know.

DR. MARKS: Yeah.

DR. BOYER: But, you know, just for example, is the hair dye ingredient that we were talking about earlier, where Dr. Shank was uncomfortable because it's specific information or lack of information although we have [for] that particular ingredient. I think that's that the N2.

DR. HILL: Well, and one of the things that came up with kinetics studies I was talking about earlier, although they keep getting shoved back -- keep getting stuff -- because there were some coupling agents that do form, that do form intermediates, that do reach (inaudible) levels, for (inaudible) periods of time, on the skin.

That's not true of all of the coupling agents, but there some that notable of that, right, so then in that particular case, when something comes up it might need at least closer scrutiny toward that and include safe.

DR. BOYER: And here we are focused on the epidemiology.

DR. MARKS: Right. That is studied before -- or I mean, in mentioned that a sense before. So Ron Shank, you were fine with that; the way that was stated?

DR. SHANK: It didn't hit me, so.

DR. MARKS: Okay, fine. If it didn't hit you it's fine, and okay. Any other comments about the hair dye epidemiology?

DR. LORETZ: I just had a comment on the review, the background document, and I'm just wondering if maybe upfront it can be stated a little directly kind of what it covers. Because there are other studies to go back earlier in time and so forth, that aren't in here, so suppose you're not comprehensive on every study, so maybe a little more -- I guess I was -- in reading it I wasn't quite sure what the rules were about what was included and what wasn't.

DR. BOYER: Okay. Yeah, I mean -- the original version of this was written sometime ago, and basically what we did was take where we left off and then we moved forward.

DR. LORETZ: But you might just mention, because there are studies going back to the '90s and so forth, that aren't included that were big and --

DR. MARKS: Okay. Anything else about -- So the European update in self-testing, how are you going to do that in September? Was that just going to be a memo or something?

DR. BOYER: They are in the midst of that investigation. The Panel could request an update of the other study at that point. I think they are still a year or two from finishing.

DR. LORETZ: Yeah. According to the schedule that was given at the last update that came to the Panel, at December 2012, this year they were doing the PPD positive people, next year they are doing the control, so I think a memo would be probably more appropriate. I don't think there would be enough data to present, but certainly we can -- HCTC can certainly provide that.

DR. MARKS: To me I look at it and see other ingredients we've already ruled on come -- you know, make conclusions, and as new data comes in we will look at that and react to it appropriately. So I don't think we are waiting for any action based on the self-testing studies that are going on in Europe. So yeah, I think if you'll bring us abreast of it, it will be great.

DR. LORETZ: Okay.

Full Session

DR. BERGFIELD: … The special subject review, we looked at or actually, the staff of the CIR looked at, on our boilerplates, which includes guidelines for certain groups of ingredients in our discussions and specifically in the areas of pesticides, contaminants, monolayer residues, formaldehyde, formaldehyde inducers, hair dye epidemiology, penetrations (inaudible) by the way they open or not, and we've taken a glance at these, and we'll be working with these over time, but they look really good. I want to really thank the CIR staff for all the work that went into putting those together. Very helpful to have that organized for us, so we could have that to reflect upon…

HAIR DYE EPIDEMIOLOGY – through July, 2014

Hair dyes may be broadly grouped into oxidative (permanent) and direct (semi-permanent) dyes. The oxidative dyes consist of precursors mixed with developers to produce color, while direct dyes consist of a preformed color.

Epidemiology studies that seek to determine links, if any, between hair dye use and disease provide broad information and have been considered by the CIR Expert Panel, although these studies do not specifically address the safety of individual hair dye ingredients.

The following provides a brief summary of the many relevant epidemiological studies that have been published since about 2010, as well as older epidemiological studies that were included in comprehensive reviews, such as that published by the International Agency for Research on Cancer (IARC) in 2010[1].

Conclusion

The CIR Expert Panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer, based on the lack of strength of the associations and inconsistency of the findings. In addition, the Panel noted that there was no consistent pattern of genotype/phenotype influence on hair dye epidemiology findings.

Background

The CIR Expert Panel reviews selected, new epidemiological studies addressing the personal use of hair dyes as these studies become available. Table 1 summarizes these studies specifically addressing bladder cancer, lymphoma, and leukemia. Occupation as a hairdressers, barber, or cosmetologist involves exposures to multiple products used during work, making it difficult to use the results of such studies to inform the assessment of the risk, if any, associated specifically with hair dyes. Accordingly, such studies are not summarized here.

The CIR Expert Panel considers that epidemiological studies based of better information about exposure, compared with other such studies, can provide more useful findings. Rollison et al. (2006)[2] noted that exposure assessments in hair dye epidemiology studies ranged from minimal information (e.g., ever/never use) to subject-recalled information on type, color, duration and frequency of use. These authors developed a scale from + to ++++ to score the quality of hair dye exposure assessments in hair dye epidemiology studies. This scale was used to score the studies that are summarized in Table 1.

An IARC working group summarized the relevant epidemiology studies and observations on bladder cancer and hematological concerns.[1,3] The working group concluded that the data are of insufficient quality, consistency, or statistical power to establish the presence or absence of a causal link between personal use of hair dyes and cancer. They also concluded that the animal studies provided limited evidence for the carcinogenicity of hair colorants. Occupational exposure during work as a hairdresser, barber, or beautician was also assessed. The working group found that exposures from these occupations are probably carcinogenic, based on limited evidence of increased risk for bladder cancer in hair dressers and barbers.

Bladder Cancer

Turati et al. (2014) performed a meta-analysis of 15 case control and 2 cohort studies.[4] The pooled relative risk (RR) of bladder cancer incidence/mortality was 0.93 (95% CI 0.83-1.05) for personal use of any type of hair dye, compared with no use, and similar results were obtained when the subjects were stratified by sex. The RR for personal use of permanent hair dyes from 7 of the studies was 0.92 (95% CI 0.77-1.09). Similarly, no association was found between bladder cancer and the duration or lifetime frequency of use of any type of hair dye or use of permanent hair dyes, compared with never used hair dyes. The RR for the use of dark-color hair dyes was 1.29 (95% CI 0.98-1.71).

Ros et al. (2012)[5] performed a population-based case-control study of hair dye use and bladder cancer in the Netherlands. The subjects were 246 cases and 2587 controls; all of the subjects for which the analyses were performed were women (less than 5% of the men selected for the study reported ever using hair dyes). The hair dye exposure assessment

was ++++ on the Rollison et al. (2006) scale. No association was found between bladder cancer and ever use of permanent hair dyes (OR 0.87; 95% CI 0.65-1.18) or temporary hair dyes (OR 0.77; 95% CI 0.58-1.02). Similarly, no association was observed when hair dye use was defined by type, duration or frequency of use, dye color, or extent of use or when the patients were stratified by aggressive and non-aggressive bladder cancers.

Koutros et al. (2011)[6] conducted a population-based case-control study in Maine, Vermont, and New Hampshire. The subjects were 1193 cases of urinary bladder cancer diagnosed from 2001 to 2004 (911 male and 282 female), and 1418 controls (1039 male and 379 female). The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale.

No association was found between ever/never use of hair dyes and bladder cancer – the odds ratio (OR) and associated 95% confidence interval (CI) for women was 0.7 (95% CI 0.5 – 1.0), and for men 0.7 (95% CI 0.4 – 1.0). Because of the excellent exposure assessment, the authors were able to examine subsets of the population studied. Women who used red hair colors, for example, exhibited an OR of 0.4 (95% CI 0.2 – 0.8), suggesting a significantly lower risk of bladder cancer associated with the use of such hair dyes. A similar lower risk of bladder cancer was reported for women who used hair dyes for a duration between 10 and 19 years (OR 0.5; 95% CI 0.27 – 0.79). As the data were further analyzed, the authors considered women with and without college degrees. Women without college degrees who used permanent hair dyes exclusively, for example, had a significantly lower risk of bladder cancer (OR 0.5; 95% CI 0.4 – 0.7). Exclusive use of permanent hair dyes by women with college degrees was associated with a significantly higher risk of bladder cancer (OR 4.9; 95% CI 1.7 – 14.6).

Shakhssalim et al. (2010)[7] reported a population-based case-control study of bladder cancer in Iran with 692 cases and 692 controls. Cases were identified using the Iranian cancer registry. The hair dye exposure assessment was a + on the Rollison et al. (2006) scale. The OR for hair dye use and bladder cancer was 1.99 (95% CI 1.02 – 3.82). When women and men were analyzed separately, no significant association with hair dye use and bladder cancer was found.

Lymphoma and Leukemia

Wong et al. (2009)[8] reported a hospital-based case-control study of acute myeloid leukemia (AML) in Shanghai, China. There were 722 cases and 1444 controls, and the evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. The study found no increase in the risk of AML and personal use of hair dyes; OR of 0.98 (95% CI 0.8 – 1.2).

Lv et al. (2010)[9] conducted a hospital-based case-control study of myelodysplastic syndromes (MDS) in China. There were 403 cases and 806 controls, and the evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. In a univariate analysis, the OR for hair dye use (≥2 times per year) and all MDS was 1.46 (95% CI 1.03 – 2.07). In a multivariate analysis, the OR was 1.31 (95% CI 0.88 – 1.93).

Wong et al. (2010)[10] conducted a hospital-based case-control study in Shanghai of non-Hodgkin's lymphoma (NHL). There were 649 cases and 1298 controls, and the evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. No increased risk of NHL was reported (OR 0.93; 95% CI 0.75 – 1.16). For chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), the authors reported a significantly lower risk associated with hair dye use (OR 0.37; 95% CI 0.18 – 0.76).

Chang et al. (2010)[11] re-evaluated tissue samples from a NHL case-control study in males from Iowa and Minnesota using FISH (fluorescence *in situ* hybridization) cytogenetic technique to evaluate both *t*(14;18)-positive and *t*(14;18)-negative NHL subtypes. The evaluation of hair dye exposure scored + on the Rollison et al. (2006) scale. An association between ever/never use of hair dyes and *t*(14;18)-negative NHL was reported, but no association was found with *t*(14;18)-positive NHL.

Glioma

Shao et al. (2013)[12] performed a meta-analysis of 4 case-control and 2 cohort studies of personal hair dye use and the incidence of gliomas. Summary relative risks (RRs) for ever use of any hair dyes were 1.132 (95% CI 0.887-1.446) for all studies, 1.291 (95% CI 0.937-1.777) for case-control studies, and 0.903 (95% CI 0.774-1.054) for cohort studies. Similar results were obtained when the subjects were stratified by geographic regions and sex. No significant associations were found among the studies that evaluated permanent hair dye use and duration of any hair dye use.

NAT1, NAT2, GSTM1, and GSTT1 Genotype/Phenotype

The study by Koutros et al. (2011)[6] is the latest in a series of studies that have examined the influence of genotype and phenotype of liver enzymes that may activate or inactivate potential carcinogens.

NAT1 and NAT2 genes encode arylamine *N*-acetyltransferases that can function to activate or deactivate arylamine and hydrazine chemicals. Polymorphisms in these genes determine, in part, the liver function phenotypes. Human populations segregate into rapid, intermediate, and slow acetylator phenotypes. *N*-acetylation is a major route of biotransformation of aromatic amine compounds, including those found in hair dyes.

The GSTM1 gene encodes a cytoplasmic glutathione *S*-transferase that belongs to the μ class, which functions in the detoxification of electrophilic compounds, including carcinogens, therapeutic drugs, environmental toxicants, and products of oxidative stress, through conjugation with glutathione. The GSTT1 gene encodes the glutathione *S*-transferase that belongs to the θ class, which catalyzes the conjugation of reduced glutathione to a variety of electrophilic and hydrophobic compounds. Genetic polymorphisms in *GSTM1* and *GSTT1* also may affect the metabolism of the constituents of hair dyes.

Koutros et al. (2011)[6] performed genotyping for NAT2, NAT1, GSTM1, and GSTT1. An increased risk of bladder cancer was reported primarily among exclusive users of permanent dyes who had NAT2 slow acetylation phenotypes, compared to never users of dye with NAT2 rapid/intermediate acetylation phenotypes, in females with a college degree, but the difference was not statistically significant. The authors concluded that NAT1, GSTM1, and GSTT1 genotypes did not appear to be important modifiers of the association between ever, permanent, or exclusive permanent use and bladder cancer.

Gago-Dominguez et al. (2003)[13] reported that individuals with the NAT2 slow acetylator phenotype who exclusively used permanent hair dyes had an increased risk of bladder cancer (OR 2.9; 95% CI 1.3 – 7.5) compared to individuals with the NAT2 rapid acetylator phenotypes (OR 1.3; 95% CI 0.6 – 2.8). Individuals with a NAT1*10 genotype who were non-smokers and used permanent hair dyes exclusively had an OR of 1.0 (95% CI 0.2 – 4.3), and those with a non-NAT1*10 genotype had an OR of 6.8 (95% CI 1.7 – 27.4).

Kogevinas et al. (2006)[14] evaluated the association of hair dye use with bladder cancer among females in a case-control study that also examined the effect of hair dye use among genetic subgroups. No statistically significant differences in bladder cancer incidence were noted as a function of any of the genotypes examined, including those with slow or intermediate/rapid NAT2 acetylator phenotypes. For NAT2 slow acetylator phenotypes, the OR was 0.6 (95% CI 0.3 – 1.4), and for NAT2 rapid/intermediate phenotypes, the OR was 0.9 (95% CI 0.3 – 2.6). Individuals with a NAT1*10 genotype had an OR of 2.9 (95% CI 0.7 – 11.6), and those with non NAT1*10 had an OR of 0.6 (95% CI 0.2 – 1.6). These findings were directionally opposite to those of Gago-Dominguez et al. (2003).[13]

Morton et al. (2007)[15] conducted a U.S. population-based case-control study of NHL. Women with the NAT2 slow acetylator phenotype or who had no copies of the NAT1*10 allele and used intense-tone permanent hair dyes before 1980 did not have an increased risk of NHL (OR 1.5; 95% CI 0.6 - 3.6 and OR 1.5; 95% CI 0.7 - 3.3, respectively), but women with the NAT2 rapid/intermediate acetylator phenotype or 1 or 2 copies of the NAT1*10 allele did exhibit a potential increased NHL risk (OR 3.3; 95% CI 1.3 - 8.6 and OR 2.5; 95% CI 0.9 - 7.6, respectively).

Zhang et al. (2009)[16] re-evaluated data from a case-control study of NHL in Connecticut (Zhang et al. 2004)[17] to consider NAT1 and NAT2 genotype/phenotype and other single nucleotide polymorphisms (SNPs). None of the different individual genes was associated with a significant change in the risk of NHL overall or for any of the NHL subtypes considered. The finding that the NAT2 rapid/intermediate acetylator phenotype or the presence of copies of the NAT1*10 allele in this study was not associated with an increase of NHL is not consistent with the findings of Morton et al. (2007),[15] but the finding in this study that the NAT2 slow acetylator phenotype is not associated with and increased risk of NHL is consistent with the findings of Morton et al (2007).[15]

Table 1. Recent Original Hair Dye Epidemiology Studies considered by the CIR Expert Panel.

Study Type/Methodology	Results	Reference
Bladder Cancer		
Population-based case-control study in The Netherlands. Cases diagnosed between 1975 and 2009 for a total of 246 female cases with 2587 female controls; Analyses were not performed for the men selected for the study because less than 5% reported ever using hair dyes. Exposure assessment was on the Rollison et al. (2006) scale.	No association between bladder cancer and ever/never use of permanent hair dyes – permanent OR 0.87 (95% CI 0.65-1.18); temporary OR 0.7 (95% CI 0.58-1.02) No association between bladder cancer and duration of use, number of times used per year, total number of times used over a lifetime, dying all the hair or only part of the hair, or dye color (none of the subjects reported use of black dye). No association found when patients stratified by aggressiveness of the cancer.	Ros et al (2012)[5]
Population-based case-control study in Maine, Vermont, and New Hampshire. Cases diagnosed 2001 to 2004 for a total of 1193 cases (911 male and 282 female) with 1418 controls (1039 male and 378 female). Genotyping done for NAT2, NAT1, GSTM1, and GSTT1. Exposure assessment ++++ on the Rollison et al. (2006) scale.	No association between ever/never use of hair dyes and bladder cancer – women OR 0.7 (95% CI 0.5 – 1.0); men OR 0.7 (95% CI 0.4 – 1.0). No association between hair dye use, NAT2 phenotype or NAT1 genotype and bladder cancer risk. Increased risk of bladder cancer with permanent hair dye use in a subgroup of women with a college degree, but no dose-response for color, duration of use, or total lifetime uses. NAT2 phenotype was associated with a suggestive, but not statistically significant, increased risk when college degree women were stratified by education – this was based on 15 cases and 6 controls.	Koutros, et al. (2011)[6]
Population-based case-control study of bladder cancer in Iran with 692 cases and 692 controls (identified using the Iranian cancer registry). Exposure assessment was a + on the Rollison et al. (2006) scale.	Overall (male and female) OR for hair dye use and bladder cancer was 1.99 (95% CI 1.02 – 3.82). When women and men were analyzed separately, no significant association with hair dye use and bladder cancer was reported.	Shakhssalim et al. (2010)[7]
Lymphoma and Leukemia		
Hospital-based case-control study of acute myeloid leukemia (AML) in Shanghai, China. There were 722 cases and 1,444 controls. Evaluation of hair dye exposure that was a ++ on the Rollison et al. (2006) scale.	No increase in the risk of AML and personal use of hair dyes with an OR of 0.98 (95% CI 0.8 – 1.2).	Wong et al. (2009)[8]
Hospital-based case-control study of myelodysplastic syndromes (MDS) in China. There were 403 cases and 806 controls. Evaluation of hair dye exposure that was a ++ on the Rollison et al. (2006) scale.	Univariate analysis: OR for hair dye use (≥2 times per year) and all MDS was 1.46 (95% CI 1.03 – 2.07). Multivariate analysis: OR was 1.31 (95% CI 0.88 – 1.93).	Lv et al. (2010)[9]
Hospital-based case-control study in Shanghai of non-Hodgkin's lymphoma (NHL). There were 649 cases and 1298 controls Evaluation of hair dye exposure that was a ++ on the Rollison et al. (2006) scale.	No increased risk of NHL, with an OR of 0.93 (95% CI 0.75 – 1.16). For chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), the authors reported a significantly lower risk associated with hair dye use with an OR of 0.37 (95% CI 0.18 – 0.76).	Wong et al. (2010)[10]

Re-evaluated tissue samples from a non-Hodgkin's lymphoma case-control study in males from Iowa and Minnesota using FISH (fluorescence *in situ* hybridization) cytogenetic technique to evaluate both *t*-positive and *t*-negative NHL subtypes. The evaluation of hair dye exposure that was a + on the Rollison et al. (2006) scale.	An association between ever/never use of hair dyes and *t*(13:18)-negative NHL was reported, but no association was found with *t*(14:18)-positive NHL.	Chang et al. (2010)[11]

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Ivan J. Boyer
Senior Toxicologist
Date: August 18, 2014
Subject: Dermal Penetration, Absorption and Other Considerations for Neonates and Infants in Safety Assessments

Please find the most current version of the infant skin resource document (*Infskn092014rep- final*, which is included in the Admin file) for your final review before posting the document on the CIR Website. The previous draft was presented to the Panel at the June 2014 meeting, during which Dr. Elias delivered his presentation by teleconference. The current draft addresses all of the comments received to date from the CIR Expert Panel (Panel), Dr. Elias, and the Personal Care Products Council (Council).

A version of the revised resource document was sent to Dr. Elias for his review on July 9, 2014. Although we have not received additional comments from him on that version, we have received his responses to two specific questions that we posed to him after the June 2014 meeting. The questions and Dr. Elias' responses are summarized below.

Question 1: The first question relates to statements made in the Preamble and Discussion sections of the draft of the resource document:

- "The decrease in skin pH that occurs especially in babies from birth to about 6 months of age, which may continue up to 2 years of age, can help to explain, in large part, the corresponding decrease observed in the potential dermal absorption of many substances"

- "The pH of the surface of the skin, and thus the maturity of the barrier function of the skin, does not become similar to those of adults until sometime between 6 months to 2 years of age, and the exact time of the maturation within this period varies considerably from individual to individual."

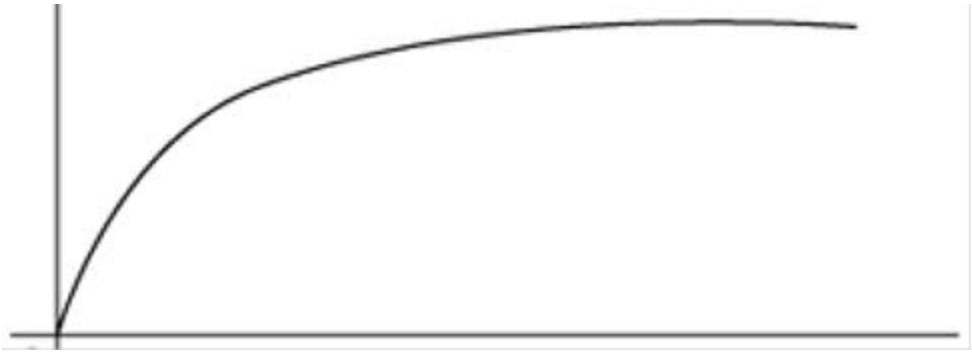
Instead, I (Dr. Boyer) would have stated something like:

- "The decrease in skin pH that occurs especially in babies from birth to about 6 months of age, but also in infants from 6 months to 2 years of life, can help to explain, in large part, the differences observed in the potential dermal absorption of many substances"

We state earlier in the discussion: "However, the Panel was confident that the SC in normal, full-term neonates is an efficient barrier that continues to develop incrementally throughout childhood."

Is the emphasis on variability from 6 months to 2 years of age warranted, or should we be looking at barrier-function maturation in babies and infants as a process that, in general, proceeds most rapidly for a few days after birth, still rapidly, but less so over the next six months, and then still less rapidly from 6 months to two years of

life? In other words, can we conceptualize the maturation of the barrier function of the skin from birth to two years of life as depicted in a figure like the one below?



Where maturity is represented on the y axis and time up to 2 years is on the x axis. We are not suggesting adding such a figure to the report – We are including it here only to help contrast the two perspectives (i.e., inter-individual variability of the maturation of the barrier function vs. development of the barrier as a process that "asymptotically" approaches adult-like maturity over the first two years of life.

Can you tell us whether we should adopt one or both (or neither) of these perspectives in the report?

Response 1: As I (Dr. Elias) understand it, Question 1 relates to the rate of normalization of skin pH and barrier maturation in neonates. Your diagram shows it perfectly - skin maturation is largely completed by 6 months, but in some individuals, there may be a further decline in surface pH and improvement in barrier function between 6 months and two years.

Question 2: The other question relates to a discussion about keeping the skin of babies and infants dry. Here is an excerpt from the transcript:

- DR. BELSITO: Well, what I take away from Peter and dry, dry, dry and petrolatum was he was talking about atopic kids. I don't think he was talking about the general population. He was talking about using petrolatum to help the barrier in children who have atopic disease which is what we do. In answer to your question, Rachel, I just Googled The American Academy of Pediatrics and moisturizers, and the only thing that I can get is they actually recommend twice a day moisturizing for children with atopic eczema. Otherwise it doesn't appear that they have a standard saying you shouldn't or should. The only other thing they say that would regard what we do is that if your child is less than six months of age and sun exposure is unavoidable to use zinc oxide, titanium dioxide rather than chemical sun screening. Those seem to be the only two things that they're saying about topicals and infants, so they don't seem to have a position.
- DR. BELSITO: Right. So, I mean what I would like to see clarified is when he said, "dry, dry, dry" was he recommending that you dry baby skin because my understanding was that what he was saying is 20 to 30 percent of infants or children, babies, will develop atopic eczema by the time they're three months, six months of age, and their skin is dry and we use petrolatum because there are no fragrances and there are no preservatives and there are none of these things that we're concerned about them being allergic to. And not that he was saying that you want to dry baby skin because I would disagree with that. I don't think you want to dry baby skin.
- DR. BELSITO: I think "keep dry" he meant diaper area because of pH and infection. I don't think he's telling us to put our kids under blow dryers.

Can you confirm that Dr. Belsito is correct in his interpretation? For context, Industry proposes that (Dr. Boyer's nutshell summary follows) some products, including "moisturizing" products, made for babies are good for babies, although some pediatricians may advise new parents to put nothing on their baby's skin, and to keep them dry.

Response 2: I (Dr. Elias) believe that the confusion has arisen because of the separate issues of what's best for normal vs. atopic (or skin at risk for atopic dermatitis) infants. Drying of normal infants' skin accelerates barrier maturation, and therefore, it would be theoretically beneficial for hydrated surfaces such as body folds that exhibit delayed maturation due to prolonged hydration due to occlusion or diaper use. The skin of babies at risk for atopic dermatitis is excessively dry, so it would benefit from moisturization strategies.

Dr. Elias also noted "I have tried to keep my answers as terse as possible, so as to avoid ambiguities, but would be happy to continue this dialogue, if there are further questions."

The most current version of the infant skin resource document, below, reflects Dr. Elias' responses to the above two questions. The Panel should review this document and determine whether it requires additional revisions before it is posted.

131th COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING - MAIN SESSION

Monday, June 9, 2014

DR. BOYER: I ask the panel's indulgence. I have to call our next speaker. It's just going to take me a couple of minutes to do that.

All right, Peter, are you on line?

DR. ELIAS: I'm on the line. Thank you.

DR. BOYER: Okay. Excellent. I'm going to make a few introductory remarks to introduce you before you get started. So let me do that. In March of 2013, the CIR staff presented a draft resource document on the subject of infant skin, and in fact, specifically on the subject of the dermal penetration and percutaneous absorption of topically-applied ingredients on infant skin as compared to adults, for instance.

There are two major subjects that were covered in that draft report, including the diffusion barrier of the skin, which has been attributed primarily to the stratum corneum, and also the development of the biotransformation capacities of the skin, for which we have very little specific information.

The draft report stimulated a good deal of discussion among the panel, and the decision was to move forward with the development of the document with the preamble that outlined some of what is not really covered under the purview of the panel's reviews in a general sense, such as prescription and nonprescription drugs. Strictly speaking and by definition, those are not cosmetic ingredients and so forth. Not covered also is the application of cosmetics or cosmetic products to preterm babies. That is not within the purview within the scope of the use, of the intended use, of cosmetic ingredients.

One of the recommendations that we got from the panel, from Dr. Marks in particular, was to invite two researchers, physician researchers to speak to the panel, and they include Dr. Peter Elias and Dr. Mary Williams. Dr. Elias and Dr. Williams, they are both dermatologists. They are both professors at the University of California. Dr. Elias, in addition, serves as a physician at the Veterans Affairs Medical Center in San Francisco, and he heads a research group. The research that has been involved has been focused on elucidating the factors that are important for maintaining and for restoring the skin barrier. And he's also very knowledgable, he's had a good deal of experience researching ceramides, the role of ceramides. And in addition, he has been intimately involved in the development of pseudo-ceramides as therapeutic agents.

So I encourage the panel to also ask questions of Dr. Elias on that subject as well, because one of the important questions that's on the table for today's meeting is whether or not pseudo-ceramides are suitable analogs (inaudible) across to the ceramides that are used as cosmetic ingredients.

Dr. Williams, in addition to being a dermatologist, is a pediatrician, and her research has been focused on the development of the barrier function of the skin, both prenatally and perinatally. And she may, toward the tail end of Dr. Elias's presentation, be able to, be available to us to answer some questions as well.

So with that I'm going to turn it over to Peter -- Peter Elias. Peter, I have your title slide up and I'm ready to advance your slides when you tell me to do that.

DR. ELIAS: All right. Good morning, everyone. Just to let you know that Dr. Williams helped me

prepare this presentation. She's a pediatric dermatologist. I have been involved in the research program on fetal and neonatal skin, and so she's empowered me to give the presentation this morning and she will not be available because she has -- it turns out she has a doctor's appointment at 8 o'clock, so she'll be leaving before being able to participate. But she'll be here in spirit.

Basically, my expertise is on the biological front. I'm not a physical chemist, and all the issues related – saran-wrap type issues of the skin are not in my area of interest, so there are some natural conflicts here between the information in the CIR resource document and between the biophysical and the biological points of view with regards to cutaneous structure and function. But I think Ivan has done a really nice job of resolving some of those issues and synthesizing them in the current draft of the documents.

What I'm going to do today is really talk about the neonatal skin and we're going to define it by different age groups within the neonatal category. If you want to go to the next slide then, Ivan.

Within the neonatal category, we'll talk about classification of neonates, problems -- specific problems with the biology within each age group, and then issues and potential therapy for the immature skin within each category.

Next slide. So from a biological perspective, you can break up neonatal skin into three major categories. Infant skin; Pediatric dermatologists refer to as children from six months to two years of age. Babies are basically from up to six months of age and any premature infant that's born after 34 weeks of gestation is considered to have skin that's as mature as any baby up to six months of age.

Then, there are premature infants who are 28 to 34 weeks of gestational age. Then you have the problems, of course, of the extremely premature infants who are less than 20 weeks of gestational age. And so we'll go over these categories and what we know about each of them and how we can possibly take care of these categories of skin and within each of these categories as we go through this talk.

Beginning first with the most mature, the infant skin, up to two years of age, even though their skin is relatively mature, they still have important issues related to occlusion in the diaper area and body folds. They don't have a fully mature permeability barrier. If you challenge their skin with an irritant or with a surfactant or a solvent or with tape stripping, their barrier recovers more slowly than normal. They also continue to have a higher than normal pH. We'll hear a lot about pH as we go through this talk. PH does not become completely equivalent to the pH of adult skin until about six months of age. So infants certainly up to six months of age will continue to have a pH abnormality, and that's part of the problem with a delayed barrier, even in unoccluded skin.

And because of the pH issue, and because of the occlusion and super moisturization, they continue to have an increased risk of dermatitis, infections, and of course, they are -- a large proportion of them are pre-atopic and can be considered in the earliest stages of the atopic march, which can appear as early as three months of age in infants who are predisposed genetically to develop atopic dermatitis.

But let's go on to the next slide then. What I've done in this slide is try to explain the basis for the functional abnormalities in infant skin, but this will continue to apply to the functional abnormalities of the earlier age groups as well, although it will become more severe as you'll see as we go through the talk.

Barrier abnormalities in infants can be largely ascribed to the increase in pH because we did experiments where we re-acidified infant skin. Well, this was in a neonatal wrap model. And simply by re-acidifying the stratum

corneum or lowering the pH of the stratum corneum to a level comparable to adult pH, we were able to completely normalize function in the equivalent of the infant skin.

Increase in pH in infant skin is due to one particular endogenous acidifying mechanism. Let me explain that for a moment. There are both exogenous and endogenous mechanisms that are responsible for the skin's acid mantle. The exogenous mechanisms are those that derive from eccrine glands, like lactic acid being deposited on the skin surface; fatty acids of sebaceous gland origin being deposited on the skin surface. It turns out the exogenous sources are not very important because pH is equally low in non-sebaceous gland-enriched- and sebaceous-gland-enriched areas of the body. So the exogenous sources are not major contributors.

The major contributors are a set of endogenous mechanisms within the epidermis itself, and these include an isoform of the enzymes secretory phospholipase A2, specifically the sPLA2-Xisoenzyme. And this enzyme is responsible for breaking down all the phospholipids in the epidermis so that when you get into the stratum corneum there are no longer any phospholipids. Instead, you have a substantial number of free fatty acids, most of which are "nonessential" free fatty acids in the sense that they don't include linoleic acid, but they're certainly essential for the skin barrier, since they are one component of the three key lipids that comprise the barrier.

So the major acidifying mechanism that's abnormal in neonatal skin is the sPLA2 mechanism.

Other acidifying mechanisms that are important include the conversion of filaggrin to so-called (inaudible), which is really a series of polycarboxylic acids. As the stratum corneum matures, filaggrin detaches (inaudible) the cornified envelope and it begins to be hydrolyzed by caspase-14 and other hydrolases into its constituent amino acids, which then get de-amidated, both enzymatically and nonenzymatically into its polycarboxylic acid -- PCA, if you like -- one of which is the very important ingredient that's been used in the past in many cosmetic products, urocanic acid, which was taken out of cosmetic products several years ago because of the fear that the isomerization of (inaudible). Every photon that hits a trans-urocanic acid molecule converts that molecule into cis-urocanic acid, and cis-urocanic acid at the time was thought to be a potent immunosuppressive molecule within the skin and linked to the development of non-melanoma skin cancers. As a result of that, urocanic acid was taken out of many cosmetic ingredients in spite of the fact it's the most important endogenous sunscreen in the skin of lightly pigmented individuals, far more important than melanin in lightly pigmented individuals. It accounts at the level of the stratum corneum for at least 50 percent of UVB absorption by the stratum corneum, so it's very important.

So you have the filaggrin, the polycarboxylic mechanism. And within that you have the (inaudible) to urocanic acid, which is one of the polycarboxylic acids.

Then you have a proton exchange mechanism in the outer-most granular layer called the sodium proton exchange or NHE1, which takes in sodium molecules and pumps out protons, and it acidifies the stratum granulosum/stratum corneum interface so that even though the pH of the stratum corneum is close in neutrality as you tape-strip down close to the stratum corneum -- close to the stratum granulosum, the pH, the membrane domains between the cells remain highly acidic, and this is where all the action is, of course. So this mechanism which operates in this very important site has its acidity maintained by the sodium/proton antiporter.

And then there are other mechanisms that may contribute as well. Melanin extrusion. I just wrote a paper that came out in the JID [Journal of Investigative Dermatology] last month if you're interested in looking at that. It

turns out that the extrusion of melanin granules, the release of melanin from the phagolysosomes that contain it within keratinocytes...

DR. BOYER: Excuse me, Peter -- Peter? We're kind of losing track of the slides at this point. Can you tell us what slide --

DR. ELIAS: Well, I'm still on the same slide. You know what, I can skip over the rest of this.

Okay. So the other -- unless people are interested in it. We can come back to it.

The super hydration is a problem, and that is partly due to the problem with the barrier. Much more water to the stratum corneum and that's contributing as well as the occlusion that we talked about earlier. Then the reduced inflammatory thresholds are also a problem related to the barrier. Whenever the barrier -- and also, the entry's pH. Whenever the barrier is compromised, the pH goes up. The pH activates serine proteases which then release pro-inflammatory cytokines. And that's why babies have this increased tendency to get diaper dermatitis and other types of inflammatory reactions.

So we're still in infants. Next slide. Based on what I've just told you about the abnormalities, logical management might be something that provides a partial barrier, like petrolatums, which functions like a vapor permeable membrane. Strategies that would reduce pH, strategies that keep the skin dry, and physiologic lipids would be appropriate. Physiological lipid replacement with a stearamide-dominant preparation would make sense for babies who are at risk for atopic dermatitis, which is probably about 20 to 30 percent of the population.

So in infant skin who are 34 weeks of gestation or older -- next slide -- the barrier is sufficient for life in a terrestrial environment, there continue to be problems with barrier repair and a high pH, which predisposes the inflammation and infections, and it continues -- and there is a problem also due to the serine proteases again being elevated, activated, with cohesion which may explain the reduced thresholds to blistering that we encounter in babies' infant skin.

All right. Now we're in babies, 34 weeks to six months of gestation. Pretty much like infant skin. So the treatment and management would be very similar. We consider them part of the same category since their skin is -- their barrier is sufficient for life in a terrestrial environment.

Then we move to premature infant skin, 28 to 34 weeks. Next slide. These babies have a partially competent barrier. These infants, their basal function is normal but they have an even more impaired response to insults. What's interesting about these infants, these premature infants in this age category is that they catch up very quickly. So if they are, let's say, born in 28 weeks, by 30 weeks of age they'll have a barrier that's comparable to an infant that's 34 weeks of age. The exposure to the dry environment accelerates the development and maturation of the barrier. pH is even higher of the stratum cornea in these infants, so they have an even greater tendency for infections, inflammation, and blistering, but again, it would be just for the first two weeks until they catch up. And note, they have a lamellar body secretory system, so they have the full capacity to make the ingredients that they need for the permeability barrier, and that will become functional after two weeks of exposure to the dry environment.

So within that age group, we can do things -- the same kinds of things to manage the skin -- are you on the next slide, I presume? Yeah. We would continue to provide them with a partial barrier with things like petrolatums. It's even more important to reduce pH, and we might look at other strategies to reduce pH. We have shown that

activators of both the PPARs and LXR, which are what we call the lipo-sensor receptors in the epidermis. They're members of the same family, receptors for retinoic acid and vitamin D and thyroid hormone. But these have as their ligands – naturally-occurring ligands or free fatty acids and oxygenated sterols, and they're formed in the epidermis during normal metabolism in the epidermis. So if you wanted to accelerate maturation, and we have done this in the fetal rats, you simply give them additional PPAR and LXR activators and you'll very quickly, even faster than two weeks, mature the stratum corneum. Again, physiologic lipids would be appropriate if there's a risk of atopic dermatitis, and drying the skin becomes very -- continues to be very important.

The basis for these recommendations comes from our work -- next slide -- in the neonatal rat model where we showed that the timetable for maturation of newborn rats -- they're with the same kind of problems that we see in newborn infants where they have the high pH and the delayed barrier recovery and the super moisturization, but the timetable for maturization, instead of being weeks to months, is all telescoped within the first eight days. And using this model, we've been able to look at various approaches that will accelerate the maturations of the barrier, and that included the PPAR, LXR activators that I mentioned earlier. We also have accelerated maturation with the application of the acidifying agents, which include, by the way, two GRAS ingredients -- lactobionic acid and, gosh, what's the other one, gluconolactone, both of which are GRAS ingredients. They are so-called super acids because they are as acidic as one normal sulfuric acid, and yet they are nonirritating. They're much milder on the skin than our alpha hydroxy acids, and they should not be confused with alpha hydroxy acids. These are pure acidifying molecules.

Okay. Let's go to the review then, the treatment of premature infants in the 28 to 34 week category. We have a partially competent barrier. Running it over again, they have -- the only new thing that I would add on this slide is that there are naturally-occurring ingredients again that are PPAR and LXR activators. For example, borage oil contains a huge amount of gamma-linolenic acid, which is a very potent PPAR alpha activator. So putting ingredients like that into formulations could be very useful for neonatal skin. Reducing pH, petrolatum. I would like to add one more thing here that's important. When you have a defective permeability barrier, you also have a defective antimicrobial barrier. We can only explain that in part by the high pH and by the moisture -- increased moisture content. The other problem is that they have defective antimicrobial peptides. So strategies to induce antimicrobial peptide expression, which are currently being developed in several laboratories, some of which are naturally-occurring products, could also be very useful for the treatment of the barrier problems in this particular age group.

So I'm going to move on now to the category of infants who are at the greatest risk, of course, and these are the extremely premature infants who formerly did not survive. Initially, they didn't survive because of problems with -- surfactant replacement was not yet available. Their lungs are just as immature as their skin. And now that they have surfactant replacement, these babies are surviving, and then the major dominant problem that's emerging in this age group is their immature -- their very immature skin. And they have essentially no barrier, which puts them at great risk for sepsis. The skin becomes a portal of entry (inaudible) innate immunity. They have even more problems -- they have a terrible problem with barrier function, so they're at risk for dehydration and hyponatremia. They get necrotizing enterocolitis due to rapid fluid shifts. Get intracranial bleeding due to rapid fluid shifts. And it

can even – (inaudible) patent ductus arteriosus can also be triggered by the fluid instability. So (inaudible) all these other problems in the premature infants, these serious problems ultimately come down to problems with their skin barrier. And they don't have a lamellar body secretory system, so it would not be useful to apply topical physiologic lipids, like ceramides, free fatty acids, or cholesterol to the extremely premature infant skin.

But what can we do? We can give them -- continue to treat them with the vapor permeable dressing equivalents, like petrolatums. We can continue to try to stimulate and accelerate epidermal maturation with PPAR and LXR activators. We can reduce the pH with the grass ingredient super acids, and we can do various strategies to improve innate immunity, which are still very early in their development. I won't say any more about those at this time, but if anybody would like to talk about that in the future, they're welcome to get in touch with me.
I think, Ivan, that's probably it for my formal presentation. I hope I've introduced people a little bit to the biological problems of the infant and premature infant skin, and I'd be happy to take any questions.

DR. BOYER: Okay. Thank you very much. Are there any questions for Dr. Elias?

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DR. MARKS: Peter, this is Jim Marks.

DR. ELIAS: You're welcome. Yes?

DR. MARKS: When you look at infant skin and neonate skin, not the premature child, and we look at applying cosmetics to that skin, is there anything that we should be overly concerned about? You talk about delayed barrier recovery and so on, but is there something unique either in the barrier or in the, say the handling of various cosmetic ingredients we should be overly concerned in the infant or the neonate that has normal skin?

DR. ELIAS: Well, obviously, you have surface area to volume issues that are very well described and documented in the CIR resource document. So anything that would have active ingredients in it, the active ingredient could be absorbed at substantially higher concentrations. I've seen that problem even with naturally-occurring ingredients that are considered safe, like propylene glycol that induced hyperosmolar coma in infants if it's in a skin care product in that particular age group. I think there would be probably other GRAS ingredients if we looked at the list carefully -- that we consider GRAS ingredients that might be absorbed and could -- you know, salicylic acid could induce salicylism for example.

So there would be other examples, I would think, that would become an issue in that particular age group. If there's a defective permeability barrier, there's also going to be an equivalent defect in the outside-in barrier in terms of molecules getting in, not just water getting out. Those two barriers are one in the same thing.

Dr. Belsito's Team

DR. BELSITO: So then, we're moving to the dermal penetration, absorption for neonates, Ivan's paper which is in the admin, correct?

SPEAKER: Page 62.

DR. BELSITO: Sixty-two, okay. So, I thought it was great. I do agree with Council's comments that there is no data to suggest that infant skin is more likely to be sensitized, at least not that I'm aware of.

And then I guess Peter sort of threw me a curve because when I read through this I was under the assumption that the barrier for full-term babies was as good as that for adults, and he seemed to be saying this morning that the pH doesn't get down to 5 until sometime after two years of age.

I don't know how we deal with the idea that damaged baby skin heals or repairs itself more slowly, because then there are -- I guess there are ingredients where we've taken away all the damaged skin, right, because PEG was the only one that we said that shouldn't be used on damaged skin, and we changed that conclusion.

MS. FIUME: I believe so. There may have been one more. I can't remember what it was, but it was very carefully worded on -- it was more broken skin rather than damaged skin.

DR. BELSITO: Right. Propylene glycol?

MS. FIUME: May have been propylene glycol.

DR. BOYER: And actually Peter, as I understood it, was saying that as far as the basal barrier is concerned, they have a fairly complete and full protection from that standpoint, but their barrier is more vulnerable to perturbation and to recovery from perturbation.

DR. BELSITO: Right. So, I guess the pH issue was -- but the pH as I understood it had to do not only with risk of infection but with absorption, right?

DR. BOYER: That's correct.

DR. BELSITO: It changes your relative absorption.

DR. SNYDER: (inaudible) delayed barrier repair once you damage the stratum corneum, that inhibits the repair of that.

DR. BELSITO: But as I read the document, and again I'm not a chemist, but high pH allows for more hydrophilic or hydrophobic to penetrate and the normal 5.5 is just the opposite. Is that not the case?

DR. BOYER: Yes, actually the pH is a very important element in the mechanism of the development of the skin barrier and the maintenance of the skin barrier, so if the pH is too high or if it's higher in neonates and infants than in adults, then that's going to have an effect on the effectiveness of the barrier. So, it's become known fairly recently that that is, in fact, a very important parameter to consider.

DR. BELSITO: But I guess my question is I recall reading something some place that pH also influences the absorption of chemicals through the stratum corneum.

DR. SNYDER: He related specifically to that (inaudible) lipase in the skin and its activity, so when you have an elevated pH, you have decreased ability (inaudible), right? Wasn't that? Yeah.

DR. KLAASEN: Yeah, that's what he had referenced to, but in addition to that, pH can alter the, you know, Henderson-Hasselbalch equation that you're going to have more or less than the lipid size before, so there's a couple things going on there theoretically.

But I think what he is saying that skin under two years of age isn't like an adult's, and while he's mainly interested in things like water going from the body out of the skin, he was saying that it's the same thing in relationship to -- the same parameters for getting things from outside of the body through the skin. So, I guess what he was saying, the bottom line is that skin of babies less than two years of age is more permeable to chemicals including chemicals that we have an interest in. Right?

DR. BELSITO: Well, potentially. I mean I think that basically, I guess, when we make a decision that something is not absorbed across cadaver skin or whatever model that we have used, and we're not looking for internal organ problems because it's not absorbed or we don't have that data, we may, if it's used in a baby product, want to consider that aspect a little bit more closely and look and see are there reports out there of a toxic end point or use in silico models like TopKat or whatever to look and see what the predictability is and not simply say, well, it's not absorbed and, you know, across human cadaver skin and let it go at that.

DR. BERGFELD: I thought an important aspect also was the absorption regarding body size and application.

DR. BELSITO: Well, yes. In fact --

DR. BERGFELD: -- as well as the pH, and I also thought as he was presenting that we were dealing with children two and above where they should be using cosmetics on their skin. Certainly those under should not be.

DR. BELSITO: No, that's not true. They do -- use baby lotions that aren't OTC.

DR. BERGFELD: No, looks like Vaseline is what they're using.

DR. BELSITO: Well, he's using Vaseline as a barrier, but I mean people are putting --

DR. WEINTRAUB: There's tons of baby lotions on the market.

DR. BELSITO: What?

DR. WEINTRAUB: There's tons of baby lotions --

DR. BELSITO: Yes, exactly.

DR. WEINTRAUB: Many baby lotions on the market.

DR. BELSITO: I mean you're sent home from the hospital with a little bag that contains baby lotion and talc powder that are not OTC diaper-rash creams.

DR. BERGFELD: Not talc.

DR. BELSITO: No, but anyway. Shampoo and, you know, so there are a ton of cosmetics that are used from the --

MS. FIUME: OTC's or cosmetics?

DR. BELSITO: Cosmetics. Shampoos aren't OTC. Soaps aren't OTC.

MS. FIUME: Are the diaper cremes because --

DR. BELSITO: Diaper cream

s, some of them are OTC.

DR. KATZ: Actually if the cream is being sold as a diaper cream, it would be OTC. If it's just a cream that one could use but it's not necessarily safe for diaper rash, then it would be cosmetic. Soaps may or may not be cosmetic, or they could be drugs depending upon what, again, is in the soap and what the indication is. So, some of them, if it's for cleansing only, it would be cosmetic. If it's antimicrobial, it would be a drug, so it really depends on what the product is.

And for shampoos, most shampoos, again, for cleansing would be cosmetic, but if it's to treat something like dandruff, and they go on to say seborrhea or anything else, then it would be a drug.

DR. SNYDER: So, I think Ivan did a really nice job with this. I think the preamble was a good idea. I

think we need to tweak it a little bit because a couple issues for me came up that appears to be that baby is defined as gestation date 34 weeks to 6 months, and so in our data collection we only have a category of baby use, and certainly I don't consider a 34-week as a baby. I wasn't thinking that until his presentation this morning because premature is 28 weeks to 34 weeks, and then an early-early premie or whatever he called it was before that. And so I don't think we're talking about -- I've never evaluated an ingredient based upon gestation -- nothing that was not out of the womb as far as a baby, but he used the classification. So, is that common? Thirty-four weeks is considered "baby" -- under definition of "baby?"

DR. BOYER: That's consistent with our --

DR. SNYDER: And then it goes up to six months, and then from 6 months to 2 years it's an infant. And so, do we collect data on baby and infant, because again, I think there functional differences with regards to the pH and the barrier in that window that we're talking about up to two years of age.

DR. BOYER: Also, another thing that you might consider is the development of the barrier function --It goes very rapidly very early on after birth, and so, it's more or less, you can imagine a curve that isn't steadily approaching adult levels over a two-year period, but over the first few weeks, or even within that first week after birth, is going to go up very quickly, and then more slowly, at a less rapid rate, is going to continue to develop over the six-month period until about six months of age. And then the changes, the development, is going to occur much more slowly until the end of that two-year period.

DR. SNYDER: So, I think your preamble needs to be expanded to include a little bit of this information about the barrier function in that up to 6 months, 2-year range, and then also about the pH changes because that does affect absorption, both ways as Kurt said, in or out. And so I think we need to capture that so we constant reminder of that.

But again, I'm not certain about the data that we're collecting, that you're collecting, Carol, in regards to the use category is baby.

DR. EISENMANN: The use category -- some the FDA developed a long time ago in the baby products, and that's the same -- we use the same terminology as the FDA product categories.

DR. BELSITO: So, that would zero to two; from day of birth to two years of age is a baby.

DR. EISENMANN: That's what I would -- for them.

DR. BELSITO: No, I mean, but as -- they don't have -- the FDA doesn't have an infant-baby whatever category. They just have a baby category, and that I believe is zero to two years of age. Is that correct?

DR. KATZ: It's my understanding for drugs that it is, although for certain areas they stop at about six months because that there's less difference between six months and two years, but I'd have to check to see. Again, we don't have that distinction for cosmetics, but it would be a distinction that drugs might make.

DR. BELSITO: Right, so baby -- when we say baby, that's the minute they're out of the womb.

DR. SNYDER: Until?

DR. BELSITO: Until two, six months, we don't know. But the bottom line is the more sensitive sub-population is the newborn, right?

DR. SNYDER: But I think as a resource document it's going to be important to us because we may make

certain interpretations if we do identify toxicities or concerns to -- you know, we may be more worried about up till six months, and after six months we may not be concerned. So, I think as a resource document I think you need to clearly capture the changes in the pH and the changes in that barrier function.

DR. BELSITO: I understand, but the bottom line is if we're not concerned after six months and concerned before six months, then we should say it's not safe in baby products, because you can't market a product, at least in my opinion, and say "should not be used in skin in children less than six months of age" and yet it's in a Johnson's baby shampoo, and in print say "Do not use on infants less than six months of age." I mean, that's not logical.

DR. SNYDER: No, I understand. But I think for us for interpreting data we have to --

DR. BELSITO: Yes, I think we need to look at that. We certainly need to be aware that when it says it's a baby product it's going to be used on a child two hours after it's born.

DR. SNYDER: Potentially, yeah.

DR. BELSITO: Yeah. On page 77 of your document, which by the way, Ivan, I thought was really good. Again, I would get rid of the sensitization, as I mentioned.

When you're going through the current scientific literature revealing no difference in physical chemical barriers needs to be tweaked a little bit with pH, as we just mentioned. It says "and some compounds may inhibit or induce bio-transformation enzymes in the skin as well as adults," And going through all of that, I would say something about the fact that we are aware that this population is going to have a greater body-surface-area to weight ratio, because we don't mention that again, and that needs to be factored in as well. So, not only do we need to be concerned that absorption may be a bit higher, particularly in the zero to six months of age, but what's absorbed is going to have a greater effect on the internal organs than it would on an adult simply because of the greater body-surface-area ratio. So, I would just throw a sentence in there someplace in that paragraph that we factored that in as well.

DR. BERGFELD: Do you want to throw in a sentence that caution should be given to the use of topical products in infants?

DR. BELSITO: No, because there are some topical products --

DR. BERGFELD: I said caution. I didn't say --

DR. BELSITO: But this is sort of a draft boilerplate that is for all --

DR. BERGFELD: Yeah, but we're going to have to be cautious.

DR. BELSITO: No, we're going to have to be cautious.

DR. BERGFELD: (inaudible) do that to tell you the truth. No data.

DR. BELSITO: But I think that would impact only when we were dismissing systemic data because of lack of absorption. Otherwise I don't think -- the other thing we would worry about it because of the pH we know that infant skin can be more irritable, so another reason if we're picking up any hints of irritation as with the alkyl phosphates that are used in baby products that we say when formulated not to be irritating, so someone is marketing a baby product, you know --

DR. BERGFELD: Do you think because of the importance of the issue that in our discussion when we're talking about irritancy, absorption, sensitivity that we should include some sentence about baby products?

DR. BELSITO: I think that when irritation is a factor and it's been introduced into our discussion, we probably should come up with some sort of boilerplate and penetration. Those would be the two issues, right? Penetration and irritation, so whenever we, in our discussion, are bringing up penetration, or lack thereof, as a reason for irritation as a concern, we should have a boilerplate that refers back to this document that these products are used on infant skin and --

DR. KLAASEN: A comment.

DR. BELSITO: Oh, okay. Sorry, I didn't mean to pick on Johnson and Johnson.

MR. MC CARTHY: Hi, this is Tim McCarthy, J&J, and you should pick on us because we make these products and that's why I'm here, and I thank you.

Doctor, to your point of using cosmetic products on very young children, for the very reasons that were discussed earlier, newborn skin is more irritant, more prone to infection, does lose water more rapidly. That's why we do make these products. Babies need to be moisturized because their skin loses moisture. Baby skin is more prone to irritation, therefore you have to be able to wash the dirt and the soil away, but you have to do it gently because the skin's -- that's why like the surfactant systems for our company are different, and the release criteria that we use for a baby product are different, than what we would use for adults.

For general population there's a certain standard that we all use, I think, as common practices. I'll speak for J&J and I'm sure my peers from other baby companies, there are other standards that go above that that we do for baby products.

DR. BERGFELD: Is that something we could reference?

MR. MC CARTHY: Yes, I could probably -- I can't say anything right now on the specifics, but I will go back to my professional communications. They have put slide decks together, talking to dermatologists, talking to midwives, and there are slide decks talking about why it's important to moisture a baby, why it is important to use gentle surfactants, why preservation -- thank you earlier for that, by the way -- why preservation is important.

The other thing I'll share, I don't know if I have it in a slide deck, and this is -- hit me for this because I presented it two years ago at SOT and I have yet to get it published -- but I did a pediatric dermal penetration study using porcine skin, four-day-old porcine skin, at which it's very simple. It's was caffeine and water, and I got -- I can put it flash right now and show the poster because it's been public two years. I need to get it out in a journal article. We're working on it now, but it did show four-day-old porcine skin. It did show an increase in caffeine dermal penetration, but it wasn't like an order of magnitude. It was like a doubling of the dermal penetration, and so it appears that did not violate the cosmetic directive on animal testing. We made sure of that, how we did it. But I could share it with you. We do have the data on that, and hopefully in a couple months we'll get that published.

DR. BERGFELD: Now, when you say that you used different surfactants, are you using different concentrations of surfactants or different surfactants?

MR. MC CARTHY: Well, it is -- we in the past have used more (inaudible) than SLS, for example. We've got, because of the (inaudible) issue, we've gotten away from that, but it's not just -- there shouldn't be a focus on this surfactant's good and that surfactant's bad. It should be how you formulate it and then how you test it to make sure it's ultra-gentle. That's the criteria. It's not the -- the selection of raw materials aren't critically important. It's the

balance of them and then the release criteria of what you do for baby products verse an adult product that's really critical.

DR. BERGFELD: We would appreciate any information you could supply us.

MR. MC CARTHY: Sure, I will gladly --

DR. WEINTRAUB: Just one point of clarification. So, my children are older now, but I recall that each time I had a baby, the pediatrician said not to moisturize their skin when they were very young and not to use anything, if possible. So, I don't know if maybe we should look to the American Academy of Pediatrics to see what their recommendations are because that was certainly very clear from pediatricians when you have a newborn that even using diaper cream should only be used if necessary. That really, there shouldn't be any lotion or cream used, so I don't know if that's a distinction.

DR. LIEBLER: In Dr. Elias's presentation, I think, for an almost all of his -- when he had the management slides -- in almost all of those, except for the extremely premature, it was edited with "dry, dry, dry."

DR. WEINTRAUB: Yeah, right.

DR. LIEBLER: And I'm trying to reconcile that with your comments. I'm not sure if they're really at odds with each other or not, but it sounded more like what you're just saying, and this is not my area at all, but I was struck by "dry, dry, dry" on all those slides.

MR. MC CARTHY: I think Doctor, dry that's -- Don may be able to help, that, particularly with the diapering area, where cloth diapers verses the synthetic material, the polyacrylate ones. The whole point of polyacrylate is to wick away to keep moisture being occluded against the skin or in the folds of the skin. But you definitely want to make sure that the skin is not dry so there's far more evaporation. I think that's what we're talking about.

And where he said with petrolatum, that's an occlusive barrier, and that's what they're talking about, so we're not talking about pools of water. We're not talking -- obviously cleaning, like, formula from the folds of skin is very important, but part of that, what he was saying about petrolatum is because the higher transepidermal water loss of a newborn.

And I've got to say in comment to that, petrolatum -- couple things about it. It's not completely innocuous. It is also -- does get through the skin, and that's even adult skin. You can find petrolatum does permeate the skin, and so we --

DR. BERGFELD: Does it accumulate in the lungs?

MR. MC CARTHY: That I do not know. That I do not -- but it is systemically absorbed, that's why I do not know that if it goes from that data.

And the other thing, too, is when you face it, like if you grease up a little baby with petrolatum that would be a difficult thing to pick up (laughter), so let's -- yeah, I'm a little bit too -- I'm not a big advocate --

DR. BERGFELD: You can close on that, right?

MR. MC CARTHY: Okay, well, okay, but thank you. Yes, I will go back the office and see because we put professional communications to it and what you're saying also, A1, there's several midwife organizations and pediatric nursing organizations that set up guidelines on first bath that we could definitely work (inaudible).

DR. BERGFELD: Are all those guidelines following some kind of science or are they just good-thought guidelines?

MR. MC CARTHY: We have provided science on that. Again, what is the transepidermal (inaudible)? That came in when the things -- we have researchers that were in the summary document that you have here. I'm looking at the transepidermal water loss on newborns, and even transepidermal water loss on the buttocks, under the diaper versus the thigh versus when the baby has diaper rash, and obviously with the diaper rash there's a lot more transepidermal water loss in those babies.

DR. BELSITO: Well, what I take away from Peter and dry, dry, dry and petrolatum was he was talking about atopic kids. I don't think he was talking about the general population. He was talking about using petrolatum to help the barrier in children who have atopic disease, which is what we do.

In answer to your question, Rachel, I just Googled The American Academy of Pediatrics and moisturizers, and the only thing that I can get is they actually recommend twice-a-day moisturizing for children with atopic eczema. Otherwise it doesn't appear that they have a standard saying you shouldn't or should.

The only other thing they say that would regard what we do is that if your child is less than six months of age and sun exposure is unavoidable to use zinc oxide, titanium dioxide rather than chemical sun screening. Those seem to be the only two things that they're saying about topicals and infants, so they don't seem to have a position.

DR. WEINTRAUB: I wonder if it's not publicly available because it was very clear as a parent of a newborn I was strongly recommended not to use lotions.

DR. KLAASEN: But that could easily -- I don't know anything about this area, but this could be very pediatrician dependent. The question is all these recommendations (inaudible) or is it based on science, and I don't know the answer to that question.

MR. MC CARTHY: I can go back again, because my company does work a lot with nurses on pediatric wards, midwives very huge in the Commonwealth. I found out working here that it doesn't matter what the doctor says in the Commonwealth. It matters what the midwife says. I learned that. And so those organizations, we could try to get those guidelines together for you on dealing with what's first bath, first moisturization.

DR. BOYER: Thank you, and we can approach Dr. Elias and get some clarification on just exactly what he meant, so I can ask him some questions.

DR. BELSITO: Right. So, I mean what I would like to see clarified is when he said, "dry, dry, dry," was he recommending that you dry baby skin ,because my understanding was that what he was saying is 20 to 30 percent of infants or children, babies, will develop atopic eczema by the time they're three months, six months of age, and their skin is dry and we use petrolatum because there are no fragrances and there are no preservatives and there are none of these things that we're concerned about them being allergic to. And not that he was saying that you want to dry baby skin, because I would disagree with that. I don't think you want to dry baby skin.

DR. BERGFELD: He has one of his slides here, "keep dry."

DR. BELSITO: Well, that's diaper area.

DR. BERGFELD: We better clarify that.

DR. BELSITO: I think "keep dry" he meant diaper area because of pH and infection. I don't think he's

telling us to put our kids under blow dryers.

DR. SNYDER: If we could go to page 77 you were on before -- of that document.

DR. BELSITO: Yeah.

DR. SNYDER: And the paragraph that begins, "the panel concluded that the information currently available."

DR. BELSITO: Yeah.

DR. SNYDER: So, I think it has to be completely rewritten now because I think there are differences.

DR. BELSITO: Right.

DR. SNYDER: So, that conclusive statement -- that paragraph there has to really be polished according to the -- to note differences in the barrier and the pH and how that affects activation of the biotransformation enzymes and things like that, so I think we just need to capture that because here we say there's no differences.

DR. BELSITO: Right, that's what I said when I started that he sort of threw me for a loop with his presentation today because, based upon everything I had seen up until now, I thought that was true. So, there are differences, and I mean what we need to tweak is say that the basic physical-chemical barrier is intact, more easily damaged, takes longer to repair when damaged, has a pH that doesn't get to adult level till sometime between six months to two years of age, that that time, he said, seems to be very variable, and what that pH means, that the -- in terms of phospholipases and the detoxification mechanisms. So, yeah, I mean, I think we need to rewrite that based upon his comments today, and probably send him back to it and ask him for his comments and make sure that we captured everything correctly, because there was that 10-minute interlude when he was talking on the same slide and, like everyone else in the room, I was trying to figure out where he was, and I don't know that I processed all the data or everything that he said during that time.

DR. BERGFELD: It seems to me that we'll have to have another pass at this at the next meeting, to tell you the truth. We have to have some questions answered, get some other data in, and so I think this is a good working document. Thank you.

DR. BELSITO: Yes, any other comments? So then the BSA [body surface area] to weight ratio should be in that paragraph some place too. Get rid of the increased sensitivity. I don't know that that's ever been shown, that babies are more likely to be sensitized, and just, other than that, some typos on my part. Okay. Yes, Monice?

Ms. FIUME: Can I ask then, as far as the discussion, the boilerplate on baby's skin, are you going to address that now?

DR. BELSITO: Yes, we can, because I had some comments here on that. So, in the discussion boilerplate --

DR. BERGFELD: I don't have the -- I have a Word document. Let me see if I can find it in the admin document.

DR. BELSITO: I just thought that, in the boilerplate discussion, it says that, when we're talking about biotransformation pathways of an ingredient, to indicate whether there is reason to be concerned about the potential metabolism and likely metabolites, I thought we should add looking in the liver or other internal organs and specify.

DR. BERGFELD: It's PDF page 31.

DR. BELSITO: PDF 31, so just saying, like, there may be available unknown or likely biotransformation pathways in the liver or other internal organs, because we don't specify where we're looking, and yet the document, we're really basing it off the liver, which is the one that's really been studied. And then the caveat, well, we really don't know if the enzymes in the skin develop along the same time for us. We're sort of working on the assumption that they do, but we don't know, but there may be data on the development of pathways in the kidney or something that we could use as well. Otherwise, I had no comments on the boilerplates.

MS. FIUME: Should there also be a statement about the body-surface-area to weight ratio?

DR. BELSITO: Yes.

DR. EISENMANN: I just wasn't sure when this would be used in a report?

DR. BELSITO: It would be used in a report, I think, again, this particular document, when absorption was not considered to be an issue in adult skin, but we felt could be an issue in infant skin, wouldn't you want to use something like this? Because we talk about, okay, things may get through more easily, but then once they get through, the development of the dermal capillary system is delayed, so that gives, on the other hand, less an option for what gets through to get absorbed. But then we have a greater body-surface area, so what gets through is going to get poured into something that's smaller than in an adult. So, I think all of that would come in primarily when absorption was an issue. If it wasn't an issue, we probably would not need this type of boilerplate. We certainly wouldn't need it for irritation, at least not as extensive. So, maybe there should be two infant-skin boilerplates; one for irritation and one when -- because the two areas we're concerned about are irritation and absorption, so there should be one for documents where we're concerned about absorption and one for documents when we're concerned about irritation.

DR. BERGFELD: The other thing, it will be like the white paper that we have for hair dyes that has to be looked at every couple years and updated, and it serves to be a reference document that we can go back to, and it also is mounted on the website.

DR. BELSITO: Anything else?

DR. LIEBLER: No.

DR. BERGFELD: Nice work though.

DR. BOYER: I wonder if we could get your take on whether or not we should be addressing susceptibility to carcinogens in this particular document or in a separate document? This was actually included -- incorporated into this report, this version, that we've incorporated at the request of Dr. Slaga, and the Council's commented on that as well.

DR. BERGFELD: It was negative though, was it not? I mean as I looked at it --

DR. BOYER: For promoters they -- neonatal skin doesn't seem to be particularly sensitive, in general, but for initiators, they tend to be relatively sensitive for that mechanism.

DR. BERGFELD: Completeness.

DR. LIEBLER: I think it's fine to have that in there. It's two paragraphs. There's a lot of uncertainty, because of the question about the ability of infant skin to bioactivate carcinogens, so if there's no initiation, promotion is irrelevant, but it's worth saying it's considered. These are the factors that might affect it, so I think it's okay to leave it in. Would the Council want to take it out?

DR. EISENMANN: Well, it didn't match the previous title. Now it provides the title. It's --

DR. BELSITO: Before the title was just dermal penetration. Now it says another, something or other -- what's it say?

DR. EISENMANN: And other considerations (inaudible).

DR. BELSITO: And other considerations, right.

DR. EISENMANN: So, it's and other considerations,, so you revised the title so it's not as much of an issue.

DR. LIEBLER: Okay, I think it's appropriate.

DR. KLAASEN: Yeah.

DR. BELSITO: Okay, any thoughts? Yeah, Monice?

MS. FIUME: Before, I'm guessing you were going to get to priorities. This conversation was for the infant skin as well as the full boilerplate document. If there's anything in particular you have that you'd like to point out, or unless there's -- maybe it's just in your notes, that's fine, but I didn't know if there was anything that needed to be brought up now.

DR. SNYDER: You've got to make sure parallels some of the stuff, because you don't have in here the pH stuff and what I think (inaudible).

DR. BELSITO: Right.

DR. SNYDER: I think you just -- I think it could actually be reduced down a little bit to talk about the diffusion barrier and the physical-chemical composition of the barrier related to biotransformation activities or something like that, so I think there's -- your boilerplate could actually be reduced down.

And then I think it would have to be tailored like Don said, if there's general absorption then we may expand on it a little bit, but talk specifically about exposure to enzymes that metabolize things and more toxic things and stuff like that, so I think that, from the other standpoint, I think it would be actually smaller.

MS. FIUME: And I was talking the whole boilerplate document as well, if you have any specific comments. I know the Council's going to comment in the 60-day comment period. They had submitted some comments but they're going to comment on it. I didn't know if you had anything that needed to pointed out or just --

DR. BELSITO: So, we're talking about not just infant skin. We're talking now about the boilerplate separately, so I need to close out of infant skin and go to boilerplate.

Dr. Marks' team

DR. MARKS: Next on the agenda, we need to go the (inaudible) administrative document, and we have infant skin, and hair dye and priorities.

DR. HILL: We are going to have to log (inaudible)

DR. MARKS: And I think that finishes what we have to evaluate --

SPEAKER: In the report?

MS. FIUME: Yes. They are in Table 2.

DR. HILL: Are we back on the one we were just looking -- on admin?

DR. MARKS: No. That's sounds like -- Tom, what did you have a question about?

MS. FIUME: To the very bottom of the page.

DR. MARKS: Are you okay, Tom?

DR. SLAGA: Mm-hmm.

DR. MARKS: So shall we go page 38 on the admin, is the memo from -- I think, it's admin, isn't it? Let me pull it up. Yes. And then let me go to -- the conclusion was on page 76, the draft is on page 60, so which one of these do we want to focus on?

Discussion and conclusions, the Expert Panel concludes that stratum corneum provides an effective diffusion barrier of both, or within a few days of birth. Absence of capillary loops until about two weeks, will reduce the rate of systemic absorption, for information on biotransformation -- I don't think that was addressed much this morning in there by Dr. Elias. The Panel concludes that the information of available on scientific literature, there's no differences in the physical-chemical of biotransformation process in the skin. This suggests that neonates in infants will [not] exhibit unique toxic effects, that would not also be detected in adults of (inaudible).

Then Ivan goes on to talk about margin of safety estimates. So Ron, and Tom, I know we are going to see another format of this probably after today's. But did I capture the highlights, Ivan, of what you --

DR. BOYER: Yes.

DR. MARKS: -- wanted to --

DR. BOYER: Yes. Yes. It's all pre Dr. Elias' presentation (inaudible).

DR. MARKS: Yeah. Exactly. And he defines of course infants and neonates -- he didn't talk about the capillary loops at all.

DR. BOYER: No.

DR. MARKS: What did you hear Ivan, since you are the in-house expert now on infant skin, from Peter, that might change the way we work, can I put you on?

DR. BOYER: Well, he was not so emphatic that within just a week or two the infants have -- neonates and infants have a barrier that is equivalent to an adult epidermal [barrier], starting to (inaudible). And he -- actually I think, based on what he said, was that the window is broader than that, and it really takes up to two years of so, before you get something that is equivalent to the adult, or close enough to the adult, to say that they are equivalent.

And, you know, I think what you get is a fairly rapid development of the epidermal barrier early on, right after birth, and that rate more or less plateaus probably fairly quickly. But it continues to -- it continues to rise, and continues to develop over the course of that two- year period. So I think that what we probably have to do is change the discussion, and change of the language in the background document to reflect that.

DR. MARKS: Tom? Ron? Ron? Does it affect what we do? And our conclusions, kind of interesting because I didn't ask Peter Elias if this -- if he thought about it, and then he got on to other things, but I believe that if you look at (inaudible) folders, that many of them will say don't use until six months of age, and I wonder if that's because of the issue of the barrier. If I heard incorrectly, like you said, Ivan, within two, three weeks, it has really gained a great deal, and any after that, it's a slower progress, and it sounds like six months it was pretty much, where an adult might be.

DR. BOYER: Yeah. And he also mentioned the term basal level, so.in neonate, in an infant, very, very rapidly achieved a sort of basal level of a barrier, which is more vulnerable to perturbation, and it's also more [vulnerable] -- essentially more time to be repaired once it has [been]-- perturbed, so that's something else to consider.

DR. HILL: And the diaper area and (inaudible) skin are something we've talked about before, and the nappy area, as (inaudible) call it.

DR. MARKS: And he addressed that. We know that oftentimes you are dealing with damaged skin layer, so we are talking about application of personal care products on normal skin, and it's a little bit different. Not only do you have damaged skin, but you also have occlusion, so you are really, potentially driving ingredients into the systemic circulation, and potentially, also, increase the sensitization.

What was your reaction? Again, maybe you've done this before, Ivan, but I think the purpose was to try and get a handle on either significant toxicologic concerns in the neonate, in the infant, that when we make a conclusion that's safe, we don't separate out “except for infant skin,” or something like that.

DR. BOYER: Right.

DR. MARKS: And the purpose -- the purpose of this review is to try and be sure we are not missing something in infant skin, say, or neonatal skin, [that] would make us much more cautious. Is that correct?

DR. BOYER: Not necessarily much more cautious, but to make it clear what the considerations are, when neonates and infants are exposed to personal care products.

DR. MARKS: And any comments about the document, or? I know we are going to see another rendition of it. Ivan, you've done a great job. I know you addressed some of the concerns by the Council also in this.

DR. BOYER: Well I -- I thought it was good to refresh our memories on all those things, and some of the things, obviously, you haven't -- I haven't studied in the past, but I think it's a very nice document, I mean, it's evolving to be even better, so.

DR. MARKS: Any other comments? So I think --

DR. SHANK: It's very helpful to have this. It's very well done, thinking back over the many, many, many hundreds of ingredients we have reviewed, where the use includes applications to babies, we have been consistent with the adequate safety evaluations considered for babies, and this reinforces that.

DR. MARKS: Okay. Any other comments? Yes?

MR. McCARTHY: Can I answer this?

DR. MARKS: Yes. Absolutely. Come on up to the microphone so we can get it recorded.

MR. McCARTHY: Yes. Thank you. Yeah. I'm just saying I shared with Dr. Bledito’s group as well (inaudible). I'm Tim McCarthy, I'm with Johnson & Johnson, and support babies. So I was listening on both sides, and I also want to comment on some of the things you had mentioned with -- that Dr. Elias had said.

First of all with, like the diaper and occlusion, I hope you can bring -- try to get P&G to comment on that one, because the polyacrylate, poly -- the super absorbent diaper material, from my understanding; and I'm not the expert, P&G is, is actually wicking. So cloth diaper -- wet cloth diaper is really bad on the baby's skin, because you are just leaving a damp surface, and that's what Elias was saying about dry, dry, dry. You don't want to leave a wet cloth diaper on a baby's skin, because while the polyacrylates actually wick moisture away.

So it's not as occlusive, I don't believe, as you might think. And again, I think -- and again, I think P&G needs to comment on that. A couple things as well, with agreeing, also, with what Elias had said, about baby's skin has higher evaporative properties to it. It loses more water, and that's why -- so one of the things I mentioned to Dr. Bergfeld when she was asking was, knowing what we do know about baby skin, you do need to moisturize a baby's skin, because it loses more moisture very quickly.

You do have to cleanse the baby's skin, but when you cleanse it, you have to be careful of all these things. It is more fragile when it comes to irritants, and so -- and you don't want to dry it out, you have to watch that pH -- that pH that is developing. The (inaudible) is very important, and so it's not a matter of these ingredients are good, these ingredients are bad; often times it's how you blend them, and then the testing criteria that goes into what we would do for a baby product, above and beyond what we would do for an adult product.

What I told Dr. Belsito as well, I had already communicated after the last session with Dr. Belsito's group, we worked with the Midwives Groups. We worked with Neonatal Nursing groups, of setting up bad baby practices, so it wasn't so much based on folklore, which is out there. And I'll tell you, there are pediatrician groups who don't want you to use anything, and we are trying to show them, with data, what is appropriate when it comes to moisturization, what is appropriate when it comes to washing a baby.

And so we will be sharing that -- our interactions with some of these professional organizations. And I'll get to Carol, who will give it to Ivan. That's the (inaudible) of these things.

And the thing about, with petrolatum, and I get why you're saying petrolatum, because -- and I think you were using it for a -- particularly for a pre -- (inaudible) babies. I understand, to get the occlusion you want to keep the moisture in there, but also, petrolatum doesn't penetrate. It's not this inert film that forms on the stratum corneum, there is data that petrolatum does penetrate the skin so -- and can therefore get (inaudible), so.

And my concern as well, is when you start to rub a baby with petrolatum do you want to pick that baby up, so. But we had -- we have practices and why the basic research that was in -- that Johnson & Johnson did that was in Ivan's presentation of why you have to moisturize, why you have to wash.

And the other thing I was sharing with this, and this is my (inaudible) two years ago, I did a very preliminary work with caffeine and water, and I did a pediatric course skin model. So, a four-day-old -- four-day- old pig's skin pulled from a breeding colony, and we are looking at the dermal penetration of caffeine.

And it was increased. We did -- the four-day-old skin versus adolescent pig's skin, versus adult human cadaver skin, and there was an increase, but there wasn't an [order of]-- magnitude of increase in skin [penetration], it was like two to four times higher.

And we are trying -- when I'm not doing my day job, I'm trying to get that published, but I'll have -- I have the (inaudible) right now, and I'll make sure Ivan gets it by the end of the week.

DR. MARKS: Okay. Thank you. Do you have a reason why J&J has (inaudible) or to some (inaudible) companies, why six months was chosen?

MR. McCARTHY: -- You know it's --

DR. MARKS: Or is that?

MR. McCARTHY: -- first of all we do follow -- we do follow American Academy of Pediatric

recommendations, we follow globally. And I'll say that first, I mean, not just in the United States, so that sunscreen use is the third of three. Keep the baby out of the sun.

DR. MARKS: Right.

MR. McCARTHY: Cover the baby, and on exposed skin, sure put sunscreen on. And then if he does go to the next step, and Dr. Belsito pointed this out, because he just Googled the term in the meeting, that they preferred the metal oxides, because they are known to sit on the top of the skin. My understanding of that was actually my prior company, and it was verbal tradition given to me, I didn't have empirical data, but the reason was, it had nothing to do [with] chemical toxicity.

It's that if the baby does not have the formal regulation mechanisms in the skin, and the baby can't just crawl away when it gets too hot, so you don't want to slather a baby up, and sit it out in the sun, because it might die of something other [than] chemical toxicity. And that's the main reason that we shouldn't be putting it on.

DR. MARKS: Okay.

MS. GILL: So this is like behavioral phase. If you put it on the baby (inaudible) --

MR. McCARTHY: Yeah, and it should not be a panacea. Yeah, exactly. You don't want to slather the baby up and go, I'm done. I'm a good mom, I did my job, my baby is going to be fine. No, your baby is not going to be fine sitting out in the heat like that. That's the -- the verbal history that was given to me in a prior job, which also is a major sunscreen manufacturer in this country, so.

DR. MARKS: Okay. Thank you. The record said, it's Belsito, it's the team, the other team.

MR. McCARTHY: Yeah. Thank you.

DR. MARKS: On Belsito with that. Okay. Any other comments about the infant skin? If not then -- Ivan, did you have any questions, queries for the team?

DR. BOYER: No. Nothing for me. I think we are good.

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DR. BERGFIELD: …Do we need to go forward with the infant skin? Any kind of comments on the infant skin, since we've had a full discussion of both teams on the infant skin manuscript and the changes that will be made after the presentation by Dr. Elias? Ivan are you around?

DR. BOYER: Yes.

DR. BERGFIELD: Do we need to do anything else as a panel?

DR. BOYER: I think we are pretty clear. We have some marching orders and we can go forward. If we have any additional comments, we'd be glad to entertain those as well.

DR. BERGFIELD: Well we have one additional comment and that is to thank you for a magnificent piece of work, and the modifications will be an enhancement of what we do, so thank you…

COSMETIC INGREDIENT REVIEW

CIR Resource Document

Dermal Penetration, Absorption, and other Considerations for Babies and Infants in Safety Assessments

09/2014

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1. Introduction

1.1. Preamble

The purpose of this report is to serve as a resource document to which the CIR Expert Panel will refer in safety assessment reports when appropriate. This report summarizes and evaluates information gathered from the scientific literature that compares the potential for the systemic absorption of ingredients of topically-applied cosmetic products in babies and infants, with the potential for systemic absorption in older children and adults. Among the topics addressed here are the development of the diffusion barrier of the skin, which is largely attributed to the *stratum corneum* (SC), and the development of biotransformation capacities of the skin, which can also influence systemic absorption through the skin. In addition, this report addresses some of the issues that the CIR Expert Panel considers when assessing the safety of cosmetic ingredients used on children.

The focus of this report is on the barrier function of the skin in normal, full-term babies and infants compared with that of adults. The primary issue addressed is whether normal, full-term babies and infants have unique susceptibilities to topical exposures to cosmetic ingredients, because of differences in the diffusion or functional barriers of the skin, compared with adults.

For example, the solubility, and thus the rate of percutaneous absorption, of weak acids and bases in aqueous solutions will generally depend on the pH of the solution, as described by the Henderson-Hasselbalch equation. However, the natural pH of the skin is a critical parameter that determines the permeability of the skin. The decrease in skin pH that occurs especially in babies from birth to about 6 months of age, which may continue up to 2 years of age, can help to explain, in large part, the corresponding decrease observed in the potential dermal absorption of many substances, including ingredients (not limited to weak acids and bases) of topically-applied cosmetic products. The CIR Expert Panel considers such factors in cosmetic ingredient safety assessments when appropriate.

It is important to emphasize, at the outset, that cosmetic products are intended to be used on healthy, intact skin. Accordingly, the purview of the CIR Expert Panel includes assessing the safety of cosmetic ingredients applied to normal skin, and not to damaged or diseased skin. For example, over-the counter (OTC) and prescription products used to treat atopic dermatitis or diaper rash are regulated as drugs by the U.S. FDA, and should be used under medical supervision; ingredients as used in such products are outside the purview of the CIR Expert Panel. The Panel acknowledges that some cosmetic products could be confused with OTC products for treating diaper dermatitis. However, the focus of the Panel is on assessing the safety of ingredients as used in cosmetic products, not in prescription or nonprescription drugs.

Further, this report does not address the potential for enhanced penetration or systemic absorption of ingredients of topically-applied products through the skin of pre-mature neonates. Cosmetic products are not intended for use on pre-term neonates, whether or not they are also pre-mature.

Finally, this document does not provide a detailed account of the Panel's approach to addressing the greater ratios of body-surface area / body mass of babies, infants, and young children compared with those of adults. The CIR

Expert Panel recognizes that babies, infants and children represent a distinct subpopulation for risk and safety assessments, and routinely considers the greater skin-surface area to body-mass ratio in children when performing cosmetic ingredient safety assessments.

1.2. Age Groupings

Children and adults can be grouped approximately as follows, based on anticipated differences in development, susceptibilities, and exposure characteristics, and a variety of similar groupings given in the literature.[1-6] The following groups are recognized for the purposes of this resource document:

- Neonate (newborn)
- Baby (birth up to 6 months)
- Infant (6 months up to 2 years)
- Preschool (2 years up to 6 years)
- Preadolescent (6 years up to 12 years)
- Adolescent (12 years up to 18 years)

Neonates can be pre-term (i.e., born at estimated gestational age, GA, < 37 weeks; 9¼ months) full-term (GA 37 to 42 weeks; 8½ to 10½ months), or post-mature (GA > 42 weeks; 10½ months).[7] From the biological (as opposed to biophysical) perspective, pediatric dermatologists refer to children from birth to 6 months of age as babies and from 6 months to 2 years of age as infants.[6]

1.3. Anatomy of the Skin

The skin, in cross-section, has three distinct, primary layers or regions, including the epidermis, the dermis and the subcutis or hypodermis (see illustrations: Integumentary System, Structure and Function of the Skin, or The Integumentary System). The epidermis is the outer layer of the skin, which can vary in thickness from ½ mm on the eyelids to 1½ mm on the palms and soles. The epidermis contains connective tissue, hair follicles, and sweat glands. The five layers of the epidermis include (from outermost to innermost) the *stratum corneum* (SC), *stratum lucidum*, *stratum granulosum*, *stratum spinosum*, and the *stratum basale*. The outermost layer, the SC, consists of corneocytes (i.e., fully mature keratinocytes that originate and migrate from the *stratum basale* to the SC), which are enucleated, packed with keratin, highly interlocked with one another, and embedded in an extracellular hydrophobic lipid matrix.

The dermis, which lies beneath the epidermis, contains collagen and elastic fibers, as well as the dermal vasculature, lymph vessels, and nerves. The dermis projects into the overlying epidermis in ridges called papillae in the outermost (papillary) layer of the dermis. The epidermal swellings that project downward between the papillae of the dermis are called rete ridges (see illustration: Structure and Function of the Skin). Sweat glands and sebaceous glands lie in the deeper (reticular) layer of the dermis.

The hypodermis, also called the subcutis or superficial fascia, is a layer of subcutaneous tissue beneath the dermis, consisting of a network of collagen and fat cells that provide a cushioning function, among other functions.

1.4. *Stratum Corneum* (SC) and Significance of Body-Surface / Body-Mass Ratio

The outermost layer of epidermis, the SC, is generally considered to be the primary rate-limiting barrier to loss of water from the body, the absorption site of most topically-applied substances, and a significant route of systemic exposure to microorganisms in full-term neonates, babies, infants and adults.[8-18] In comparison, the layers of the epidermis and dermis under the SC, although much thicker than the SC, offer little resistance to the evaporation of water or the systemic absorption of toxicants.[9]

The SC is a tough, cohesive layer composed of flat, enucleated cells lacking energy-dependent synthetic capacity, corneocytes packed with the fibrous protein keratin and held together by a lamellar matrix of an extracellular lipid mixture of ceramides, cholesterol, and free fatty acids.[10,18-20] The SC is often thought of as a passive, inert barrier to the diffusion of water and other substances through the skin.[9,10,12,17]

The importance of the barrier function of the SC is magnified in babies and infants.[8] Percutaneous absorption and systemic exposures in babies and infants are generally assumed to be greater than in older children and adults because of the immaturity of the skin as a barrier to absorption (higher pH of the skin yields decreased barrier function and increased risk of irritation) and the greater body-surface-area to body-mass ratio of babies and infants compared with older children and adults, among other reasons.[2,21-24] For example, neonates have approximately three times the body-surface-area to body-mass ratio of children about 13 years old.[24]

The default inter-individual uncertainty factor of 10 routinely used to evaluate margins of safety (MoS) estimates in safety assessments is generally considered to be adequate to address potential differences between children and adults in relative absorption through intact skin.[23,25-28] However, an additional safety factor may be considered if there is data indicating that the inter-individual variability for a specific ingredient may exceed a factor of ten.[24,29]

2. Development of the Skin

The development of the skin is not fully complete at birth. Parturition and early postnatal life involves a rapid adaptation of the skin to life outside the uterus, including maturation of the structure and function of the skin, which begins during the third trimester (28-36 weeks; 7-9 months) of pregnancy.[7,10,30]

2.1. Skin Function and Physiology

The physical barrier properties of the skin are generally considered to be located almost entirely in the SC, and dependent on its thickness and integrity.[31] The viable epidermis below the SC continually replenishes the SC by cell division in the basal layer.[31] When the mitotic rate of the basal layer increases, because the skin is damaged for example, there are two histological changes: (1) the basal layer increases in area and heaps up to form undulations (i.e., the rete ridges) of the dermal-epidermal junction, and (2) the epidermis becomes thicker as the number of keratinocytes increases, especially in the *stratum spinosum*, and the keratinocytes differentiate and migrate into the SC.

The complex protective barrier of the SC is made up of lipids synthesized by the epidermis and natural moisturizing factors (NMFs), known as the hydro-lipid system.[31] NMFs are hygroscopic substances in the SC involved in water binding within corneocytes.[32]

2.2. Development of Epidermis and Dermis

The coordinated development of the dermis, epidermis, and associated tissues begins during the first trimester (around the 2nd month of gestation).[9,32-34] The following subsections provide additional detail.

2.2.1. Stratum Corneum Development

The development of the SC begins during the third trimester, around week 24 (month 6) of gestation, and continues through weeks 32 to 40 (months 8 to 10).[9,12,18,35-39]

2.2.2. Gestational Age (GA) 24 Weeks (6 months) to Full-Term Birth

The cellularity and thickness of the epidermis steadily increase from gestational week 24 (month 6) to term. Before GA 30 weeks (7½ months), the epidermis is thin and is characterized by few cell layers, barely perceptible rete ridges (i.e., the undulations of the basal layer of the dermal-epidermal junction), and a poorly formed SC.[31] Well-defined rete ridges and well-developed SC appear around the 34th week (8½ month) of gestation.[9,18,31,32] The barrier function of the skin at 34th weeks (8½ months) of gestation is comparable to neonates.

The vernix caseosa develops at the end of the third trimester, coincident with terminal differentiation of the epidermal keratinocytes of the SC.[18,23,32,40-43] The vernix caseosa is a protective hydrophobic biofilm (i.e., hydrophobic mantle) containing fatty acids, squalene, wax esters, triglycerides, cholesterol and ceramides.[7,18] The vernix caseosa does not directly contribute to the barrier function of the skin, although it contains some lipids that help maintain hydration levels of the skin, and may have some antimicrobial properties as well.

2.2.3. Full-Term Birth to Two Years of Age

The full-term neonate has all of the skin structures of an adult, and these structures do not undergo substantial changes after birth.[4] The epidermis continues to thicken for about four months after birth, attributable primarily to the proliferation of cells in the basal layer, which causes a mounding or heaping of that layer and a corresponding deepening of the rete ridges. However, the SC of the full-term neonate is remarkably capable of fulfilling its key functions soon after birth, especially that of providing an effective semipermeable diffusion barrier between the inside and outside of the body under basal conditions.[23]

On the other hand, the skin of babies and infants is continually adapting during the postnatal period, in a manner that optimizes the balance among growth, thermoregulation, and the water-barrier and protective functions of the skin, in contrast to the relatively steady-state of adult skin.[4,12,18,32,43-46 35,43]

As noted above, full-term neonates are born after 37 weeks GA. Premature neonates born after 34 weeks GA generally have dermal barrier functions similar to full-term neonates and babies up to 6 months of age.[6] The skin of infants is relatively mature, compared to the skin of babies, but does not yet function as a fully-mature permeability

barrier. As explained below, the immaturity of the barrier in babies and infants can be largely attributed to the elevated pH of the skin, as well as to the super-moisturization of the skin in the diaper area and body folds. The normalization of the pH of the surface of the skin, and thus the maturity of the barrier function of the skin, is largely complete by 6 months of age, although in some individuals there may be a further decline in surface pH and improvement in barrier function between 6 months and 2 years of age. This factor helps to explain why babies and infants continue to have increased risk of dermatitis and infections and why they recover more slowly from damage by exposures to irritants.

There are exogenous and endogenous dermal acidifying mechanisms in the skin, which are responsible for the development and maintenance of the skin's protective "acid mantle." The major acidifying mechanism that is immature in neonates is the endogenous secretory phospholipase A2 (sPLA2) mechanism, which breaks down phospholipids to release free fatty acids (FFAs) in the skin.[6] Delayed maturation of the barrier function of neonatal skin is attributable to the low expression and activity sPLA2). As the expression and activity of these enzymes increase in the skin after birth, they yield free fatty acids that acidify the skin and contribute to the barrier function of the skin.

When the barrier is compromised in babies, the pH of the skin increases, and this increase activates serine proteases (SPs) that release pro-inflammatory cytokines, which helps to explain the increased tendency for dermatitis and other types of inflammatory reactions.[6]

The barrier function of the skin at about 34 weeks GA and thereafter is sufficient for life after birth. However, barrier repair is slower in babies than in adults, and can continue to be delayed for up to about 2 years of age.[6]

The immature barrier of babies and infants will be manifested by increased potential for evaporative water loss from the skin, increased potential for dermal penetration and percutaneous absorption of ingredients of topically-applied products, increased susceptibility to infections, inflammation, and blistering, and delayed repair. These signs of immaturity are notable especially in the skin of pre-term neonates until postnatal age (PNA) 2 to 3 weeks and in full-term neonates during the first 3 to 5 days of life.[6,9,12,22,47,48]

For example, the blanching response to topical phenylephrine increases in pre-term neonates (GA < 37 weeks; 9¼ months) with decreasing GA at birth, and disappears 2 to 3 weeks later, demonstrating that the dermal penetration of the drug in pre-term neonates is attributable to the poor epidermal barrier.[8,9,12,12,47] The blanching effect, which is attributable to the phenylephrine-induced local contraction of blood vessels in the skin, was minimal or absent in full-term neonates (GA > 37 weeks; 9¼ months), indicating low skin penetration and absorption of the drug.[8,12,47] There is no clear consensus about the relative effectiveness of the SC barrier in babies after about the first postnatal month.[18,32] SC barrier function involves a complex interplay of factors such as corneocyte maturity/hydrophilicity, lipid amount and phase, density of appendages, surface micro-relief, and diffusion-path length, all of which could help explain some of the differences between the skin of babies and infants and adult skin.[32]

2.2.4. Histological and Other Changes

The following subsections describe some of the histological and other changes of the skin during development.

2.2.4.1. Basement Membrane and Dermis

The cohesion structures in the basement membrane of neonatal skin are similar in type and density to adult skin.[4,49,50] There are also many fibroblasts producing elastic and collagen fibers in the newborn dermis, although fewer than in adult skin.[4] The elastic fibers develop further after birth, and are completely mature at about 3 years of age. The water, glycogen, and hyaluronic acid contents of the dermal extracellular matrix decrease during development after full-term birth, while dermatan-sulfate content increases.[4,51]

2.2.4.2. Epidermis

Histologically and ultrastructurally, the epidermis of full-term neonates (GA > 37 weeks; 9¼ months) is well developed, and does not show much difference compared to the epidermis of adults.[4,4,34,52,53] The dermis is somewhat thinner, the rete ridges shallower, and the appendages denser, but the epidermis and SC are nearly identical to their adult counterparts.[8-10,12,18,23,31,53,54]

The full thickness of infant skin (epidermis and dermis) is about 40–60% that of adult skin.[18,55] The cohesion and adhesion of epidermal cells in newborn skin are not fully developed and the connection at the epidermal/dermal junction is weaker than in adult skin.[23] Thus, infant skin blisters more readily than adult skin, for example. The rete ridges progressively deepen in the skin of infants during GA 36 to 40 weeks (9 to 10 months), yielding a thicker and more cellular epidermis up to PNA 16 weeks (4 months).[9,31]

2.2.4.3. Stratum Corneum

Histologically, the SC does not appear to be fully differentiated in newborn skin before GA about 34 weeks (8 ½ months), based on the fewer layers of cornified cells compared with adult skin, and SC maturation may not be complete until GA about 37 weeks (9¼ months).[7,31,32,43,56]

2.2.4.4. Microstructure of the SC/Epidermis

Stamatas et al. (2010)[57] investigated skin microstructure in babies and infants *in vivo* and compared it with that of adult skin using fluorescence spectroscopy, video microscopy, and confocal laser scanning microscopy. The SC of the babies and infants was 30% and the epidermis 20% thinner than in adults. The corneocytes and granular cells were 20% and 10% smaller, respectively, in the skin of the babies and infants compared to adults, suggesting more rapid cell turnover in babies and infants. The skin of the babies and infants also differed from adult skin in papillae density and size distribution. A direct relationship between SC morphology and the structure of dermal papillae was observed only in baby and infant skin. The transition from papillary to reticular dermis was observed only in adult skin. The authors indicated that the qualitative and quantitative differences in the microstructure may help explain some of the reported functional differences, especially the differences in water-handling properties, between adult skin and the skin of babies and infants.

2.2.4.5. Hydrolipid Film

The hydrolipid film of the skin is a protective water-in-oil (w/o) mixture composed mainly of sebum from sebaceous glands and water from eccrine glands. It is not fully developed in babies.[4]

Sebum consists mainly of squalene, wax esters, cholesterol esters and triglycerides, and possibly free cholesterol and free fatty acids.[7,18] Sebum secretion increases after birth, reaching rates during the first week of life comparable to adult rates.[7] Sebaceous gland activity in the neonate during this first week is thought to be stimulated by preceding transplacental exposure to maternal hormones, because sebum secretion is greater in the early neonatal period than at PNA 6 months.[7,18,58] Sebum secretion then remains relatively low and constant until pre-puberty, when an increase in sex-hormone production causes a new rise in secretion.[7]

Sebum lipids are major constituents of the Marchionini's protective cutaneous hydrolipid film, which has primarily an antimicrobial function. This hydrolipid layer is also thought to serve as a plasticizer, lubricant, and antioxidant.[7,18,59]

2.2.4.6. Triggers and Mechanisms of Structural Development

During the postnatal period there is development of the SC, so that even pre-term neonates born at GA greater than about 35 weeks (8 ¾ months) have barrier function, as determined by reduction in transepidermal water loss (TEWL) similar to that of full-term neonates and infants within 2 to 4 weeks after birth.[7-9,12,18,31,36,56,59-61] The stimulus for rapid epidermal maturation and skin-surface acidification, especially in the pre-term neonate, appears to be the change from the amniotic fluid environment to extra-uterine air, and the accompanying low external humidity that stimulates cell turnover in the outer layers of the skin.[7,9,12,31]

The molecular mechanisms of postnatal epidermal-barrier development in neonates are not fully understood, although there is evidence for a complex interplay of regulatory mechanisms involving skin-surface acidity, calcium-ion gradient, and nuclear-hormone receptors/ligands (i.e. topical peroxisome-proliferator-activated-receptor activators and liver X-receptor activators).[7,60,62]

2.2.5. Changes in Biophysical Measurements

The development of the functional transepidermal-barrier properties of the skin parallels the histological development of the dermis and epidermis before and after birth.[12,18,31,63] The morphology and lipid composition of the epidermis in full-term neonates closely resemble those of older children, and the basal transepidermal barrier is effective at birth, although recovery from external insults that affect the barrier function of the skin is slower in neonates than in older children. The parameters of skin physiology undergo dynamic changes during the first 3 months of life, especially during the neonatal period.[10,31,63,64] These rapid changes during the first months after birth are reflected in measurements of biophysical parameters, such as TEWL and skin-surface pH, as well as measures of the total water content of the SC, water gradient through the SC, and water absorption and desorption rates in the skin. This is discussed in greater detail in the following subsections. These biophysical measurements are used to assess skin function, but they are generally not good indicators of the ability of the skin to serve as a barrier to skin penetration and absorption.

2.2.5.1. Transepidermal Water Loss (TEWL)

Based on TEWL and percutaneous absorption studies, full-term neonates (GA > 37 weeks; 9¼ months) and even late pre-term neonates (GA > 30 weeks; 7½ months) appear to have SC with barrier properties comparable to those of adult skin.[4,7,12,18,32,32,56,61,63]

The high TEWL associated with the drying of the skin in the first 4 hours after birth is subsequently substantially reduced to rates as low as about 6 g⁄m^2⁄h within a week or two, depending on the measurement technology, which is consistent with TEWL measurements in older children (PNA > 1 month) and adults.[4,7,9,18,23,61,63,65-67]

However, this finding is not universal. For example, Nikoloski et al. (2003) found average TEWL ranging from 15 to 30 g/m^2/h in infants 3 to 12 months of age compared with around 6 to 8 g/m^2/h in adults, using a closed chamber method, suggesting that the water-barrier function of the skin continues to develop during the first year of life.[32,46,68]

2.2.5.2. Acidity (pH)

The skin-surface pH in neonates ranges from 6.2 to 7.5 at birth, which is responsible for the immaturity of the epidermis.[4,6,7,18,23,41,46,65,69]

Most studies indicate that the pH declines rapidly in the first week of life, and more gradually up to the fourth week, to pH about 4.5 to 5.5, which is within the dermal pH range of older children and adults (4.0 to 5.9).[4,7,10,23,43,45,46,53,65 18,70] A single study reported that pH measurements of the skin of the volar forearm and, especially, the buttocks of babies and infants up to 2 years of age were statistically-significantly higher than in adults.[65]

As noted above, acidification of the skin surface (i.e., "acid mantle" development) is essential for normal SC barrier maturation, homeostasis, and repair, because it enables pH-dependent extracellular lipid processing and turnover by β-glucocerebrosidase and acidic sphingomyelinase, formation of functional lipid lamellae, regulation of desquamation, and control of bacterial skin flora.[4,6,18,23,30,65,70-75] The "acid mantle" of the SC is thought to arise from the secretion of sebum (free fatty acids), sweat (lactic acid), free amino acids, *cis*-urocanic acid (from histidine), pyrrolidone carboxylic acid, filaggrin breakdown products, and the action of the Na+/H+ antiporter during exocytosis of lamellar bodies.[4,6,7,18,43,45,65] However, the hydrolysis of phospholipids and triglycerides of epidermal origin produces most of the free fatty acids in the SC. Sebum-derived fatty acids are probably less important, because the pH of the surface is low in areas of the skin where sebaceous glands are few compared to sebaceous-gland enriched areas.

However, the buffering capacity of the skin surface is much lower in babies and infants than in adults.[4] Occlusion or bathing with alkaline soaps can readily alkalinize the skin surface of babies and infants.[70,75]

2.2.5.3. Hydration

Following a period of evaporative drying, SC hydration in full-term neonates during the first days of postnatal life is lower on most sites of the body, compared with older children (PNA 3 to 48 months) and adults.[7,18,43,46,58,76] This is partly explained by the presence of the hydrophobic mantle (vernix caseosa), which protects the fetus from

intrauterine maceration.[7,76,77] Subsequently, SC hydration increases substantially from 2 weeks to up to 1 to 3 months after birth, corresponding with a parallel increase in the permeability of hydrophilic compounds and decrease in the permeability of lipophilic compounds in the skin.[10,18,32,43,45,46,65,74]

However, some authors report measurements of hydration, pH, and other biophysical properties suggesting that, functionally, the SC continues to mature throughout the first or second year of life. For example, SC hydration (measured as capacitance) and pH were reported to be statistically-significantly greater throughout the second year of life, compared with adults.[65] Further, SC water absorption/desorption rates, total water content, and the steepness of the water gradient through the SC were greater than, and hygroscopic NMF content of the SC was less than, and more variable than in adults throughout at least the first year of life.[32]

The amount of water in the SC and the gradient of water across the thickness of the SC, in particular, reflect the maturation of the SC in the skin of babies and infants, and influence skin surface morphology, desquamation, and the expression of keratins and other epidermal proteins.[18,32]

2.3. Development of Dermal Microcirculation

Birth triggers a series of events in cutaneous vascularization, and the microcirculation of the skin continues to develop up to PNA 14 to 17 weeks (3½ to 4¼ months).[7] Immediately after birth, the microvasculature is a horizontal dense plexus with a disordered capillary network, and capillary loops are not detectable except in the nail beds, palms and soles. Capillary loops begin to appear in other areas in the second week postpartum, and are widespread 12 to 15 weeks (3 to 3¾ months) thereafter.[7] The capillary loops form lastly in the skin creases.

2.4. Summary

In summary, the SC provides an effective basal semi-permeable barrier soon after birth, if not at birth, although it continues to develop over the course of the first 6 months to 2 years of age.

3. Biotransformation in the Skin

This section discusses the effects of biotransformation enzymes on the absorption of substances topically applied to the skin.

The SC is generally thought of as a passive, inert barrier to diffusion. However, the skin can also serve as a metabolism barrier for some topically-applied substances. This is illustrated, for example, by the substantial reduction in the dermal absorption of topically-applied parabens, which is attributable to the biotransformation of parabens in the skin. The skin has all of the major biotransformation enzymes of the liver except, almost invariably, at lower levels, and at much lower levels for some enzyme systems. The biotransformation capacity of the skin is generally more saturable than that of the corresponding systems in the liver. Nevertheless, the skin has a substantial capacity to biotransform substances that enter and pass through the SC if the substances remain in the epidermis long enough.

Very little information was found to address the development of enzyme systems in human skin. Thus, the subsections below include information about the development of biotransformation capacities in the liver, which has a rich literature in comparison.

3.1. First Pass Effect

The absorption of chemicals through the skin is often thought to be the result of simple diffusion, with the SC serving as a passive, inert, rate-limiting barrier.[17] However, the skin expresses all of the major Phase 1 and Phase 2 enzymes and metabolic functions found in the liver and other tissues.[59,78] The specific activities of these enzymes in subcellular fractions of the skin are generally lower than their counterparts in the liver (0.1%–28% for Phase 1; 0.6%– 50% for Phase 2).[59] However, viable skin still has a substantial capacity to metabolize many xenobiotics.[17,59,79]

Esters, primary amines, alcohols, and acids are especially susceptible to metabolism in the skin.[59,80] Esterases and amidases are highly active in human skin, although these enzymes appear to be much more active in keratinocyte cultures than in excised whole skin or dermis-derived fibroblast cultures.[81] Esters can be extensively metabolized by non-specific esterases in the skin to yield the corresponding alcohols and acids.[59] Examples include benzyl acetate, dimethyl-, diethyl-, and dibutylphthalates, retinyl palmitate, herbicide esters, and methyl salicylate.[59] Primary amines are acetylated, alcohols and acids undergo oxidation/reduction reactions, and acids are conjugated with glycine in the skin.

In addition, conjugation with glutathione, sulfate, and glucuronic acid occurs in the skin.[59]

The capacity of the skin to metabolize xenobiotics can be an important factor determining the rates, extents, and forms (parent compounds and their metabolites) in which they exert local effects on the skin and systemic effects.[17,59] For example, *in vitro* studies clearly demonstrated extensive "first-pass" metabolism of benzo(a)pyrene (BaP) or testosterone topically applied to metabolically-viable, full-thickness skin samples from humans and other mammals, unlike previously frozen skin samples, yielding a complete spectrum of metabolites in the receptor fluid.[17] See diagram of static-type diffusion cell, for an image of the type of apparatus used in this kind of study (image is from: http://www.eurofins.com/agroscienceservices/chemistry/dermal-absorption.aspx). These studies showed that "first-pass" metabolism through mouse skin can be induced by topical BaP exposure to increase the permeation of BaP by 2- to 3-fold, and inhibited by potassium cyanide (KCN) to substantially reduce BaP permeation.

Thus, the intact, viable epidermis can function as a "metabolizing membrane," providing a metabolic as well as a diffusional barrier to percutaneous absorption, depending on the metabolic competency of the epidermal cells and the physicochemical and biological properties of the topically-applied substances and their metabolites.[17,78] The "first-pass effect" can serve as a rate-limiting barrier for compounds that bind to or otherwise remain for a sufficiently long time in the skin to produce inactive metabolites.[59]

However, the "metabolic barrier" will be negligible if the physicochemical barrier of the SC substantially limits the percutaneous penetration of a compound, or if the compound permeates the skin and enters the systemic circulation

too rapidly to enable significant "first-pass" metabolism of the compound in the skin. On the other hand, the "first-pass effect" may enhance permeation and systemic toxicity of polar metabolites formed from a lipophilic compound in the skin.[59]

It is also important to recognize the substantial differences between a "first-pass effect" in the skin after skin contact compared with the "first-pass effect" in the liver after oral exposure.[78] A compound will be susceptible to metabolism only in the relatively small area to which it is applied on the skin. In contrast, the compound will be dispersed throughout the entire liver before entering the systemic circulation after oral exposure. This factor, together with the generally lower enzymatic activities in the skin, indicates that metabolism will be more readily saturated, and the "first-pass effect" may be substantially less after skin contact than after ingestion. It is also important to note that assessing "first-pass" metabolism of a topically-applied compound, *in vivo*, is complicated by the potential for metabolites found in the skin to originate from the metabolism of the compound in the liver as well as in the skin.

3.2. Ontogeny of Biotransformation Enzymes

Unlike development of structural/anatomical and physiological/functional parameters, there is a dearth of research on the ontogeny of biotransformation-enzyme systems specifically in the skin of babies, infants and older children. Thus, little is known about differences in the metabolism of xenobiotics in the epidermis of full-term babies and infants compared with adults, although the differences could be responsible for important dissimilarities in the relative rates of metabolism, the nature of the metabolites produced and, thereby, the potential for these substances to cause local and systemic effects.[82]

In comparison, there is much more information in the scientific literature about the development and maturation of biotransformation enzymes in the liver. The ontogeny of biotransformation enzymes in the skin might be similar enough to that of liver enzymes to provide some insights by analogy. However, it should be emphasized that extrapolating information on the development of liver-enzyme systems to make assumptions about the development of dermal-enzyme systems is speculative, and must be approached with caution. This is because there is little scientific evidence to support the reliability or validity of such extrapolations. Note, for example, the substantial differences observed in the developmental timelines of the biological functions of several organ systems that can play critical roles determining the susceptibility of children to exposures (Figure 1).[2]

3.2.1. Neonatal Biotransformation Capacity in the Liver

Neonates display both Phase I and Phase II metabolic capacity for most substances in the liver, although it may be immature and can be quite low for some substances.[5] Generally, the biotransformation capacity in neonates and infants is difficult to predict based solely on PNA, because the maturation rates of Phase 1 and Phase 2 pathways vary widely by metabolic pathway and inter-individually, and the metabolic pathways can be induced by *in utero* or *post-partum* exposures to inducing agents.[83] In non-induced neonates (pre-term or full-term), the overall capacity for biotransformation is low, especially during the first two weeks of life, compared with older children and adults.[4,83,84]

Ginsberg et al. (2002) demonstrated the immaturity of metabolic and clearance systems in the first weeks to months of life, based on the evaluation of a pharmacokinetics database of 45 drugs covering a wide range of chemical structures, mechanisms of action, and metabolism and clearance pathways, including Phase I, Phase II and renal excretion pathways.[85] On average, half-lives were 3 to 5 times longer in premature neonates, and 2 to 3 times longer in full-term neonates, compared with the corresponding half-lives in adults, although the half-life for CYP1A2 substrates were 9 times longer in full-term neonates than in adults. However, these differences disappeared by 2-6 months of age, after which the half-lives were comparable to, or shorter than, those of adults for specific drugs and pathways.[4,10,83,85-87]

The biotransformation rates of several drugs in the neonate can increase precipitously from about 1/3 to 1/5 of adult rates to 2 to 6 times greater than adult rates by 2 to 3 months up to 2 to 3 years after birth, followed by a gradual decline to adult rates after puberty.[88]

3.2.2. Development of Biotransformation Capacity in the Liver

Figure 1.d, below, illustrates general trends in the timelines for the development of several major Phase I and II hepatic biotransformation pathways.[2] The specific enzymes involved in xenobiotic metabolism, as well as intermediary metabolism, typically develop at different ontogenic stages. Some enzymes increase rapidly days before birth, some increase soon after birth, and others develop around the time of weaning.[23,86] Hines (2008) suggested three categories of individual hepatic drug-metabolizing enzymes (DMEs), based on current knowledge of their ontogenies, including the following:[89]

(1) Enzymes with concentrations that peak during the first trimester (GA < 12 weeks; 3 months), remain high or decrease during gestation, but are absent or greatly diminished within 1 to 2 years after birth (e.g., CYP3A7, FMO1, SULT1A3/4, SULT1E1, and perhaps ADH1A)
(2) Enzymes with relatively constant concentrations throughout gestation and postnatal life (e.g., CYP3A5, CYP2C19, and SULT1A1)
(3) Enzymes with undetectable or very low concentrations during the second or third trimester (GA 16 to 37 weeks; 4 to 9¼ months), but which increase substantially at birth or within 1 to 2 years after birth (e.g., ADH1C, ADH1B, CYP1A2, CYP2C9, CYP2D6, CYP2E1, CYP3A4, FMO3, and SULT2A1)

The enzymes in category (3) that have onset or significantly increasing expression during the perinatal period (e.g., CYP3A7, CYP2C, CYP2D6 and CYP2E1) typically also exhibit substantially greater degrees of inter-individual variability during this period, compared with later postnatal ages.[89-92] Based on limited data, the polymorphic enzymes CYP2D6 (category 3) and CYP2C19 (category 2) appeared to exhibit especially high inter-individual variability, leading Dorne et al. (2005) to suggest that some neonates could be particularly susceptible to compounds that are deactivated by these enzymes.[92]

Generally, the variability in elimination half-lives for many chemicals tends to be greatest for full-term neonates between 1 week and 1 month of age, presumably because of the developmental changes taking place during that period.[2,93]

3.2.2.1. Glucuronidation

Glucuronidation reactions are greatly reduced in neonates, compared with older children and adults, corresponding to the substantially lower activities of uridine 5'-diphosphate (UDP)-glucuronosyltransferases (UGTs) in the neonates.

Reduced glucuronidation capacity in neonates is responsible for a number of well-characterized medical conditions, including neonatal jaundice caused by the accumulation of bilirubin in the serum and typically lasting for about 10 days in full-term neonates. Subsequently, the serum bilirubin concentrations decline steadily for about two weeks, and reach adult levels by about 3 to 6 months of age, corresponding to increases in UGT activity toward bilirubin.[22,94,95]

Other examples of medical conditions attributable to the immaturity of conjugation enzyme systems include "gray baby" syndrome from the systemic accumulation of the antibiotic chloramphenicol administered *i.v.* in neonates, and ''gasping baby'' syndrome from the systemic accumulation of benzoic acid after exposure to the preservative benzyl alcohol in umbilical catheter flushing solutions or *i.v.* injectable products.[10,84,95-99]

Strassburg et al. (2002) detected no transcripts of 9 UGT genes (i.e., UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B4, UGT2B7, UGT2B10, UGT2B15, representing the "typical repertoire" in humans) in the livers of two fetuses (GA ~ 20 weeks), but found transcripts of all of the UGT genes in all liver samples from children (PNA 7 to 14 months) and adults.[100] The expression levels of these genes were constant in the livers of all subjects more than 6 months old, except for UGT1A9 and UGT2B4, which appeared to be up-regulated in an age-dependent manner from 6 months up to 18 months (UGT1A9) or 24 months (UGT2B4) after birth.

However, the catalytic activities of hepatic microsomal preparations tested *in vitro*, using 18 substrates, appeared to be 3- to 40-fold less in children 6 to 12 months, 13 to 18 months and 19 to 24 months of age, compared with adults, including ibuprofen (24-fold), amitriptyline (16-fold), 4-tert-butylphenol (40-fold), estrone (15-fold), and buprenorphine (12-fold) in 13- to 24-month old children.[100] The authors concluded that hepatic glucuronidation does not correlate well with the expression of UGT genes, and may not approach adult rates until after 2 years of age for numerous substrates, including steroid hormones, phenolic substances, and opioids.

3.2.2.2. Sulfation

Sulfation appears to provide a major, broad-spectrum detoxification mechanism during human development, as well as playing a central role in steroid hormone biosynthesis, catecholamine metabolism, and thyroid hormone homeostasis, among other processes.[101,102] In contrast to glucuronidation, sulfation reactions display considerable capacities in the fetus, at birth, and thereafter.[22,84,92,95,102,103]

For example, acetaminophen sulfate is the major metabolite of acetaminophen from birth to about 9 years of age, after which acetaminophen glucuronide is the major metabolite.[84,95,104-106] Thus, the active sulfation of acetaminophen appears to compensate, at least to some extent, for the reduced glucuronidation of acetaminophen in neonates and older children up to around adolescence.[10,95,101,102,107] The weight-normalized clearance of

acetaminophen in infants 6 to 16 months of age is the same as the clearance observed in adults, and exceeds adult clearance for a period thereafter.[105,108,109]

As for acetaminophen, the sulfate conjugation of salicylamide and morphine has been reported to be similar in neonates and adults, in contrast to glucuronidation.[10,95,104,105,110] In particular, morphine is sulfated at rates comparable to adults by 2 to 6 months of age, although it is only poorly sulfated in neonates.

3.2.2.3. Glutathione-, Acetyl-, and Thiopurine-S-methyl- Transferases

Like the UGTs, glutathione-transferase activity is low during the first 6 months of life, and acetyltransferase activity remains low until about 2 years of age.[22,27] On the other hand, thiopurine *S*-methyltransferase (TPMT) activity is reported to be about 50% greater in neonates than in race-matched adults, although exhibiting polymorphism consistent with that observed for this enzyme in adults.[10,111]

3.2.2.4. Carboxylesterases

Carboxylesterases (CEs) play integral roles in the metabolism and detoxification of xenobiotics by hydrolyzing chemicals containing carboxylic acid ester, amide, and thioester functional groups.[112] CEs can also catalyze transesterification reactions.

The liver has the highest carboxylesterase (CE) activity of all of the organs, and expresses two major isozymes, including hCE1 and hCE2, although hCE2 is predominately expressed in the gastrointestinal tract.[112] Additionally, hCE1 and hCE2 differ markedly in the ability to hydrolyze some substances. For example, oseltamivir and deltamethrin are rapidly hydrolyzed only by hCE1, but aspirin and irinotecan are hydrolyzed predominantly by hCE2.

Pope et al. (2005) found no statistically significant difference between mean baby/infant (PNA 2 to 24 months) and adult (20 to 36 years old) hepatic CE activities in an *in vitro* system, using p-nitrophenyl acetate as the substrate, and the IC_{50}s of the CE inhibitor chlorpyrifos oxon in this system were comparable across the liver samples from all subjects ≥3 months of age. The amounts of carboxylases measured in the microsomal preparations were lower, and the sensitivity of the *in vitro* system to chlorpyrifos was statistically-significantly greater, for liver samples from the single 2-month-old subject, compared with the older subjects (3 months to 36 years of age).[113] The authors noted the limited scope of their study, which evaluated only 5 liver samples from individuals ≤ 2 years old, some of whom were on medications (e.g., corticosteroids) that could have influenced CE expression.

In comparison, Yang et al. (2009) found that hepatic hCE1 and hCE2 gene expression was about 70% in a group of 34 children (0 days to 10 years old), compared with 22 adults (≥ 18 years of age).[112] In addition, the hydrolysis rates of aspirin, osetamivir, deltamethrin and permethrin by the liver microsomes obtained from the group of children were only about 25% of the rates using microsomes prepared from the adults. Further, the authors noted substantially greater within-group inter-individual variability of the expression of both hCE1 (218-fold) and hCE2 (21-fold) among the children, compared to those of the adults (12-fold for hCE1; 4-fold for hCE2), which corresponded well to the elevated inter-individual variability in the hCE1 and hCE2 protein content (100-fold) and hydrolytic activity (127-fold) of liver extracts from the children.

Except for hCE1 among the children ≤ 1 year of age ($p = 0.004$), these researchers found no statistically significant linear correlation between age and either hCE1 or hCE2 expression, which they speculated is attributable, at least in part, to diseases and exposure to therapeutic agents in the older children and adults studied.[112]

3.2.2.5. Summary

The metabolic capacity of many, if not most, hepatic enzyme systems mature rapidly in the neonates, exhibiting, and even exceeding, adult capacities within about 6 months to 1 year after birth.[5,10] The capacities of these systems to detoxify or potentiate xenobiotics can reasonably be assumed to be lower in neonates and infants ≤ 6 months than in older children and adults.

However, for some substrates, the metabolizing capacity may more gradually approach adult levels only after 1 to 3 or more years of age, particularly for substrates for which metabolism may depend exclusively or almost exclusively on the activity of UGTs or glutathione- or acetyl-transferases.[10,114] Thus, with the possible exception of the latter substrates, children older than about 6 months probably have hepatic enzyme capacities similar to those of adults.

The information currently available in the scientific literature is not sufficient to establish that generalities based almost entirely on studies on the development of hepatic enzyme systems in humans can be extended to the development of such systems in the skin. However, extrapolating the hepatic developmental data to infer the likely corresponding development of cutaneous metabolic activities appears to be the best we can do, given the substantial gaps in current knowledge and the uncertainties about the ontogeny of these systems in the skin. Thus, as for the liver, the enzymatic activities in the skin of neonates and infants ≤ 6 months of age may be assumed to be lower, and more variable, than in the skin of older children and adults.

4. Susceptibility to Carcinogens and Tumor Promoters

The potential for greater susceptibility of neonates and infants to carcinogenicity has been explored in numerous animal studies since around the mid-1940s.[115-123] The neonatal mouse, in particular, is highly sensitive to direct-acting genotoxic carcinogens, which cause mutations by covalently binding to DNA to form exogenous DNA adducts.[119,120,120,124] Direct-acting carcinogens include electrophiles that bind to DNA without requiring metabolic activation, as well as chemicals (procarcinogens) that require biotransformation to produce metabolites (proximate carcinogens) that bind covalently to DNA.

Most direct-acting chemical carcinogens are procarcinogens, which require biotransformation to produce reactive proximate carcinogens.[119,120,124-126] For example, neonatal mice are extraordinarily susceptible to direct-acting hepatic carcinogens, in part because they possess biotransformation capacities sufficient to produce reactive metabolites.[120,124] However, the greater susceptibility of neonatal mice is often largely attributable to substantially greater DNA-replication rates in the liver, compared with those of adult mice. Observations such as these have led to the development of neonatal rodent tumorigenicity bioassays as animal models for testing chemicals for the potential to cause cancer.[124-126]

However, neonatal mice have proven to be insensitive to indirect-acting carcinogens that can yield tumors through secondary mechanisms.[124,125] Secondary mechanisms, which do not involve direct reaction of the carcinogen with DNA, include tumor promotion through the stimulation of cellular proliferation or the inhibition of programmed cell death (i.e., apoptosis).

In sum, the animal studies noted above, which were performed mostly on particularly sensitive strains of mice, suggest that neonates may be more susceptible than adults to exposures to direct-acting genotoxic carcinogens, but not to exposures to indirect-acting nongenotoxic carcinogens, such as tumor promoters.

5. Discussion and Conclusions

The potential dermal penetration and systemic absorption of ingredients of topically-applied cosmetic products in normal, full-term babies and infants is governed by two major factors, including the development of the (1) SC as a diffusion (physical and chemical) barrier, and (2) biotransformation-enzyme systems and capacities in the skin.

The CIR Expert Panel concluded that the SC provides an effective basal diffusion barrier at birth or within a few days of birth. The Panel considered evidence that the SC continues to develop over the first 6 months to two years of life. However, the Panel was confident that the SC in normal, full-term neonates is an efficient barrier that continues to develop incrementally throughout childhood.

The Panel noted the absence of capillary loops in the dermal papillae of neonates until about 2 weeks after birth, which continue to develop gradually until about 3 months of age. The absence of these loops probably reduces the rate of systemic absorption of lipophilic and other ingredients that can penetrate the SC, compared to the absorption rates in older children and adults.

However, the biotransformation capacities of the skin represent an important consideration for topically-applied ingredients that penetrate the SC and remain in the dermis for durations sufficient for the production or deactivation or potentially toxic metabolites. Unfortunately there is very little information available on the development of biotransformation capacities in the skin. To the extent that development in the skin parallels development in the liver, many enzyme systems in the skin will be fairly mature by about six months of age. Liver-enzyme systems, in general, tend to mature very rapidly in newborns. The major exceptions are the enzymes that catalyze glucuronidation reactions. Enzymes that catalyze reactions other than glucuronidation can increase substantially by about six months of age, and even exceed biotransformation rates of adults during childhood (e.g., sulfotransferases).

The Panel noted that toxicokinetic information in ingredient safety assessment reports include metabolism data when appropriate. Thus, for, example, if an ingredient can be expected to penetrate the SC and its metabolism in the liver depends primarily on glucuronidation pathways, then topical exposures to babies and infants may warrant greater scrutiny and caution from the Panel. This is because glucuronidation activity is generally an effective detoxification and elimination mechanism that is lower in the liver, and probably in the skin as well, in babies and infants than in adults. On the other hand, the Panel will be less concerned if an ingredient that penetrates the SC is metabolized by sulfotransferase pathways to produce nontoxic metabolites, because sulfotransferase activity is

typically much greater in babies and infants than in adults.

The Panel concluded that the information currently available in the scientific literature reveals that the skin of babies and infants is capable of fulfilling its key functions, especially that of providing an effective semipermeable diffusion barrier under basal conditions. However, susceptibility to external insults that affect the barrier function of the skin is greater, and recovery from such insults is slower, in babies than in older children. As the expression and activity of sPLA2 increase in the skin after birth, they yield free fatty acids that acidify the skin, which is a critical factor in the complete maturation of the barrier function of the skin. The normalization of the pH of the surface of the skin, and thus the maturity of the barrier function of the skin, is largely complete by 6 months of age, although in some individuals there may be a further decline in surface pH and improvement in barrier function between 6 months and 2 years of age.

The Panel recognized the substantial knowledge gaps in the scientific literature about the development of biotransformation capacities specifically in the skin, and the significant uncertainties of extrapolating from the ontogenetic information about the liver to the skin. The greatest uncertainties appear to be associated with the reported differences in biotransformation capacities between adults and babies/infants up to about 6 months of age. Some of these differences, for example differences in caboxylesterase activities, are not clearly attributable specifically to differences between adults and babies/infants, rather than simply to inter-individual differences. Further, some compounds may inhibit or induce biotransformation enzymes in the skin of babies and infants, as well as adults.

However, the nature and significance of these factors has been ill-explored in the scientific literature. The Panel encouraged basic-science investigators to explore these gaps and develop information likely to help refine safety assessments in the future, and resolved to monitor the pertinent scientific literature.

Further, the CIR Expert Panel recognizes that, in exposure assessments, babies and infants represent a distinct subpopulation because they have a greater skin-surface area to body-mass ratio, as well as greater dermal permeability for up to 6 months to 2 years of age, compared with adults. Thus, the Panel routinely considers the greater skin-surface area to body-mass ratio in children when performing cosmetic ingredient safety assessments. The Panel also emphasized that they will continue to interpret MoS estimates, as appropriate, to ensure the safety of cosmetic ingredients for babies, infants and other children.

In addition, the CIR Expert Panel is keenly aware of the potentially greater susceptibility of neonates to carcinogens, as well as to other potential toxicological effects. The postulated reasons for greater susceptibility of neonates are many, including the effect of the rate of cell division on the fixation of mutations before repair can occur, the immaturity of biotransformation systems that can deactivate direct-acting carcinogens, the proliferation of mutated cells together with normal cells in target organs as part of normal ontogeny, and the hormonal status of the neonate, to name a few.[115,116,124] The Panel routinely evaluates the physicochemical properties of cosmetic ingredients and data from carcinogenicity, genotoxicity, and other relevant toxicological studies to ensure that cosmetic ingredients do not have the potential to cause cancer in babies, infants, or any other members of the human population.

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7. Figure

a

Developmental Stage:	NEONATE (Birth – 1 month)	INFANT (1 month – 2 years)	PRESCHOOL (2 – 6 years)	CHILD (6 – 12 years)	ADOLESCENT (12 – 18 years)
Time:	0 … 0.5… 1 month	… 2… 4… 6… 8… 10… 12… 14… 16… 18… 20… 22… 2 years	… 3… 4… 5… 6 years	… 7… 8… 9… 10… 11… 12 years	… 14… 16… 18

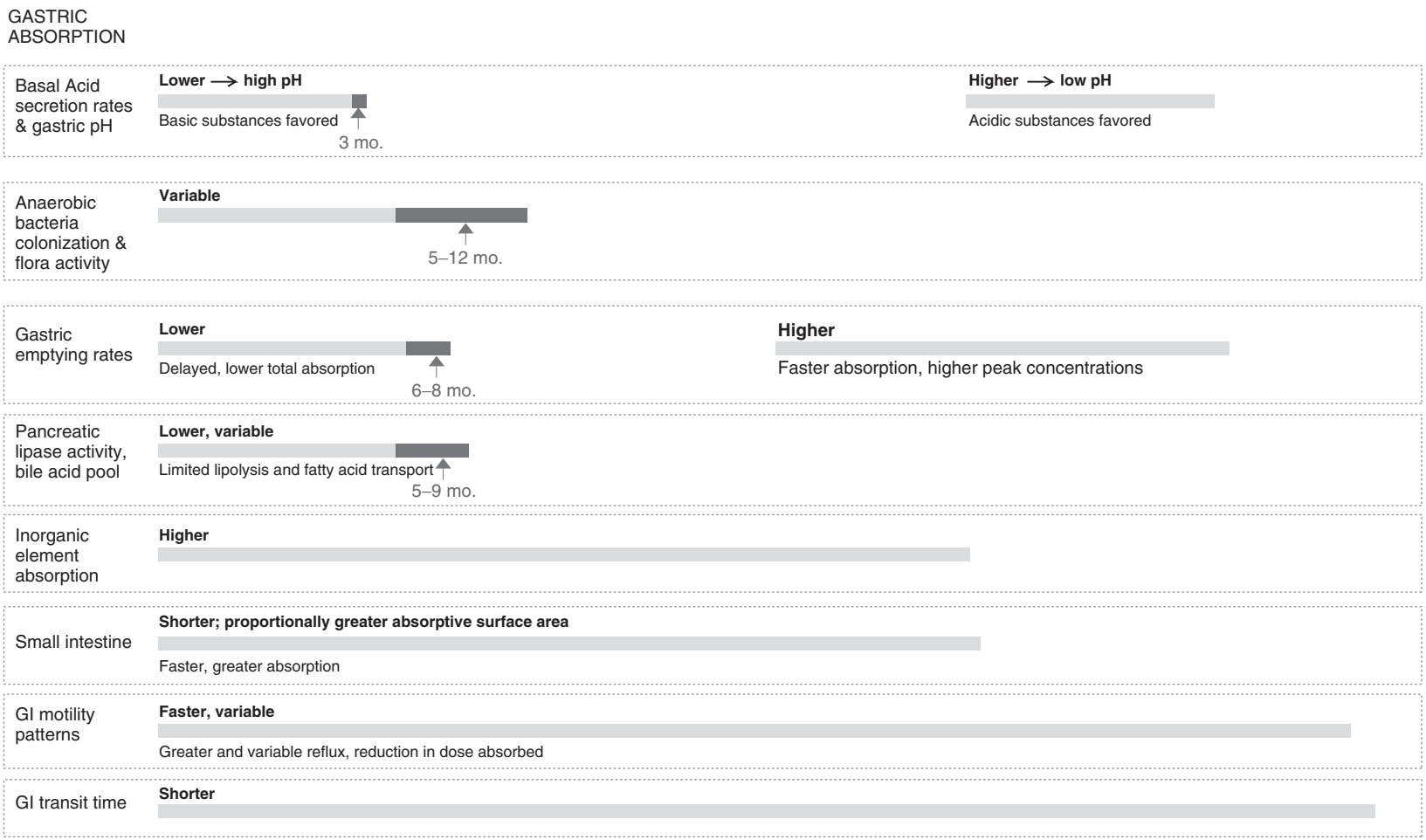

FIGURE 1. Developmental timeline of biological functions relevant to pharmacokinetics. Light bars indicate known time period of development. Dark bars indicate timing of maturation. Unless otherwise indicated, the function is assumed to be mature for the remaining years of development. Maturation points are missing from some functions due to lack of data. (a) Gastric absorption.

b

Developmental Stage:	NEONATE (Birth – 1 month)	INFANT (1 month – 2 years)	PRESCHOOL (2 – 6 years)	CHILD (6 – 12 years)	ADOLESCENT (12 – 18 years)
Time :	0 … 0.5… 1 month	… 2… 4… 6… 8… 10… 12… 14… 16… 18… 20… 22… 2 years … 3… 4… 5… 6 years … 7… 8… 9… 10… 11… 12 years … 14… 16… 18			

FIGURE 1. (*Continued*) (b) Dermal and pulmonary absorption.

c

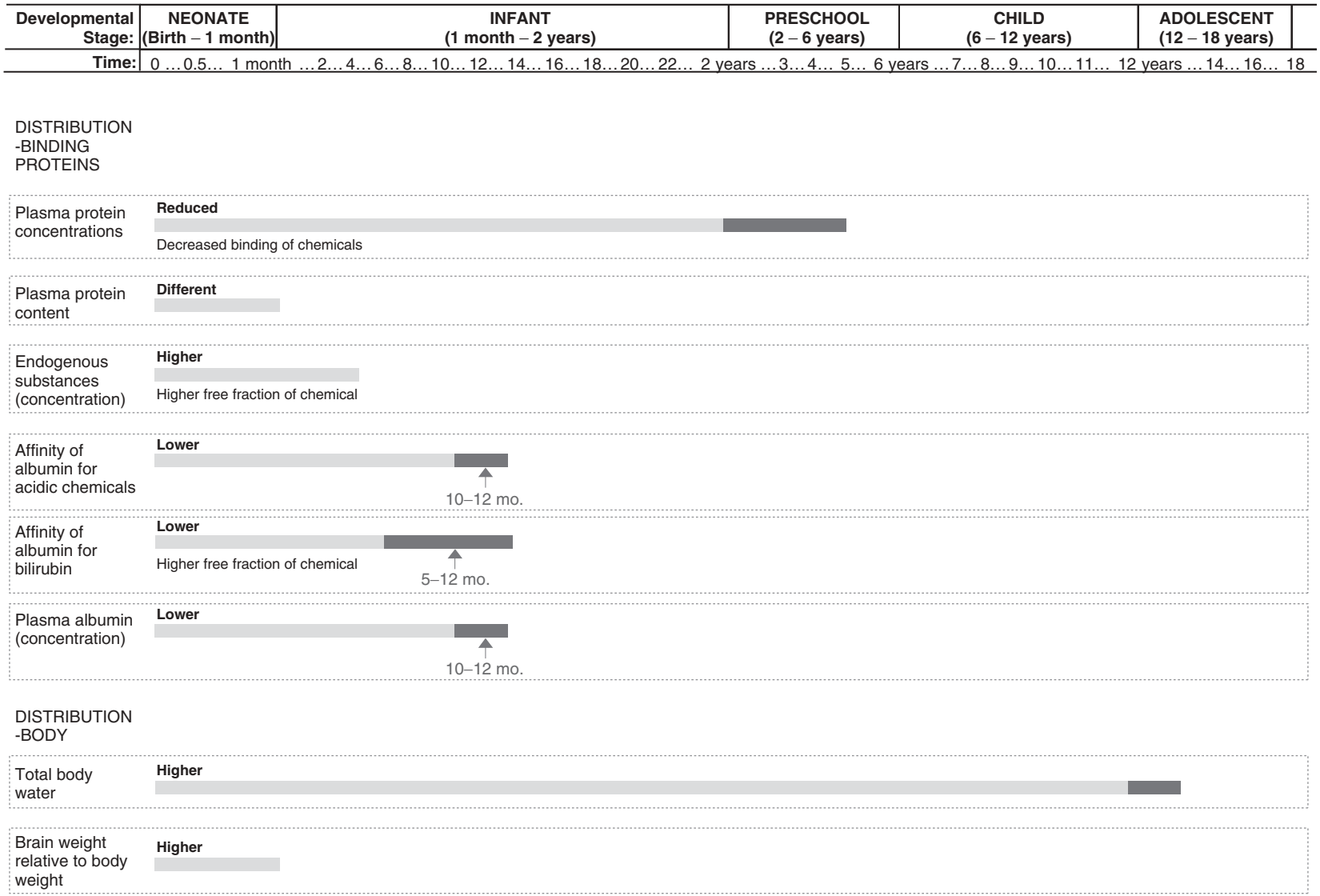

FIGURE 1. (*Continued*) (c) Distribution.

d

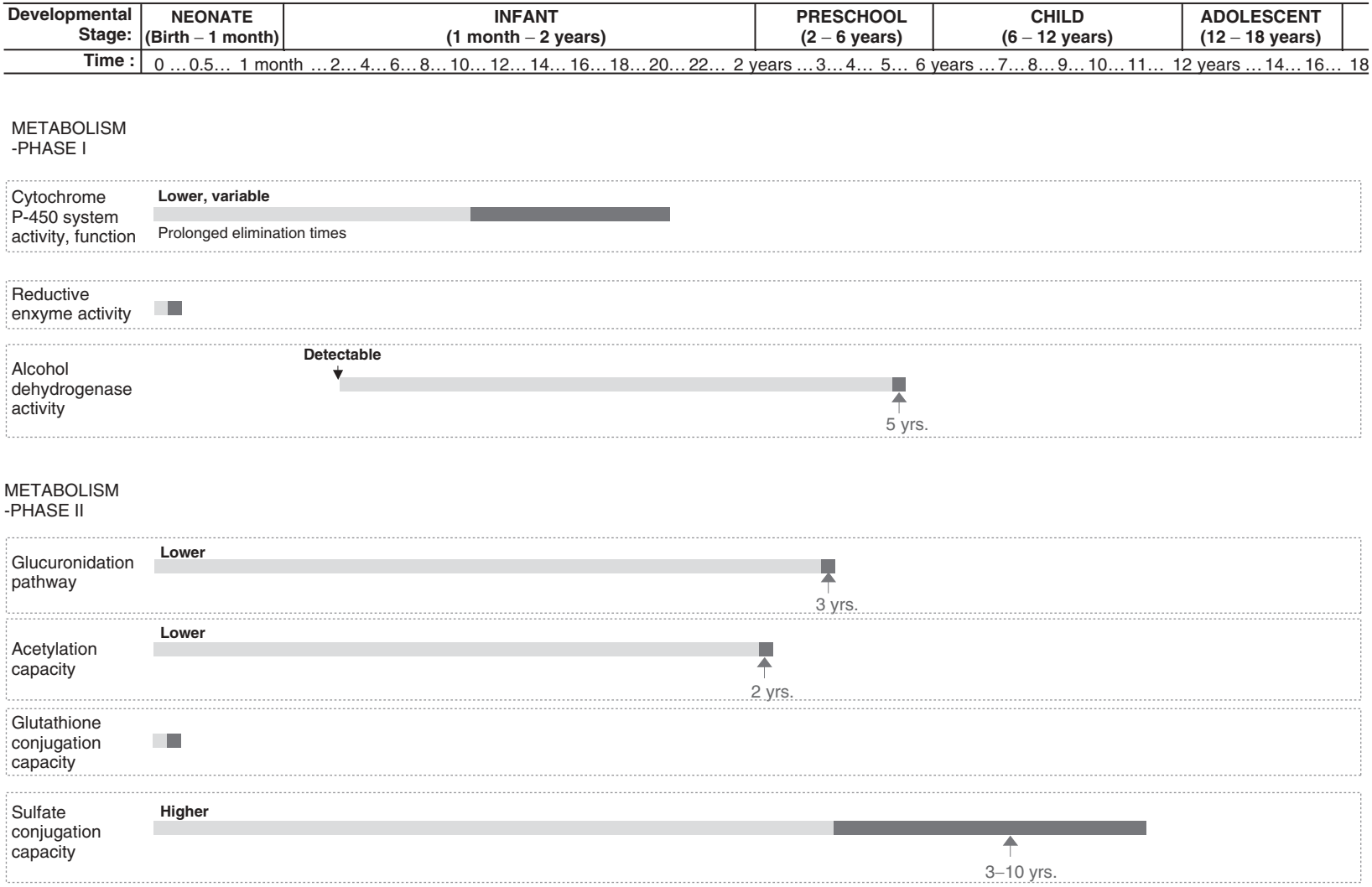

FIGURE 1. (*Continued*) (d) Metabolism.

e

Developmental Stage:	NEONATE (Birth – 1 month)	INFANT (1 month – 2 years)	PRESCHOOL (2 – 6 years)	CHILD (6 – 12 years)	ADOLESCENT (12 – 18 years)
Time :	0 … 0.5… 1 month	…2… 4… 6… 8… 10… 12… 14… 16… 18… 20… 22… 2 years	…3… 4… 5… 6 years	…7… 8… 9… 10… 11… 12 years	… 14… 16… 18

ELIMINATION

FIGURE 1. (*Continued*) (e) Elimination.