BUFF BOOK 1

Memo/Agenda
Minutes
Workshop
Aerosols
Re-review Summaries
- Methyldibromo Glutaronitrile
- Plyvinyl Acetate

CIR EXPERT PANEL MEETING

MARCH 5-6, 2012

Memo/Agenda

Cosmetic Ingredient Review
Commitment . . . Credibility
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MEMORANDUM

To:	CIR Expert Panel Members and Liaisons
From:	Director, CIR
Subject:	122nd Meeting of the CIR Expert Panel — Monday and Tuesday, March 5-6, 2012
Date:	February 10, 2012

Enclosed are the agenda and accompanying materials for the 122nd CIR Expert Panel Meeting to be held Monday and Tuesday, March 5-6, 2012 at the Renaissance Hotel, DuPont Circle, 1143 New Hampshire Ave., NW, Washington, DC 20037; Phone: 1-202-775-0800; Fax: 1-202-331-9491.

We will begin the meeting with an SAR Workshop that Ivan J. Boyer has put together, with the support of the Council's Dr. Linda Loretz and the CIR Science and Support Committee, to bring us all better up to speed on the current uses of structure activity relationships. The workshop will feature:

- Chihae Yang, Ph.D., Work Package Leader, COSMOS Consortium; Chief Scientific Officer, Altamira LLC, Columbus, OH;
- Andrew Worth, Ph.D., Leader, Computational Toxicology Project, Institute for Health & Consumer Protection, European Commission Joint Research Centre, Ispra, Italy;
- Kirk Arvidson, Ph.D., Chemist & Team Leader, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, U.S. Food & Drug Administration, College Park, MD; and
- Karen Blackburn, Ph.D., Research Fellow, Central Product Safety, The Procter & Gamble Co., Cincinnati, OH

After lunch the formal meeting agenda will begin with consideration of 12 ingredient groups. The Panel also needs to review and approve two re-review summaries from December. We have received further comment on formaldehyde and methylene glycol in nail products for consideration, and the Personal Care Products Council has asked the Panel to re-examine its amended safety assessment of parabens in light of recent activity in Europe.

Schedule and hotel accommodations

We will reserve rooms for the nights of Sunday, March 4 and Monday, March 5 at the Renaissance Hotel, DuPont Circle. If you have any travel problems, please contact me on my cell phone at 301-512-7846.

Team meetings

Re-review summaries - buff book 1 - you'll be able to review the re-review summaries of methyldibromo glutaronitrile and polyvinyl acetate.

New issues

1. formaldehyde/methylene glycol - Women's Voices for the Earth has expressed disappointment in the Panel's conclusion that formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail hardeners, given the adverse reaction reports provided to CIR by the organization. CIR has drafted a response that we think captures the Panel's thinking.

2. parabens - after the December, 2011 meeting, the Council asked the Panel to re-examine (see attached December 15, 2011 memo) its recent review of Parabens, and, if needed, re-review the use of Parabens as ingredients for use in cosmetics and personal care products in light of opinions issued in 2011 in Europe.

New re-reviews – there are 3 safety assessments originally published in 1997 to re-review and make a determination on the need to reopen to revise the conclusion or, if the conclusion is still valid, to consider opportunities to reopen to expand the scope.

1. cetyl esters – in 1997, this ingredient is a mixture of esters of saturated fatty acids and fatty alcohols with carbon chain lengths between 14 and 18 found safe as used in cosmetics. Because cetyl esters is a member of a broader group of cosmetic ingredients, alkyl esters, it may be appropriate to re-open this safety assessment to include all of the relevant ingredients as an "alkyl esters" report. For many of the alkyl esters, one or all constituents have been reviewed by CIR and have been included in data profiles along with the limited new safety test data actually available for cetyl esters.

2. PEG castor oils – in 1997, PEG-30, -33, -35, -36, and -40 castor oils were found safe for use in cosmetics at concentrations up to 50% and PEG-30 and -40 hydrogenated castor oils were safe for use at concentrations of up to 100%. Numerous newly available studies discussed the use of PEG-35 castor oil and PEG-40 hydrogenated castor oil as surfactants in drug delivery systems. Because these studies tend to focus on the efficacy of the drug that is being tested, the re-review includes only the most recent studies and those that indicate any information on dermal toxicity. The opportunity exists, based on similarities in chemical properties and cosmetic function, to add other ingredients into a report on "PEGylated oils." The cosmetic ingredients proposed to be incorporated into such an expanded report include components that have been previously reviewed and concluded to be safe for use by the CIR Panel, most notably the recent safety assessments on plant-derived fatty acid oils and PEGs with an average of 4 moles of ethylene oxide or greater.

3. PPG-5 lanolin wax and PPG-5 lanolin wax glyceride – in 1997, these two ingredients were found safe as used in cosmetics. In 1982, a safety assessment of PEG lanolins (PEG-20, 27, 30, 40, 50, 60, 75, and 85) was published. The cosmetic ingredients were found to be safe as presently used in cosmetic products. In 1999, an addendum was published adding more PEG lanolins (PEG-5, 10, 24, 25, 35, 50, 55, 50, 75, 85, 100, and 150), and PEG hydrogenated lanolins (PEG-5, 10, 20 24, 30, and 70) to the safety conclusion. These ingredients were found to be safe for use in cosmetic formulations under the present practices of use. While these original safety assessments include 22 ingredients, by considering them all together as polyether lanolins, and in keeping in line with our endeavor to group chemically similar ingredients into the same reports, other PPG lanolins and PEG lanolins could be added for a total of 38 ingredients.

Draft reports - there are 3 reports under green cover. The Panel is seeing these reports for the first time. For each of these reports, if we have all the data we need, we can issue a tentative report. If not, we should ask for whatever additional data are needed.

1. amino acids – In October 2011, CIR issued the Scientific Literature Review (SLR) for amino acids. As the strategy was developed for how to approach this safety assessment, the Panel's recommendation was to rely heavily on the GRAS direct food additive status of many of these common amino acids to demonstrate the absence of significant oral toxicity --- and to do this safety assessment first, as a prelude to considering other high priority ingredients such as protein hydrolysates. That is the approach we have taken. As a result, the draft report for amino acids is limited to the common amino acids and emphasizes available information on adverse reactions to dermal exposures.

2. Bis-Diglyceryl Polyacyladipate-2 – in August 2011, due to a lack of published safety data on bis-diglyceryl polyacyladipate-2 and bis-diglyceryl polyacyladipate-1, a Scientific Literature Review notice was issued that listed the little information that was available. Industry has provided a great deal of unpublished data that have been incorporated into the draft report for review.

3. Cucumis sativus (cucumber) derived ingredients - The Scientific Literature Review was issued in September 2011. Published toxicity data were not readily available on these seven ingredients. Limited dermal irritation and sensitization data are available. Industry provided a great deal of unpublished data that have been incorporated.

Draft final reports - there are 6 reports under blue cover. After reviewing these drafts, especially the rationale in the discussion section, the Panel should issue them as final reports.

1. Alkyl PEG Sulfosuccinates – a tentative report with a safe in the present practices of use and concentration conclusion was issued in December. Comments and additional data received during the 60-day comment period have been addressed/incorporated. The CIR Science and Support Committee has raised a question regarding the appropriate use of statements in MSDSs about the absence of toxic effects when no studies are given as the source. CIR would appreciate some guidance from the Panel on this question. The Panel should review the discussion to make certain that it reflects the rationale for a safe as used when formulated to be non-irritating conclusion and issue a final safety assessment.

2. Ammonium Hectorites – at the December meeting, the Panel issued a tentative safety assessment with a conclusion of safe in the present practices of use and concentration. Technical comments from industry were addressed and new concentration of use data were incorporated. The Panel should review the discussion to confirm that it presents the rationale for the conclusion, and issue a final safety assessment.

3. Citric Acid – a tentative report with the conclusion that citric acid and the inorganic citrate salts and alkyl citrate esters are safe in the present practices of use and concentration was issued in December. No new data have been found or received. Technical comments from industry were addressed. The Panel should review the discussion to confirm that it presents the rationale for the conclusion, and issue a final safety assessment.

4. Ethanolamines – at the December 2011 meeting, the Panel issued a tentative amended safety assessment with a conclusion that ethanolamine and the 12 related ethanolamine salts are safe in the present practices of use and concentration (used in rinse-off products only) described in this safety assessment, when formulated to be non-irritating. The Panel cautioned that ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed. Technical comments from industry were addressed. The Panel should review the discussion to confirm that it presents the rationale for the conclusion, and issue a final safety assessment.

5. Ethanolamides – at the December 2011 meeting, the Panel concluded that these 28 ethanolamides (original 3 in the re-review + 25 additional ethanolamides) are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating. The Expert Panel cautioned that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed. Technical comments from industry were addressed. The Panel should review the discussion to confirm that it presents the rationale for the conclusion, and issue a final safety assessment.

6. Galactomannans – at the December 2011 meeting, the Panel concluded these cosmetic ingredients are safe in the present practices of use and concentration described in this safety assessment. Technical comments received from industry have been addressed, but one. It has been suggested that the flavor ingredient made from trigonella foenumgraecum that is used in curry is not a galactomannan. A reference supporting this observation was not received, and, after further review, the Panel needs to confirm whether or not the paragraph in question should be deleted. The Panel should review the discussion to confirm that it presents the rationale for the conclusion, and issue a final safety assessment.

Aerosols – CIR is seeking Panel approval to post the final aerosols background information on the CIR website. At the December 2011 meeting, the Panel discussed the draft aerosols precedents document, and made changes to both the background section and the templates of the document. The Panel directed that the revised document should be posted on the CIR Website (done in January), first to solicit public comments on the document, and then to post a final document to provide interested parties with easy access to the background information.

Full Panel Meeting

Remember, the breakfast buffet will open at 7:30 am and the meeting starts at 8:00 am on day 2.

The Panel will consider the 6 reports to be issued as final safety assessments, followed by the rest of the reports advancing in the process and the remaining items on the agenda.

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

122nd Cosmetic Ingredient Review Expert Panel Meeting
March 5-6, 2012

Monday, March 5		
8:00 am	**CONTINENTAL BREAKFAST**	
8:30 am	**WELCOME TO THE 121st EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Andersen**
8:40 am	**Introduction to SAR Workshop**	**Dr. Ivan Boyer**
8:45 am	**Chihae Yang, Ph.D., Work Package Leader, COSMOS Consortium; Chief Scientific Officer, Altamira LLC, Columbus, OH**	
9:30 am	**Andrew Worth, Ph.D., Leader, Computational Toxicology Project, Institute for Health & Consumer Protection, European Commission Joint Research Centre, Ispra, Italy**	
10:15 am	**Break**	
10:30 am	**Kirk Arvidson, Ph.D., Chemist & Team Leader of the SAR Group, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, U.S. Food & Drug Administration, College Park, MD**	
11:15 am	**Karen Blackburn, Ph.D., Research Fellow, Central Product Safety, The Procter & Gamble Co., Cincinnati, OH**	
12:00 – 12:30 pm	**Roundtable discussion**	
12:30 pm	**Lunch**	
1:15 pm	**TEAM MEETINGS**	**Drs. Marks/Belsito**

Dr. Marks' Team		**Dr. Belsito's Team**	
Buff (AA)	parabens - re-review summary	Blue (MF)	ethanolamines
Buff (AA)	methyldibromo glutaronitrile and polyvinyl acetate – re-review summaries	Blue (MF)	ethanolamides
Blue (WJ)	alkyl PEG sulfosuccinates	Blue (MF)	citric acid group
Blue (WJ)	galactomannans	Green (MF)	bis-diglyceryl polyacyladipate-2 and -1
Blue (LB)	ammonium hectorites	Green (MF)	cucumis sativus (cucumber) derived ingredients
Green (LB)	polyether lanolates – re-review	Green (MF)	alkyl esters – re-review
Green (CB)	amino acids	Buff (IB)	aerosols
Green (CB)	PEGylated oils – re-review	Buff (IB)	formaldehyde/methylene glycol
Green (MF)	alkyl esters – re-review	Buff (AA)	parabens - re-review summary
Green (MF)	cucumis sativus (cucumber) derived ingredients	Buff (AA)	methyldibromo glutaronitrile and polyvinyl acetate – re-review summaries
Green (MF)	bis-diglyceryl polyacyladipate-2 and -1	Blue (WJ)	alkyl PEG sulfosuccinates
Blue (MF)	citric acid group	Blue (WJ)	galactomannans
Blue (MF)	ethanolamines	Blue (LB)	ammonium hectorites
Blue (MF)	ethanolamides	Green (LB)	polyether lanolates – re-review
Buff (IB)	formaldehyde/methylene glycol	Green (CB)	amino acids
Buff (IB)	aerosols	Green (CB)	PEGylated oils – re-review

5:15 pm **ADJOURN DAY 1 SESSION**

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

Tuesday, March 6			
7:30 am	**CONTINENTAL BREAKFAST**		
8:00 am	**WELCOME TO THE 122nd FULL CIR EXPERT PANEL MEETING**		
8:15 am	**MINUTES OF THE December, 2011 EXPERT PANEL MEETING**		**Dr. Bergfeld**
8:25 am	**DIRECTOR'S REPORT**		**Dr. Andersen**
8:45 am	**FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, RE-REVIEW, and OTHER DISCUSSION ITEMS**		
		Final Reports	
	Blue (LB)	ammonium hectorites - Dr. Marks reports	
	Blue (WJ)	alkyl PEG sulfosuccinates - Dr. Belsito reports	
	Blue (WJ)	galactomannans - Dr. Marks reports	
	Blue (MF)	ethanolamines - Dr. Belsito reports	
	Blue (MF)	ethanolamides - Dr. Marks reports	
	Blue (MF)	citric acid - Dr. Belsito reports	
		Reports Advancing	
	Green (MF)	cucumis sativus (cucumber) derived ingredients - Dr. Marks reports	
	Green (MF)	alkyl esters – re-review - Dr. Belsito reports	
\	Green (MF)	bis-diglyceryl polydiacyladipates - Dr. Marks reports	
	Green (LB)	polyglycol lanolins – re-review - Dr. Belsito reports	
	Green (CB)	amino acids - Dr. Marks reports	
	Green (CB)	PEGylated oils - re-review - Dr. Belsito reports	
		Other Discussion Items	
	Buff (IB)	aerosols - Dr. Marks reports	
	Buff (IB)	formaldehyde/methylene glycol - Dr. Belsito reports	
	Buff (FAA)	parabens – Dr. Marks reports	
	Buff (FAA)	approval of re-review summaries - methyldibromo glutaronitrile and polyvinyl acetate - Dr. Marks reports	
	ADJOURN - Next meeting *Monday and Tuesday, June 11-12, 2012*		

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

Minutes

Cosmetic Ingredient Review
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ONE HUNDRED TWENTY-FIRST MEETING

OF THE

EXPERT PANEL

December 12-13, 2011

The Madison Hotel

Washington, D.C.

Expert Panel Members

Wilma F. Bergfeld, M.D., Chair

Donald V. Belsito, M.D.

Ronald A. Hill, Ph.D.

Curtis D. Klaassen, Ph.D.

Daniel C. Liebler, Ph.D.

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

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

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

Liaison Representatives

Consumer

Rachel Weintraub, Esq.

Industry

Jay Ansell, Ph.D.

Government

Linda Katz, MD., M.P.H.

Adopted (Date)

Wilma F. Bergfeld, M.D.

1101 17th St., NW, Suite 412 Washington, DC 20036-4702
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Others Present at Meeting

F. Alan Andersen	CIR
J. Ansell	Council
Lillian Becker	CIR
Ivan Boyer	CIR
Christina Burnett	CIR
Jon Busch	American Chemistry Council
Michael Despay	Axim
Kapal Dewa	FDA
Carol Eisenmann	The Council
Monice Fiume	CIR
Kevin Fries	CIR
James V. Hagan	Elements
Bart Heldreth	CIR
Carla Jackson	CIR
Wilbur Johnson, Jr.	CIR
Christ Kanola	Elements
William G. Kelly, Jr.	CRE
Akihu Kinoshita	Shiseido
Dennis Laba	Presperse
Dave Mallon	Unilever
Lauren Nardella	The Rose Sheet
Thomas Re	L'Oreal USA
Diego Rua	FDA
Noriko Shibuya	Shiseido
David Steinberg	Steinberg & Associates
Jane Vergnes	ISP

CHAIRMAN'S OPENING REMARKS

The 121st meeting of the CIR Expert Panel was called to order by Dr. Bergfeld at 8:01 a.m. on Tuesday, December 13, 2011. This marks the 35th year since the beginning of the Cosmetic Ingredient Review, and Dr. Bergfeld thanked the CIR staff for providing the Expert Panel with documents that are very well done. She noted that 18 ingredient reports were reviewed in Teams on the preceding day, two of which were being reviewed for the first time. However, given this level of progress, she noted that the Panel continues to be plagued with late data submissions. This was a discussion topic during yesterday's Team meetings, and it was agreed that these data submissions should be organized in a manner that enhances readability prior to submission for Panel review.

APPROVAL OF MINUTES

The minutes of the September 27-28, 2011 CIR Expert Panel meeting were unanimously approved, with corrections.

DIRECTOR'S REPORT

♦Dr. Andersen announced that Dr. Lillian Gill, 35-year veteran of the Food and Drug Administration, is the new Deputy Director of the Cosmetic Ingredient Review. Dr. Andersen remarked that the situation could not be better in terms of the skill set that Dr. Gill brings to CIR.
♦The logistics of scheduling ingredient reports for review at future Expert Panel meetings needs to be examined closely in order to establish realistic expectations for the review process, in keeping with the goal of increased throughput.
♦CIR's new website was introduced on the preceding day. The website is easy to navigate and embraces the idea that the Panel's deliberations on ingredient safety are fully transparent. Safety assessments are posted as soon as they are available and are freely accessible.
♦CIR Final Safety Assessments are published in the *International Journal of Toxicology* and CIR continues to have a reasonably good working relationship with the journal editors and publisher. Though copy deadlines are not always met, the idea that the journal wants to continue publishing CIR's safety assessments is unwavering.

Final Safety Assessments

Alkyl Glyceryl Ethers

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

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

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

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

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

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

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

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

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

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

Decyl Glucoside and Other Alkyl Glucosides

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

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

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

Were ingredients in this group not in current use (as indicated by *) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group and that they would be formulated to be non-irritating.

Pentaerythrityl tetraesters

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

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

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

Pentaerythrityl Tetraisostearate
Pentaerythrityl Tetra C5-9 Acid Esters*
Pentaerythrityl Tetra C5-10 Acid Esters*
Pentaerythrityl Tetracaprylate/ Tetracaprate
Pentaerythrityl Tetralaurate

Pentaerythrityl Tetramyristate*
Pentaerythrityl Tetrastearate
Pentaerythrityl Tetrabehenate
Pentaerythrityl Tetracocoate*
Pentaerythrityl Tetraoleate*
Pentaerythrityl Tetraethylhexanoate
Pentaerythrityl Tetraethylhexanoate/ Benzoate
Pentaerythrityl Tetrabehenate/ Benzoate/ Ethylhexanoate
Pentaerythrityl Tetrabenzoate*
Pentaerythrityl Tetraisononanoate
Pentaerythrityl Tetrapelargonate

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

Sodium Lauriminodipropionate, Lauriminodipropionic Acid, And Disodium Lauriminodipropionate

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

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

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

Tentative Safety Assessments and Tentative Amended Safety Assessments

Alkyl PEG Sulfosuccinates

Disodium laureth sulfosuccinate and the other 17 alkyl PEG sulfosuccinate salts and esters listed below are safe in the present practices of use and concentration when formulated to be non-irritating.

These ingredients share a sulfo-substituted succinic acid core and function mostly as surfactants – cleansing agents in cosmetics. The data available for disodium laureth sulfosuccinate include single-dose and repeated-dose toxicity, genotoxicity and carcinogenicity, and dermal irritation and sensitization. Because of the similarities in chemical structure and in usage in cosmetics, these data can be extended to address the safety of all alkyl PEG sulfosuccinates.

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

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

Were ingredients in this group not in current use (as indicated by *) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group and that they would be formulated to be non-irritating.

Ammonium Hectorites

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

These clay-based ingredients function as suspending agents in cosmetic products and may be used as viscosity increasing agents (i.e., they thicken the formulation). The CIR Expert Panel reviewed the available single-dose and repeated-dose toxicity data, along with specific studies addressing dermal irritation and sensitization and determined that the data support the safety of these ingredients in

cosmetics. While no data were available on dermal penetration, the Panel viewed these large sheets of octahedral magnesium/lithium silicate to which are adhered cationic surfactants (e.g., stearalkonium) as unlikely to pass the stratum corneum, which is the outer dead layer of cells that forms the surface of the skin. Components, such as lithium, in these ingredients are tightly bound and have no chance of leaching.

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

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

Citric Acid Group

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

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

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

Citric Acid

Inorganic Salts
Aluminum Citrate
Calcium Citrate*
Copper Citrate*
Diammonium Citrate
Disodium Cupric Citrate*
Ferric Citrate
Magnesium Citrate
Manganese Citrate*
Monosodium Citrate
Potassium Citrate
Sodium Citrate
Zinc Citrate

Alkyl Mono-, Di-, and Triesters
Dilauryl Citrate
Distearyl Citrate*
Ethyl Citrates
Isodecyl Citrate
Isopropyl Citrate*
Stearyl Citrate
Tributyl Citrate
Tri-C 12-13 Alkyl Citrate
Tri-C14-15 Alkyl Citrate
Tricaprylyl Citrate
Triethyl Citrate
Triethylhexyl Citrate
Trihexyldecyl Citrate*
Triisocetyl Citrate
Triisopropyl Citrate*
Triisostearyl Citrate
Trilauryl Citrate*
Trioctyldodecyl Citrate
Trioleyl Citrate*
Tristearyl Citrate*

Were ingredients in this group not in current use (as indicated by *) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group and that they would be formulated to be non-irritating.

Ethanolamine and Ethanolamine Salts

Ethanolamine and the 12 ethanolamine salts listed below were found safe in the current practices of use and concentration when formulated to be nonirritating, but these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.
The CIR Expert Panel relied on the information available for ethanolamine in conjunction with previous safety assessments of the components of these ingredients, extrapolating those data to support the safety of the ethanolamine salts in this tentative amended safety assessment. The Panel noted that small amounts of diethanolamine could be present in ethanolamine and was concerned with the levels of free diethanolamine that could be present as an impurity. Hence the need to mention that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed. Also, because diethanolamine might be present as an

impurity, the Panel re-iterated its discussion regarding the positive findings of a dermal carcinogenicity study of diethanolamine, noting that the carcinogenic effects reported in mice were not thought to be relevant to humans.

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

Were ingredients in this group not in current use (as indicated by *) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group, that they would be formulated to be non-irritating, and that they would not be used in cosmetic products in which N-nitroso compounds may be formed.

Ethanolamides

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

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

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

The Panel acknowledged the lack of reproductive and developmental toxicity data, but relied on the totality of the data set to demonstrate safety. Supporting this reasoning is the expectation that only very small amounts of the compounds will be bioavailable. Because reproductive and developmental toxicity data would enhance the data profile for this safety assessment, and biotransformation data and toxicokinetic data would also augment the data set, the Panel encouraged submission of such available data.

Isostearamide MEA*
Myristamide MEA
Stearamide MEA
Acetamide MEA
Azelamide MEA*
Babassuamide MEA*
Behenamide MEA*
C16-22 Acid Amide MEA*
Cocamide MEA
Cocamide Methyl MEA
Cocamidopropyl Betainamide MEA Chloride
Hydroxystearamide MEA*
Lactamide MEA
Lauramide MEA
Linoleamide MEA*
Oatamide MEA*
Oleamide MEA*
Oliveamide MEA*
Palm Kernelamide MEA*
Palmamide MEA*
Palmitamide MEA*
Pantothenamide MEA*
Peanutamide MEA
Ricinoleamide MEA
Sunfloweramide MEA*
Tallowamide MEA*
Trideceth-2 Carboxamide MEA
Undecylenamide MEA

Were ingredients in this group not in current use (as indicated by *) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group and that they would be formulated to be non-irritating.

Galactomannans

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

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

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

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

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

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

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

Synthetic Fluorphlogopite

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

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

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

Insufficient Data Announcement

Dialkyl Malates

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

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

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

Re-Reviews

Methyldibromo Glutaronitrile – not reopened

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

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

Polyvinyl Acetate – not reopened

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

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

Re-review summaries

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

Reports Tabled

Ginseng Root-derived Ingredients

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

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

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

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

The ingredients included in this safety assessment are:
Hydrolyzed Ginseng Root
Hydrolyzed Ginseng Root Extract
Hydrolyzed Ginseng Saponins

Panax Ginseng Root
Panax Ginseng Root Extract
Panax Ginseng Root Oil
Panax Ginseng Root Powder
Panax Ginseng Root Protoplast
Panax Ginseng Root Water
Panax Japonicus Root Extract
Panax Notoginseng Root
Panax Notoginseng Root Powder
Panax Quinquefolium Root Extract

Polyquaternium-22 and -39

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

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

Cosmetics Aerosols

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

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

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

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

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

Meeting Notes

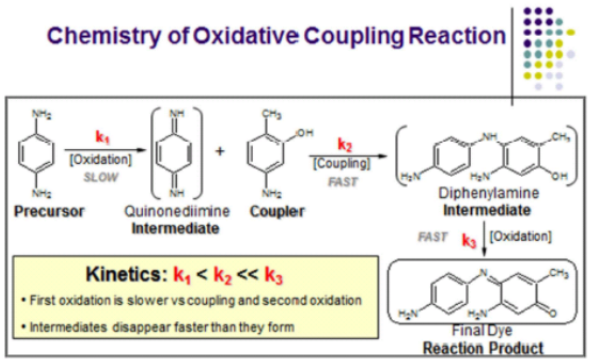
At the Food and Drug Law Institute's Annual Awards and Holiday Reception on December 6th, CIR Director, Dr. Alan Andersen, was presented with the 2011 FDLI Distinguished Service and Leadership Award. He was one of 4 recipients recognized for their contributions to the food and drug law field, to the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

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

Hair dye chemistry presentation – Dr. Julie Skare

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

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



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

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

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

Dr. Skare went on to describe studies done on representative oxidative hair dye reaction products to determine likely dermal penetration. In each case the dermal penetration of the reaction product was substantially lower than the dermal penetration of the precursors or the couplers – by as much as 3 orders of magnitude. She also described an effort to evaluate reaction products in genotoxicity assays. In vitro test used included Ames bacterial assays, hprt locus mutation assays and micronucleus assays in mammalian cells. In vivo testing included micronucleus assays and unscheduled DNA synthesis in animals. While some positive findings were reported using in vitro assays, no evidence of genotoxicity was found in vivo.

Workshop

Andrew Worth (European Commission's Joint Research Centre, Italy)

Dr Andrew Worth is the leader of the Computational Toxicology Project within the Institute for Health & Consumer Protection (IHCP) at the European Commission's Joint Research Centre (JRC). Dr Worth has degrees in Physiological Sciences and Linguistics, both from Oxford University, and a PhD in computational toxicology from Liverpool John Moores University. He has been involved in JRC activities on chemical risk assessment, alternative test methods, and computational toxicology. Since 2003, he has led the Computational Toxicology group, which promotes the development, assessment, acceptance and implementation of computational methods suitable for the regulatory assessment of chemicals. Further information on the JRC's Computational Toxicology Project can be found at: **http://ecb.jrc.it/qsar/**.

Chihae Yang

Chihae Yang is the Chief Scientific Officer of Altamira LLC, a knowledge development company based in Columbus Ohio. She is a visiting scientist at US FDA CFSAN and has been a fellow in the computational toxicology program (Nov 2008 – Feb 2011). She teaches and leads several research collaborations at Ohio State University. She previously was the Chief Scientific Officer of Leadscope, Inc. She joined Leadscope in 2000 from her position as a tenured chemistry professor at Otterbein College and an adjunct professor at the Ohio State University. She worked at the Clorox Company (1984-1992) where she incorporated computational methods into product discovery and development workflows. At Leadscope she initiated a chemical genomics program, with public funding including NIH/NCI grants, and defined and developed Leadscope's predictive toxicology platform and QSAR technology. She also established the LIST focus group with grants from the US NIST Advanced Technology Program and has delivered ToxML, a public toxicity database standard and ToxML database entry tool in collaboration with the US FDA. Her research focuses on computational chemistry and Structure Activity Relationship methods applied to pharmaceuticals, food and cosmetic ingredients, and nano-structured materials. She continues to develop methods to advance toxicity prediction and risk assessment paradigms beyond current QSAR approaches, including Threshold of Toxicological Concerns (TTC), development of mode-of-action chemotypes, and quantitative weight of evidence assessment algorithms. Altamira is currently a work package leader for the COSMOS TTC project within COSMOS consortium, an EU/COLIPA funded initiative to develop knowledge and technologies required for repeated dose systemic toxicity testing without animals for ***cosmetics ingredients***.

SUMMARY CURRICULUM VITAE

PERSONAL DETAILS

NAME: Karen L. Blackburn
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QUALIFICATIONS

DATE INSTITUTION ATTENDED	NAME OF INSTITUTION ATTENDED	QUALIFICATIONS OBTAINED
1972-1974	University of Arizona - Tucson, Arizona	B.S., 1974-Biology
1975-1977	Miami University - Oxford, Ohio	M.S., 1977-Ecology
1986-1991	University of Cincinnati - Cincinnati, Ohio	Ph.D., 1991-Physiology & Biophysics

WORK HISTORY

Brief Synopsis: Primary area of experience is risk assessment to support safe human exposures to environmental contaminants and consumer products with an emphasis on development of novel approaches. Experience gained primarily in government (US Environmental Protection Agency) and in Industry (The Procter & Gamble Co.) Educational background is diverse including biology, ecology, physiology and biophysics.

DATE(S) OF EMPLOYMENT	ORGANIZATION	POSITION(S)
2005-Present	The Procter and Gamble Co.	Research Fellow: Technical Oversight of 17 Human Safety Expert Teams. Lead/collaborate with P&G expert groups to develop or refine and implement improved risk assessment methods.
2001-2005	The Procter and Gamble Co.	Principle Scientist-Toxicologist. Responsible for managing safety for new beauty care products (pre-clinical/clinical safety programs, risk assessment, risk management, risk communication) Lead/collaborate with P&G expert groups to develop or refine and implement improved risk assessment methods.
1999-2001	Procter & Gamble Far East (Japan)	Principle Scientist-Toxicologist/regulatory manager for new business technologies

1991-1999	The Procter & Gamble Co.	Senior Scientist-Toxicologist. Responsible for managing safety for new OTC Health Care products
1984-1990	Environmental Protection Agency - Environmental Criteria & Assessment Office. Cincinnati, Ohio	Toxicologist: Development of risk assessments and associated documentation related to human health and safety to support regulatory decision making, development of new/refined risk assessment methodologies.
1982-1984	Kettering Lab, Environmental Health, University of Cincinnati. Cincinnati, Ohio	Planned, supervised, and conducted studies to evaluate the effects of various environmental toxicants on male reproductive performance and fetal development.
1981	Syracuse Research Corporation	Developed and wrote risk assessments and associated documentation for the assessment of potential human health effects for a wide variety of environmental pollutants.
1979-1981	Health Effects Research Lab, EPA, Cincinnati, OH	Conducted studies to evaluate the potential reproductive impact of exposure to a variety of environmental contaminants.
1977-1979	Health Effects Research Lab, EPA, Cincinnati, OH	Managed contracts and inter-Agency Agreements related to the development of toxicological screening tests and related to development of risk assessment documentation. Provided technical support to the Office of Drinking Water.

OTHER INFORMATION

Recent External Activities:

P&G Representative and Chair of HESI Emerging Issues Committee

P&G Representative to American Chemistry Council Exposure Workgroup and QSAR/SAR Workgroup

P&G Representative to COLIPA workgroup on refining methods for route to route extrapolation for cosmetic ingredients

Invited Expert Reviewer by the European Commission for the HEALTH-2010-Alternative Testing call

Organizing committee CEFIC workshop non-test methods for REACH (author of funded proposal)

Invited Speaker 2010. ECHA Expert Workshop "Dealing with Uncertainty of Non-Test Methods under REACH"

Invited Speaker Eurotox 2012. Application of a read-across framework provides high quality safety information. IN: Read-across in risk assessment; problems or possibilities?

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Society of Toxicology, Full Member

Publications

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Stara, J. F., Patterson, J., Blackburn, K., Hertzberg, R., DeRosa, C., Health Risk Assessment of Chemical Mixtures. *In: Trace Substances in Environmental Health*, XIS, D. Hemphill, ed. 19 Annual Conference in Environmental Health, June 3 - 6, 1985, Columbia, MO.

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Kirk B. Arvidson

Ph.D. in Organic Chemistry, Iowa State University, 1998; B.S. in Chemistry, Purdue University, 1992;

Kirk Arvidson received a B.S. in Chemistry from Purdue University and a Ph.D. in organic chemistry from Iowa State University. Before coming to the FDA, he conducted research in the area of synthesis and free radical polymerization of polar-functionalized 1,3-butadienes. Dr. Arvidson is currently a review chemist in the Division of Food Contact Notifications in FDA's Office of Food Additive Safety and an expert in assessing human exposure to food additives. In addition to his duties as a review chemist, Dr. Arvidson serves as team leader for the Office's SAR Team. The SAR Team performs computational toxicology modeling of new food additives in support of FDA's safety assessment of these materials. In addition, the team conducts research in the area of applying new computational toxicology models and paradigms such as the toxicological threshold of concern (TTC) to assess the safety of new food additives. He co-chairs the development of a food additives knowledge-base that will capture the Office's institutional knowledge as well as provide new computational toxicology tools that will be used during the safety evaluation of new food additives.

Publications

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2. Kirk B. Arvidson. Luis G. Valerio, Jr., Marilyn Diaz, and Ronald F. Chanderbhan "In Silico Toxicological Screening of Natural Products" Toxicology Mechanisms and Methods, 2008, 18, 229.
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COSMOS Newsletter No. 1
09/2011

Integrated *In Silico* Models for the Prediction of Human Repeated Dose Toxicity of Cosmetics to Optimise Safety

The COSMOS Project is a unique collaboration addressing the safety assessment needs of the cosmetics industry, without the use of animals.

The main aim of COSMOS is to develop freely available tools and workflows to predict the harmful long-term effects of cosmetic ingredients to humans.

This will be achieved using computational tools such as applying thresholds of toxicological concern (TTC), *in silico* toxicology (grouping, read-across and (Q)SAR – (quantitative) structure-activity relationships), *in vitro* data and physiologically-based pharmacokinetic (PBPK) modelling.

The five year project, which started in January 2011, is funded jointly by the European Commission (through the 7th Framework Programme) and the European trade association for the cosmetic, toiletry and perfumery industry Colipa. It is coordinated by Liverpool John Moores University, England.

In this First Issue

The project brings together expertise from industry, SMEs, academia and regulatory agencies from across Europe as well as the USA.

COSMOS Objectives

The focus of the COSMOS project is to develop an integrated suite of open source and/or open access computational models to assist in the prediction of human repeated dose toxicity for cosmetics. This suite of models will form a flexible and transparent tool within an integrated workflow.

The *in silico* workflows will allow for the prediction of repeated dose toxicity to humans through the integration of models based on threshold of toxicological concern, innovative chemistry and physiologically-based pharmaco-kinetics.

The workflows will be adaptable and form a set of building blocks allowing users to incorporate their own data and search existing data compilations.

Specific objectives:

- Collate, curate and quality control new sources of toxicological data and information from regulatory submissions and the literature.
- Establish thresholds of toxicological concern for endpoints relating to human repeated dose toxicity.
- Develop innovative strategies to use existing and novel *in silico* approaches to predict toxicity.
- Establish kinetic and PBPK models *in vitro, in silico* and other relevant data to predict target organ concentrations and long term toxicity to humans.
- Integrate open source and open access modelling approaches into adaptable and flexible *in silico* workflows.

The SEURAT-1 Cluster

COSMOS is one of seven projects forming the SEURAT-1 cluster (www.seurat-1.eu).

SEURAT is a European research initiative with the long-term goal of achieving "Safety Evaluation Ultimately Replacing Animal Testing".

In a first step, SEURAT-1 ("Towards the replacement of *in vivo* repeated dose systemic toxicity testing") will iteratively develop an innovative concept for repeated dose systemic toxicity testing based on the research work carried out by six research projects, including COSMOS:

- SCR&Tox: Stem cells for relevant efficient extended and normalised toxicology
- HeMiBio: Hepatic Microfluidic Bioreactor
- DETECTIVE: Detection of endpoints and biomarkers for repeated dose toxicity using *in vitro* systems
- NOTOX: Predicting long term toxic effects using computer models based on systems characterisation of organotypic cultures
- ToxBank: Supporting integrated data analysis and servicing of alternative testing methods in toxicology

The coordination action COACH (Coordination of projects on new approaches to replace current repeated dose systemic toxicity testing of cosmetics and chemicals), has been set up to optimise cooperation between the cluster projects and to pave the way for future research.

The Cosmetics Directive Banning Animal Testing

All cosmetic ingredients must be demonstrated to be safe for application to humans. Currently there are two distinct channels in the safety evaluation of cosmetic ingredients:

- Colorants, preservatives, UV filters and other (banned or restricted) substances appearing in the annexes of the Cosmetics Products Directive are formally reviewed by the Scientific Committee on Consumer Safety (SCCS).
- The safety evaluation of all other ingredients in finished cosmetic products is carried out by a qualified safety assessor in industry.

There is a requirement to assess the effects of repeated doses of cosmetic ingredients. However, the 7th Amendment to the Cosmetics Directive 76/768/EEC / the new Cosmetic Products EU Regulation 1223/2009 will soon ban the marketing of cosmetics tested for this purpose in animals.

In general, the Cosmetics Directive puts an end to animal testing by banning:

- Testing of finished cosmetic products (since 11 September 2004) and ingredients on animals (since 11 March 2009).
- Marketing of finished cosmetic products which have been tested on animals or which contain ingredients that have been tested on animals since 11 March 2009 for all human health effects with the exception of repeated-dose toxicity, reproductive toxicity and toxicokinetics. For products tested for these specific health effects the deadline is 11 March 2013.

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Animal tests should be replaced by alternative safety assessment methods. However, currently no validated alternatives exist for the prediction of repeated dose toxicity. In addition, there is an increasing concern that animal testing and the existing alternatives are not adequately protective of human health. Therefore, as part of the Seurat-1 cluster of alternatives projects, COSMOS will provide an integrated suite of computational prediction methods to assist in the assessment of the safety of cosmetic ingredients considering relevant information, e.g. systems biology, from the other cluster projects.

Predictive Toxicology

In silico methods are computational methods that can be used to predict the physico-chemical and biological properties of molecules. They include several approaches, such as read-across, grouping, category formation and (quantitative) structure-activity relationships ((Q)SARs). QSAR estimates have been used routinely for predicting key environmental fate parameters and for ecotoxicological endpoints, several QSARs are recommended in the Guidance Documents of the European Chemicals Agency (ECHA) .

For human health effects, non-testing methods have rarely been used, and where they have been used, it is generally in the form of grouping rather than QSAR. Currently the cosmetics industry is working on four priority areas: eye irritation, genotoxicity / mutagenicity, skin sensitisation and systemic toxicity. *In silico* approaches are used in the cosmetics industry for the prediction of these endpoints.

In COSMOS there will be a strong emphasis on optimising *in silico* approaches, such as (Q)SAR, grouping and read-across, for the purpose of long-term toxicity prediction of cosmetic ingredients.

COSMOS Kick-Off Meeting in Ispra

27 delegates met on 17–18 January 2011 in Ispra, Italy, for the COSMOS Kick-Off meeting, which was hosted by partner JRC at the Joint Research Centre of the European Commission.

The purpose of this meeting was for all partners to get to know each other and gain a better overview of the different parts of, and interactions within, the COSMOS project.

After the introduction of the delegates and partner institutions as well as an overview of the project and the work packages, the delegates discussed the scientific approaches of the working groups, the first steps to take and planning for the different workpackages as well as administrative issues and dissemination of project results.

The various samples of Italian cuisine enjoyed at the first shared project dinner also contributed to stimulate further discussions in the evening.

The second day was dedicated to an introduction to the KNIME technology, which will be an essential part of COSMOS for implementation and dissemination of the models and workflows developed. Partner KNIME gave a much appreciated hands-on demonstration of the software.

CIR Panel Book Page 23

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What We Are Doing

Databases

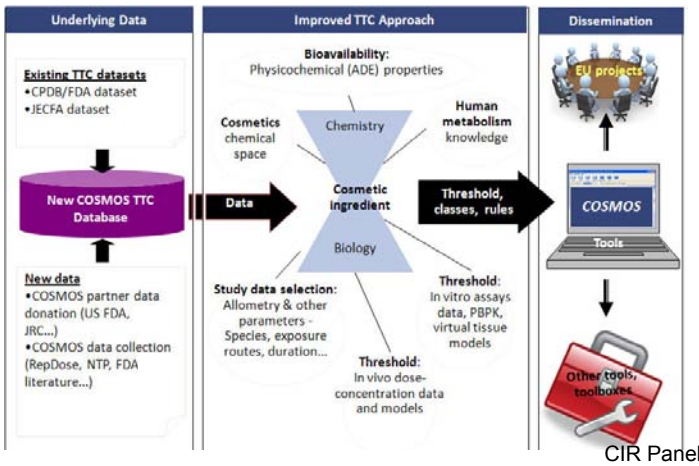
- Collation and curation of new sources of toxicological data and information from regulatory submissions and the literature, focussing on chronic toxicity assessment.
- Creation of an inventory of known cosmetic ingredients and population with chemical structures.

The data are being captured in a new logical 3-tier architecture (user interface, representation functionalities and database structure and access). The database is being built on existing approaches (e.g. the CERES project at the US FDA) and facilitates further data exchange with related or subsequent structures and databases. The data repositories will be completely open i.e. will not require other commercial or open source software to be used for search and retrieval. The information within the databases will be curated and its quality assessed.

Thresholds of Toxicological Concern for Cosmetics

- Establishment of thresholds of toxicological concern (TTC) to ensure safety of chemicals for endpoints relating to human repeated dose toxicity.

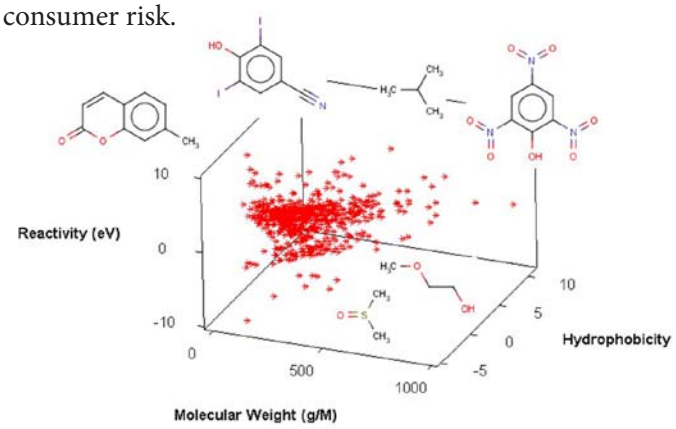
The goal is to deliver a recommendation on applying the current TTC approach to cosmetics ingredients and on the extrapolation of oral-to-dermal exposure. The COSMOS partner ILSI Europe TTC Task Force has set up two TTC expert groups (see p. 5). They will expand and review the COSMOS TTC dataset for appropriateness of relevant data and then investigate the creation of thresholds and the application of the TTC concept to cosmetics.



In Silico Predictions of Toxicity

- Development of innovative strategies based around categories, grouping, read-across and (quantitative) structure-activity relationships ((Q)SARs) to predict long-term toxicity of cosmetic ingredients and relate to adverse outcome pathways where possible.

This will be achieved by characterising the chemical space of the cosmetic inventory both in terms of the physico-chemical properties and chemical substructures covered in the inventory. In addition, *in silico* approaches will be refined to incorporate kinetic and metabolic studies to permit quantitative interpretation of results in terms of consumer risk.



In Vitro - In Vivo Extrapolations

- Establishment of kinetic and physiologically-based pharmacokinetic (PBPK) models, *in vitro*, *in silico* and other relevant data to predict target organ concentrations and long term toxicity to humans.

The aim is to predict the dose of a cosmetic ingredient at the target organ level from *in vitro* (and other) information, allowing for corrections due to experimental conditions and metabolism and to upscale the *in silico* and *in vitro* methods at organ and body level to develop complete absorption, distribution, metabolism and excretion (ADME) models for decision making and risk assessment of cosmetic ingredients. In addition, no observable (adverse) effect concentration (NO(A)EC) as a measure of toxicity will be derived from *in vitro* repeated dose systems and PBPK modelling should allow prediction of corresponding *in vivo* concentration-dose. Finally, the application of these models by predicting internal concentrations will support the application of the TTC concept.

The aim is to formulate an integrated modelling approach that will incorporate toxicological data from the corresponding levels:

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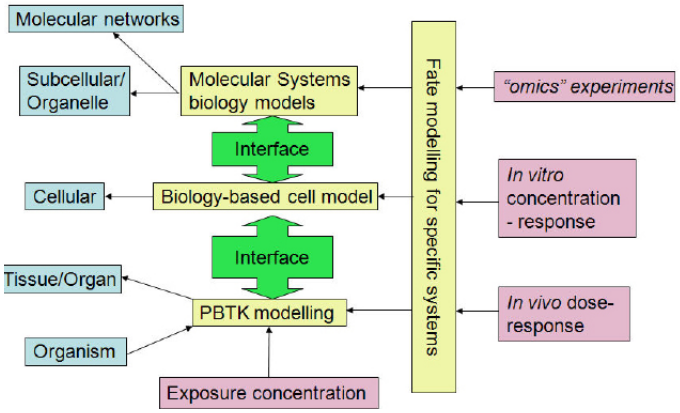
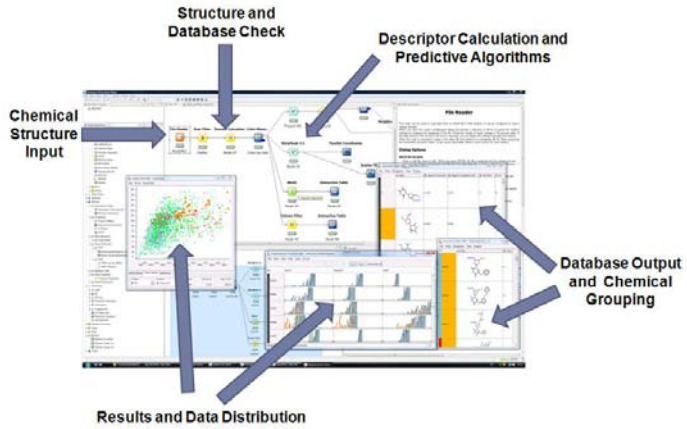


Flexible Computational Workflows for Assessing Toxicity

- Integration of open source and open access modelling approaches into adaptable and flexible *in silico* workflows using the KNIME technology.

The aim is to develop computational workflows to integrate the models and tools developed within COSMOS. This will require an enhancement of the KNIME modular integration platform and will result in an open access and transparent tool for integrating the data with predictive models such that the user will be able to transparently predict repeated dose toxicity from the outputs of the COSMOS project.



COSMOS Training

Events for external stakeholders will be organised to disseminate practical knowledge of the models and workflows developed.

COSMOS will also contribute training modules to Summer Schools set up by the SEURAT-1 cluster.

ILSI-EU TTC Expert Groups

The ILSI Europe Threshold of Toxicological Concern (TTC) Task Force is a partner in the COSMOS project and contributes to the work package on TTC. The TTC approach is pursued in this project as one of the risk assessment methods designed to address safety assessment issues in a pragmatic manner.

The task force has set up two expert groups with the aim to deliver opinions and recommendations to guide COSMOS in the effort to expand the current TTC approach so that it will have a broader applicability and regulatory acceptance for cosmetic ingredients.

Expert Group 1: Development of criteria to be applied in the extension of the current TTC approach to cosmetics ingredients

This expert group advises on the structure and creation of the database for cosmetics by recommending inclusion criteria for chemicals and toxicological studies (quality and selection) and supports the evaluation of the data collection. Using this new database, the expert group will investigate the application of TTC to cosmetics by evaluating the chemical space of cosmetic ingredients as it compares to the existing Munro database, and whether the existing Cramer Classes are appropriate, or whether additional TTC tiers and thresholds need to be established.

This expert group convened its first conference call in July 2011 to bring its members to the same level of understanding with regard to the structure, objectives and timelines of the project and to agree on the next steps. The first face-to-face meeting is scheduled for November 2011.

Expert Group 2: Evaluation of oral-to-dermal extrapolation

The current TTC approach was developed from an oral toxicity database and questions have been raised about its applicability to dermal exposure. This expert group focuses on the technical issues associated with oral-to-dermal extrapolation, identifying data needs and assessing the feasibility of extrapolation. Additionally, the group will investigate possible methods, building on the work of Kroes et al. (2007), to improve extrapolation and the appropriateness of the use of modelled data.

It is planned to organise a workshop in 2013 to present the results of the expert groups to a broader audience, before publishing them in a scientific journal.

COSMOS Partners

Liverpool John Moores University

The Liverpool School of Pharmacy at Liverpool John Moores University is the second oldest School of Pharmacy in the United Kingdom (founded in 1849), the University itself has over 24,000 students and is one of the largest Universities in the UK.

The QSAR and Modelling Group based within the School of Pharmacy and Biomolecular Sciences has undertaken research into *in silico* alternatives for over 40 years and has broad expertise in the development of *in silico* models for biological activity, and toxicity in particular. The researchers investigate the relationships between biological activity and the physico-chemical properties of compounds. This area includes the development of quantitative structure-activity relationships (QSARs) to predict toxicological and pharmacological as well as physico-chemical parameters.

The researchers in the QSAR and Modelling Group are dedicated to application of these methods to industrial settings and have experience of serving on various working groups and national committees including: OECD, ECB, ECVAM, US EPA, Cefic etc. They have expertise in training non-experts and experts alike in the development and application of *in silico* techniques for toxicity prediction, including ECB training courses, training courses on EU projects and bespoke training programmes for industry. The Group has been involved in a number of EU projects including OSIRIS, CAESAR, ReProTect, InSilicoTox, IMAGETOX, and the OECD (Q)SAR Application Toolbox.

LJMU coordinates the COSMOS project and is responsible for the day-to-day management. Other key tasks include toxicological data retrieval, curation, quality assessment and databasing as well as the development of innovative computational approaches to predict toxicity. LJMU is also leading the dissemination of results and integration of COSMOS with other projects.

The European Commission's Joint Research Centre

The European Commission's Joint Research Centre (JRC) provides customer-driven scientific and technical support for the conception, development, implementation and monitoring of European Union (EU) policies.

The Institute for Health and Consumer Protection (IHCP) is one of the JRC's seven scientific institutes and aims to protect the interests and health of the consumer in the framework of EU legislation on chemicals, food and consumer products.

Within the IHCP, the Systems Toxicology Unit includes a range of competences in computational toxicology, biostatistics, informatics, high-throughput screening and "omics". Activities are focused on the development, assessment and application of alternative (non-animal) methods for assessing the adverse effects of chemicals.

Members of the unit are involved in a number of EU-funded activities including several projects in the Seurat-1 cluster, as well as working groups under the auspices of ECHA, EFSA and the OECD.

Within the COSMOS project, the JRC is coordinating the workpackage on *in vitro - in vivo* extrapolations, and is contributing to the development of the TTC approach, innovative approaches for toxicity prediction and PBPK modelling, as well as providing a link with the European Centre for the Validation of Alternative Methods (ECVAM), which is hosted within the IHCP.

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United States Food and Drug Administration's Center for Food Safety and Applied Nutrition

The Center for Food Safety and Applied Nutrition (CFSAN) is one of six centers in the US Food and Drug Administration (US FDA) and is committed to the mission of promoting and protecting the public's health by ensuring that the nation's food supply is safe, sanitary, wholesome, and honestly labelled, and that cosmetic products are safe and properly labelled.

CFSAN has a strong history of construction of searchable toxicity databases dating back to the 1970s. It is also one of a few regulatory agencies employing the Threshold of Regulation paradigm and QSAR methods in the pre-market review process. The team recently has embarked on the establishment of the Chemical Evaluation and Risk Estimation System (CERES) to modernise the current workflow of pre-market and post-market safety assessments for food ingredients and contact substances. This system contains a knowledgebase providing integrated toxicity and advanced scientific computing methods.

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Within the COSMOS project, USFDA undertakes toxicological data harvesting, quality assessment and database construction, develops methods to extend the TTC approaches to cosmetics, disseminates results and integrates COSMOS with other US projects.

Henkel AG & Co. KGaA

Henkel, headquartered in Düsseldorf, Germany, has about 52,000 employees worldwide and counts among the most internationally aligned German-based companies in the global marketplace. Henkel has three globally operating business sectors: Home Care (e.g. household cleaning products), Personal Care, and Adhesives, Sealants & Surface Treatment (world market leader). Henkel's cosmetic division is one of the largest of its kind in the world. The safety for human health is a prerequisite for the quality of Henkel products.

VSA–Human safety assessment (HSA) is the scientific competence and service centre of Henkel for human safety and covers all aspects of human safety assessment needed for a scientifically sound and legally compatible evaluation of raw materials and formulated products. Preferentially alternative methods are used, whenever they provide a level of protection to human health comparable to the level obtained by conventional methods. For more than two decades, Henkel has worked intensively on the development of alternative methods capable of providing the information needed without animal testing. The methods developed by Henkel since 1982 include the hen's egg test and tests on cell cultures and skin models.

Henkel-HSA contributes to the development of TTC approaches in COSMOS for endpoints relating to human repeated dose toxicity and to the selection of chemical substances relevant for cosmetic formulas.

Merck KGaA

Merck is a global pharmaceutical and chemical company with total revenues of € 9.3 billion in 2010, a history that began in 1668, and a future shaped by more than 40,000 employees in 67 countries. Its success is characterised by innovations from entrepreneurial employees. Merck's operating activities come under the umbrella of Merck KGaA, in which the Merck family holds an approximately 70% interest and shareholders own the remaining

approximately 30%. In 1917 the U.S. subsidiary Merck & Co. was expropriated and has been an independent company ever since.

MERCK is a member of the European Federation for Cosmetic Ingredients (EFfCI).

The key tasks allocated to partner Merck in the COSMOS project, to be carried out in the Molecular Modelling Laboratory at Merck, include to validate the new TTC approaches for cosmetic ingredients with test cases in collaboration with Colipa members, to identify and implement reliable software packages that are supported over the long-term as well as to evaluate the possible use of grouping approaches for ingredients of cosmetics.

Institut National de l'Environnement Industriel et des Risques

INERIS is a large public institute (with a staff of 600) whose mission is to provide scientific and technical assistance to support public decision-making and help industries to manage risks. INERIS has extensive facilities and competence in *in vitro*, *in vivo*, and *in silico* toxicology. INERIS has experience in participating and managing large international projects.

The research unit METO (Models for Ecotoxicology and Toxicology) undertakes research into modelling and bioinformatics. Recently the group has been involved in a number of EU projects including 2-FUN, PREDICTIV, ERAPHARM, INTARESE, NANOSAFE II, NANOFOL.

Within the COSMOS project, the key tasks of INERIS include: QSAR modelling, PBPK modelling, DEB and DEBtox modelling, dissemination of results and integration of COSMOS with other projects.

International Life Sciences Institute – European Branch

The International Life Sciences Institute (ILSI) is a non-profit, worldwide foundation established in 1978 to advance the understanding of scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment. By bringing together scientists from academia, government, industry, and the public sector, ILSI seeks a balanced approach to solving problems of common concern for the well being of the general public.

ILSI Europe was established in 1986 to identify and evaluate scientific issues related to the above topics through symposia, workshops, expert groups, and resulting publications. The aim is to advance the understanding and resolution of scientific issues in these areas. ILSI Europe focuses on the specific needs defined by the Institute's European partners.

ILSI-EU contributes to the COSMOS project with two expert groups set up by the TTC Task Force.

Altamira LLC

Altamira LLC is a small company, located in Columbus, Ohio, USA with expertise in computational toxicology, QSAR, statistical and materials modelling. The Chief Scientific Officer of Altamira LLC, Dr. Chihae Yang, serves as an ORISE fellow at US FDA. Altamira LLC extensively collaborates and consults with many EU-based organisations.

Currently, Altamira LLC is developing the US FDA CERES knowledgebase, based on the threshold of toxicological concern (TTC) approach, and QSAR models to be used during pre-market reviews and post-market surveillance. Altamira LLC is also a project adviser for an EU SME for developing improved TTC approaches for EFSA. In 2007, Chihae Yang was appointed by JRC to prepare a scoping study for a computational tool for reactivity and fate, which eventually materialised as the START and CRAFT tools. She led the international LIST ToxML consortium to develop a toxicity database standard and QSAR modelling software application, funded by a US NIST ATP grant while she was the Chief Scientific Officer at Leadscope, Inc. (2000-2008).

The key tasks allocated to Altamira LLC in the COSMOS project include the coordination of the TTC work package;

the construction of a public toxicity database schema and a database entry tool that will be compatible with EU projects as well as US FDA and industrial partners; the development of new methods and algorithms to extend and improve the current TTC approaches for cosmetics; the development of innovative computational approaches to predict toxicity, metabolism, and physiologically-based pharmacokinetics (PBPK) modelling for internal dose estimation; as well as the design of a TTC tool to be pipelined into the overall workflow package.

Insilico Biotechnology AG

Insilico Biotechnology, a privately-owned company, located in Stuttgart, Germany, designs and optimises biotechnological processes for the pharmaceutical and chemical industries. Successful in business since 2001, Insilico provides internationally renowned expertise and a unique systems biotechnology platform. Insilico's competitive advantage is its proven track record of producing innovative solutions and IP for customers using large-scale *in silico* cells and high-performance grid computing.

Insilico have participated in a number of relevant projects including HEPATOSYS – systems oriented analysis of detoxification in hepatocytes (BMBF, Germany), ZIM-HPC – application of high performance grid computing for identifying systems dynamics in large-scale networks (BMWi, Germany), and MedSys – a systems oriented approach to cell-tissue interaction (BMBF, Germany).

Insilico contributes to the COSMOS project with *in silico* dose-effects models at molecular level, the reconstruction and validation of a 2D *in silico* liver and high-performance grid computing.

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KNIME.com

KNIME.com is a software company supporting the open source data analytics platform KNIME both with professional support and enterprise products (server, cluster execution, reporting). KNIME.com enables corporations to use the KNIME software within a real enterprise context. Among the KNIME users are many pharma companies but also users from other areas of applications such as life sciences, bioinformatics, data analytics, business intelligence.

KNIME.com's core staff consists of the development team behind the initial KNIME platform (which was initially developed in the group of Prof. Michael Berthold at the University of Konstanz) in addition to software developers and sales/marketing specialists. The chemoinformatics development team at KNIME.com has a strong background in development of components for the integration of inhouse software projects and also the integration of other open source projects, such as the Chemistry Development Kit CDK.

The key tasks of KNIME in the COSMOS project include coordination of the integration activities work package, integration of other open source and closed source projects, assisting other partners in the development of KNIME wrappers for their own tools and dissemination of the resulting predictive workflows.

Molecular Networks GmbH

Molecular Networks (MN) offers innovative chemo-informatics software products, consulting, development and research services to increase the quality and productivity of discoveries in chemical, pharmaceutical

and biotechnology research and development. Founded in 1997, Molecular Networks established international business relationships and its technology is utilised worldwide in major industrial and academic discovery laboratories to design and optimise chemical products and processes. Molecular Networks' product portfolio comprises a variety of software tools, databases and decision support systems for the design and the synthesis of chemical compounds and for the prediction of their chemical, physical and biological properties, their chemical reactivity and metabolic or environmental fate. The company provides maintenance and support and actively further develops its products.

Molecular Networks was founded and is headed by Prof. Johann Gasteiger of the Computer-Chemie-Centrum of the University of Erlangen-Nürnberg. Prof. Gasteiger is a pioneer of chemoinformatics in Germany and has built a unique expertise in this area over the last 30 years. This is documented in more than 250 scientific publications as well as in a book on Neural Networks in Chemistry and Drug Design as well as the first comprehensive Textbook on Chemoinformatics and a four volume Handbook of Chemoinformatics.

Molecular Networks has experience in conducting projects for public research organisations. The CRAFT, START, and METIS projects for the JRC Ispra were successfully completed recently. Molecular Networks is a consortium member of the EU FP7 funded projects eTox and Microme.

The key tasks of Molecular Networks within the COSMOS project include the implementation of a data entry tool, method development for metabolism prediction, the development of a TTC software tool considering metabolism and the integration of chemoinformatics software modules for descriptor calculation, prediction of metabolism, and toxicity related (Q)SAR models.

Soluzioni Informatiche

S-IN (Soluzioni Informatiche Srl), located near Venice, is a company that provides consultancy services and supplies customised computer-assisted solutions in life science frameworks.

S-IN was founded in 1994 by Massimo Mabilia after 10 years experience in the USA and UK as a researcher and consultant in the fields of molecular modelling and chemoinformatics. The S-IN team currently comprises about 12 people who provide highly-qualified support in the fields of chemistry and toxicology. The main expertise lies in computational chemistry, computational toxicology, chemoinformatics, bioinformatics, and databasing – e.g., data analysis, data mining, (quantitative) structure-activity relationships ((Q)SAR), and modelling – as well as technical and scientific knowledge on the use of *in silico* approaches for predicting physico-chemical properties of chemical compounds.

S-IN is involved in a number of contracted research projects under the auspices of the European Food Safety Authority (EFSA).

The key tasks allocated to S-IN in the COSMOS project include the coordination of the work package on *in silico* toxicity predictions, the development of innovative computational approaches to predict toxicity and the optimisation of *in silico* methods, such as (Q)SAR and read-across, for the purpose of long-term toxicity prediction of cosmetic ingredients.

Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences

The Institute of Biophysics and Biomedical Engineering (CBME-BAS) is a unit of the Bulgarian Academy of Sciences – the biggest and most active research organisation in Bulgaria. CBME-BAS has activities in quantitative structure-activity relationships and molecular modelling (QSAR-MM), biomedical signal processing and analysis, biomedical informatics, analysis and modelling excitability of biological structures, as well as modelling and optimisation of bioprocess systems.

The QSAR-MM department of the CBME-BAS was founded in 2003. Its mission is to perform theoretical and

applied studies in the fields of computational pharmacology and toxicology. The members of the group are experienced in development and application of modelling approaches such as ligand- and structure-based methods for rational drug design and predicting effects of chemicals on human health and the environment. The group members have participated in more than 10 national and international research projects in this field.

Within the COSMOS project CBME-BAS contributes to the toxicological data harvesting, as well as the development of innovative computational approaches and the optimisation of existing approaches for long-term toxicity prediction of cosmetic ingredients.

Photo: Ivaylo Mihaylov

Kemijski inštitut / National Institute of Chemistry

The National Institute of Chemistry (NIC) is the leading research institution in the field of chemistry and related disciplines in Slovenia. Currently it has over 250 staff involved in research and teaching in three Slovenian Universities. Its research profile and modern infrastructure enables top-level scientific achievements and transfer of knowledge into the economy. NIC has a good infrastructure for organisation of workshops and meetings.

The Laboratory of chemometrics (LC) was established in 1983 and is one of 16 laboratories in the Institute. Its main task has been the development and promotion of statistical and mathematical (chemometrical) tools to users from academia, industry and regulatory bodies. In 1994 LC has included QSAR modelling into its research programme. The participation of LC in EU funded projects started in the eighties with TEMPUS and COPERNICUS, followed by the projects IMAGETOX, TRACE, IBAAC, VICIM, COST D29 and CAESAR. In the framework of EU projects LC has organised over a dozen schools, workshops and meetings at national and international level. Members of the LC also participated in workshops organised by ECB, ECVAM and IRMM.

Within the COSMOS project NIC will contribute to the dissemination of results and integration of COSMOS with other projects, in particular with the organisation of training events.

University of Bradford

The University of Bradford was established as a technical college in 1882 and was granted a Royal Charter in 1966, when it became the University of Bradford; currently it has more than 10,000 students from over 110 countries. The University's core mission is "Making Knowledge Work": it provides high-quality teaching informed by internationally recognised research.

The UNIBRAD team reflects this multidisciplinary profile, and consists of staff from the Artificial Intelligence Research Group of the School of Computing, Informatics and Media (SCIM) and the Institute of Cancer Therapeutics. Research strengths include artificial intelligence, data mining, computer/mobile networks, image processing, new/digital

media, also cancer therapeutics and drug target selectivity. The school has extensive national and international collaborations (also with other European Framework projects). There is a healthy and growing programme of collaborative work with industry, much of it based in knowledge transfer partnerships, and national research funding from the EPSRC and the BBSRC.

The key tasks allocated to UNIBRAD in COSMOS are the coordination of the work package on data collection and data curation, the development of computational intelligence techniques, data and model integration, and data mining tools.

The COSMOS Consortium

Liverpool John Moores University, England (**LJMU**)

Commission of the European Communities – Directorate General Joint Research Centre, Ispra, Italy (**JRC**)

United States Food and Drug Administration, Silver Spring, MD, USA (**USFDA**)

Henkel AG & Co. KGaA, Düsseldorf, Germany (**Henkel-HSA**)

Merck KGaA, Darmstadt, Germany (**Merck**)

Institut National de l'Environnement Industriel et des Risques, Verneuil-en-Halatte, France (**INERIS**)

International Life Sciences Institute Europe, Brussels, Belgium (**ILSI-EU**)

Altamira LLC, Columbus, OH, USA (**MIRA**)

Insilico Biotechnology AG, Stuttgart, Germany (**Insilico**)

KNIME.com GmbH, Zurich, Switzerland (**KNIME**)

Molecular Networks GmbH, Erlangen, Germany (**MN**)

S-IN Soluzioni Informatiche Srl, Vicenza, Italy (**S-IN**)

Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences, Sofia, Bulgaria (**CBME-BAS**)

National Institute of Chemistry, Ljubljana, Slovenia (**NIC**)

University of Bradford, England (**UNIBRAD**)

COSMOS Meeting at SEURAT-1 Kick-Off Meeting in Cascais

Delegates from the COSMOS partners and the Scientific Advisory Board met on 28 February 2011, just before the SEURAT-1 Kick-Off meeting, in Cascais, Portugal, for the first COSMOS Annual General Meeting.

Following a brief outline of the aims and objectives of COSMOS, issues of data availability and harvesting as well as data quality were discussed in detail.

The characterisation of the chemical space of the COSMOS database and issues relating to incomplete data and non-standard formats were raised and different data types and the data entry tool development were discussed.

Delegates were informed on the setup of the ILSI-EU TTC expert groups investigating the extension of thresholds of toxicological concern to the cosmetics applicability domain, and the oral-to-dermal extrapolation. Acceptance by regulatory authorities was identified as key for the approaches for oral-to-dermal extrapolation.

The development of KNIME workflows to take account of physico-chemical properties, cell characteristics and assay characteristics were discussed.

After lunch, the work packages had separate group break-out meetings to discuss ongoing and upcoming work.

The results were fed back to the COSMOS plenum, where further administrative issues as well as dissemination and training activities were also discussed.

At the SEURAT-1 cluster Kick-Off meeting on 1-3 March 2011, COSMOS presented their objectives, scientific approach, and expected outcome along with the other cluster projects Scr&Tox, HeMiBio, DETECTIVE, NOTOX and ToxBank.

The COSMOS coordinator also contributed with an overview of challenges and pitfalls in predicting toxicity.

KNIME User and Developer Training in Zurich

On 4-7 April 2011, KNIME.com organised two training workshops for the COSMOS project partners in Zurich, Switzerland.

On the first two days, seven partners were trained in KNIME usage. On the first day, the basic KNIME concepts were introduced, such as installation, the workflow concept as well as the hiliting feature useful for analysing data in different views. Furthermore, more advanced topics such as connecting to external databases and using the built-in data mining components were covered. The day finished with exercises on how to use R and the Weka machine learning library from within KNIME. During the dinner in the evening the participants had more time to talk to the KNIME developers. On the second day, training was given in the usage of loops and flow variables for performing sophisticated tasks, and the batch executor for running KNIME workflows in an automated way was presented. Moreover, a short introduction to KNIME's reporting capabilities was given.

Following the user training, future KNIME developers were trained on the next two days. The six project members first got an introduction into the KNIME architecture covering the concepts of nodes, dialogues, and views. Using the node extension wizard the first example node was already working before lunch. The afternoon session covered data types used in KNIME's table model and programming dialogues. Again, the dinner together with the KNIME developers was a perfect opportunity to clarify outstanding questions and learn more about future plans for KNIME. On the final day, the powerful loop concept was covered from the developer's point of view, followed by programming a simple view for nodes. The training was finished by describing how the developed nodes are packaged so that users can easily install them into their KNIME.

Strong COSMOS presence at the Workshop on TTC: Scientific Challenges and Approaches on 8 – 10 June 2011 in Brussels

The International Life Sciences Institute – European Branch (ILSI Europe) took the lead in organising a workshop on thresholds of toxicological concern (TTC) in Brussels, Belgium, in order to explore the scientific challenges to the application of TTC as a tool to aid decision-making in chemical safety assessment.

The workshop was aimed at safety and regulatory scientists from industry, government agencies, animal welfare organisations and academia from all over the world to provide a global perspective.

The workshop consisted of plenary lectures and breakout group discussions. The first session aimed to set the stage, by presenting the perspectives of the EC Scientific Committee, EFSA, WHO and US FDA. The following session consisted of three presentations introducing the topic areas of the breakout groups:

- non-cancer endpoints
- cancer endpoints and
- route-to-route extrapolation.

The workshop participants have:

- Reviewed examples of the application of TTC across different regulatory evaluation frameworks and decision-making programmes;
- Identified scientific barriers to broader TTC acceptance;
- Explored potential opportunities for initiating steps to overcome such barriers.

A summary article of the workshop will be submitted for publication to Regulatory Toxicology and Pharmacology.

Further information can be found on the ILSI-EU website: http://www.ilsi.org/Europe/Pages/TF_ThresholdToxicological.aspx.

Conference Calendar

ecopa Annual Conference

"The future of the 3Rs – from innovation to validation"

11–12 November 2011, Madrid, Spain

http://www.remanet.net/ecopa2011Madrid/WORKSHOPECOPA.htm

13th Cefic-LRI Annual Workshop 2011

"Optimising resource and knowledge in risk assessment"

16 –17 November 2011, Brussels, Belgium

http://www.cefic-lri.org/eventsmanager/68/30/13th-Cefic-LRI-Annual-Workshop-2011/?cntnt01detailpage=calendar&cntnt01next_events=1&cntnt01orderby=start_date+ASC&cntnt01origid=34

7th Annual International Conference on Predictive Human Toxicity and ADME/Tox Studies

26–27 January 2012, Brussels, Belgium

http://www.mondialresearchgroup.com/index.php?whereTo=humt12

SOT 51st Annual Meeting

11–15 March 2012, San Francisco, California, USA

http://www.toxicology.org/ai/meet/am2012/

Bio-IT World Conference

22–26 April 2012, Boston, MA, USA

http://www.bio-itworldexpo.com/

EUROTOX 2012

17–20 June 2012, Stockholm, Sweden

http://www.eurotox2012.org/

15th International Workshop on Quantitative Structure-Activity Relationships (QSAR2012)

18–22 June 2012, Tallinn, Estonia

http://qsar2012.ut.ee/

Reduced Animal Testing

26–27 July 2012, Zurich, Switzerland

http://www.mondialresearchgroup.com/index.php?whereTo=ratest

19th EuroQSAR

Knowledge Enabled Ligand Design

26–31 August 2012, Vienna, Austria

http://www.ldorganisation.com/produits.php?langue=english&cle_menus=1238915416

New Horizons in Toxicity Prediction - The 3rd International Lhasa Symposium 2012

5–6 September 2012, Cambridge, England

https://www.lhasalimited.org/events/item/new_horizons_in_toxicity_prediction_-_the_3rd_international_lhasa_symposium/

ESTIV 2012

17–20 October 2012, Lisbon, Portugal

http://www.estiv.org/estiv2012.html

SOT 52nd Annual Meeting

10–14 March 2013, San Antonio, Texas

http://www.toxicology.org/ms/SOTAM_future.asp

XIII International Congress of Toxicology

30 June–4 July 2013, Coex, Seoul, Korea

http://www.ict2013seoul.org/

EUROTOX 2013

1–4 September 2013, Interlaken, Switzerland

http://www.eurotox2013.com/

SOT 53rd Annual Meeting

23– 27 March 2014, Phoenix, Arizona

http://www.toxicology.org/ms/SOTAM_future.asp

9th World Congress on Alternatives & Animal Use in the Life Sciences WC9

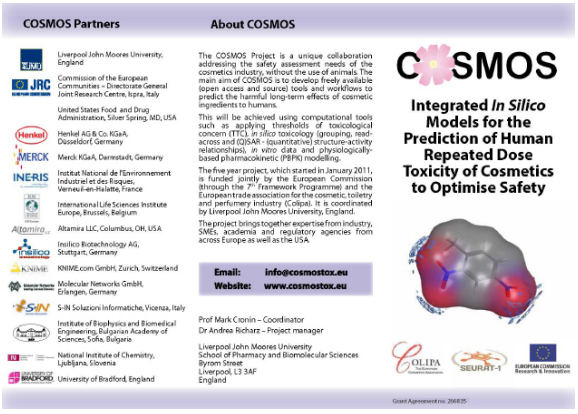
24–28 August 2014, Prague, Czech Republic

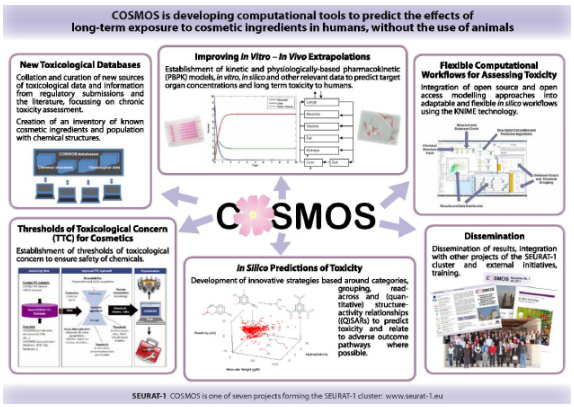
www.wc9prague.org

EUROTOX 2014

7–10 September 2014, Edinburgh, Scotland, UK

http://www.eurotox2014.com/





The COSMOS leaflet is available for download at www.staff.livjm.ac.uk/phamcron/COSMOS_leaflet.pdf.

Subscription to the COSMOS Newsletter

To subscribe to the COSMOS Newsletter, send an email with "subscription" to info@cosmostox.eu.

SEURAT-1 cluster Kick-Off meeting on 1-3 March 2011, Cascais, Portugal

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COSMOS is funded by the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 266835 and Colipa.

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Aerosols

Cosmetic Ingredient Review
Commitment . . . Credibility
Since 1976

CIR

Memorandum

To: CIR Expert Panel and Liaisons
From: Ivan J. Boyer, Ph.D., D.A.B.T.
Senior Toxicologist, CIR
Subject: Aerosols Precedents
Date February 10, 2012

At the December 2011 meeting, the CIR Panel discussed the draft aerosols precedents document, and made changes to both the background section and the templates of the document. The changes were made to clarify the Panel's perspectives on several issues and improve the presentation of the information. The Panel also directed that the revised document should be posted on the CIR Website, first to solicit public comments on the document, and then to provide interested parties with easy access to the background information, the location of which would be included in relevant ingredient safety assessments.

The background section and templates have been revised in accordance with the Panel's discussion at the December meeting. The revised document was then posted on the CIR Website on 20 January 2012 for public comments.

The revised draft aerosols precedents document (as it was posted in January) and relevant portions of the transcript of the December meeting are enclosed for your review. The Panel should review the revised document to ensure that the changes accurately reflect the Panel's views and concerns. Public comments received in time will be included in Wave 2, which will provide the opportunity for the Panel to consider those as well.

Minutes Excerpts of the 12-13 December CIR Panel Meeting

DR. Belsito's Team Discussion 12 December 2011

…DR. BELSITO: At the September meeting, we tentatively concluded that the glucoside ingredients listed were safe in the present practice of use when formulated to be non-irritating. There were some technical comments. And so we're ready to go ahead and issue this as a final "safe in the practices of use and concentrations when formulated to be non-irritating," unless someone has changed their mind since September.

Okay. In the discussion of this, I just didn't like the way things were worded in the last paragraph. It says that -- and this has to do with the aerosol boilerplate, which may get resolved when we get to the aerosol boilerplate. But it said, "In the absence of sufficient safety test data to evaluate this endpoint, the Panel considered other data that were available to characterize the potential for the alkyl glucosides to cause systemic toxicity," which implied to me that they cause systemic toxicity. And what you want to imply is that we've looked at available data to characterize the safety of the alkyl glucosides, including repeated dose toxicity studies, ocular or dermal irritation or sensitization studies, and other effects.

Again, the way it was worded, to me, made it seem like we looked for data to show that it caused toxicity. But, I mean, I think we'll get to that with the respiratory boilerplate, and that may change everything.

DR. BERGFELD: Alan, is it understood that you'll go back over all the documents and have inhalation exposure and fix it as the new --

DR. ANDERSEN: Yeah, whatever comes out of the separate aerosol discussion will be looped back. But I do want to make a note of this here, because it's a small change in focus, but I get your point. Clearly, it's a different way to say it.

DR. BELSITO: We want to stress safety, not toxicity. Anything else, other than typos? Okay.

DR. ANDERSEN: It still gets across the idea -- not to belabor this -- but when there are no inhalation tox data what you're saying is that you're going to look at whatever else you've got for red flags. And that means you're going to look at all of the safety data, including repeated-dose toxicity, yadda, yadda, yadda. Paul made the point at the last meeting that he does that anyway. This was just meant to be a way to capture that.

DR. LIEBLER: So when we refer to "inhalation toxicity," what we're really saying -- what we're really referring to is toxicity to respiratory tract, as opposed to compound is inhaled, compound produces some other systemic toxicity at some other site, other than the respiratory tract, right? So when you say "inhalation toxicity," we mean sort of airway/lung toxicity.

DR. BELSITO: Right. In the inhalation boilerplate I think that's sort of mentioned in a sentence that basically says, "The body burden through inhalation is insignificant." You know, that may, of course, be not true for a certain product. But the implication is that, you know, we've looked at how much would get inhaled and potentially be absorbed through the nasal mucosa, and compared to the other routes of exposure -- cutaneous -- that's negligible.

DR. BOYER: And I think when we refer to "inhalation toxicity," we mean the toxicity to -- the effects, adverse effects, to the respiratory tract --

DR. LIEBLER: Right.

DR. BOYER: -- at one level or another. But then there's also the inhalation route of exposure, which then could result

in systemic effects in other target organs and systems.

DR. LIEBLER: But in this context, in this paragraph, we're really talking about the fact that we don't have data on the toxicity to the respiratory tract. So we're using all the other information at our disposal to reason up probability that that is a significant hazard.

DR. BOYER: Right.

DR. LIEBLER: Right. And so I'm trying to figure out how that relates to Don's initial point about trying to shift the emphasis from looking for toxicity to evaluating safety. I'm just wondering, should we postpone this until we talk about --

DR. BELSITO: Yeah, let's --

DR. LIEBLER: -- the respiratory boilerplate?

DR. BELSITO: Yeah, probably.

DR. SNYDER: Yes, I think the discussion is going to be quite protracted regarding that aerosol language. And rather than reiterate this every time, I think we probably need -- at some point -- to deal with that, and then we can talk about how we want to address it in each report. Because, again, as we stated last time, these are going to be case-by-case instances, in instances where we have different types of aerosol use, different types of formulation with different particle sizes, different data sets. So I think that it's not going to be -- while we will have a general statement, that it will be tweaked a little bit on a case-by- case, ingredient-by-ingredient basis.

Because I think really what we're talking about is incidental exposures. We're not talking about inhalation toxicity -- there's no direct inhalation, intended inhalation. It's just an incidental exposure. In some instances, based on the formulation, that may be very, very low. And then there's attributes to the ingredients and the particles within that that even make it even lower.

And so I think there's information that we need to capture that's relevant on an individual ingredient basis.

DR. ANSELL: Yes, we would also like to have such a discussion. But moving back later is just fine.

DR. BELSITO: Yeah. Okay. Okey-dokey. So then moving to the citric acid group, we went "insufficient" at the last meeting because it was reported to be used at 35 percent in a leave-on, and we wanted an HRIPT at that level. It turns out 35 percent wasn't correct. It's actually 4 percent. We had data on 4 percent in a cuticle cream, which was negative.

There was some clarity that was provided by PCPC on spray uses, that they're at low concentrations, with the highest, a trioctyldodecyl citrate at 14 percent. And even that, it wasn't clear that it was a spray. Again, it's something we're going to have use our inhalation boilerplate on, and we'll get to that when we get to the aerosols. But I think, at this point, "safe as used," with the inhalation boilerplate that we develop for aerosols.

DR. ANDERSEN: I think, in terms of extending the systemic toxicity data -- back to the point that Curt was making at the last meeting, that there is value in asking the question about routes of exposure that might involve the respiratory tract and lung. The respiratory tract does have some routes of exposure that can lead to the brain. It also has a route of exposure that if it gets there, can lead to the lungs. And the question, as Curt posed, that I thought was excellent was, well, suppose it did? That could lead to a systemic exposure.
…Dr. BELSITO: Okay, the inhalation boilerplate, what we've been waiting for all day. I actually thought that this

was very well written. I'm not a respiratory toxicologist, but I was quite pleased with it. And we did get a few comments from the CIR Science and Support Committee, including one that looks like sample calculations from various types of hairsprays and how much exposure there would be in what would be left at various time points and just some comments on the revision that they saw. I'd be fine either way. Again, respiratory is not my area of expertise, so I'll cede to my fellow teammates on how these boilerplates should be worded and if everything's been captured.

DR. LIEBLER: I really liked the document as written. I thought it was excellent. Maybe I missed something, but where are the specific changes that we're suggesting?

DR. BELSITO: They were handed out this morning.

DR. LIEBLER: Oh, maybe that's why I didn't see it.

DR. BELSITO: There are two documents, comments on the aerosol draft revision and then sample exposure calculations.

DR. BERGFELD: Now it was my understanding that this is sort of the standing document from which we will draw our boilerplates and adjust them to whatever we're looking at in the respiratory portion.

DR. BELSITO: Well, I would actually like to see it on the website --

DR. BERGFELD: Website, right.

DR. BELSITO: Just like the hair dye epidemiology.

DR. BERGFELD: Right.

DR. ANDERSEN: That was my game plan.

DR. BERGFELD: But the statement when you reference to it would be what? It has to be shorter.

DR. BELSITO: Well, it would be --

DR. BERGFELD: You must have a summary paragraph.

DR. BELSITO: There were various options that were available depending upon --

DR. BERGFELD: What we had.

DR. BELSITO: -- the circumstances, what are the chemicals we're dealing with. And then, of course, always the option that if something was very unique, we might even have to come up with another boilerplate that would be added. But there were actually several different boilerplates that were put -- when we don't request inhalation toxicity data, when we request it but don't get it, when there actually is inhalation toxicity.

DR. BERGFELD: Page 52, right?

DR. BELSITO: Right. So I think that these -- we would choose which of the boilerplates was appropriate for the specific family we are looking at with the idea that maybe somewhere out there there's a family that doesn't fit into any

of these, and we'd have to create a new category.

DR. BERGFELD: So the intent -- just for clarification -- the intent would be to use this as a standing document, which we look at every whatever interval to update, like the hair dyes --

DR. BELSITO: Well, the part -- right.

DR. BERGFELD: -- and then to remove from it the various sections that are needed for that particular ingredient we're reviewing.

DR. BELSITO: I think the background would be on the website and wouldn't be repeated. So what starts on -- and please correct me if I'm wrong, Alan -- but what starts on page 53 as to the background of how we reach these boilerplates, that would not be repeated in a document. That would be on the website and people would be referred to the website just as they're referred to the website for the hard data on hair dye epidemiology. What would be in the report would be one of the three selected cosmetic use section options and one of the three selected discussion options. And the background would not be in each and every report; that would simply be on the website.

DR. BERGFELD: But then -- I want to clarify this again -- so then if you didn't put these various options on Panel Book 52 and 53, then you would move those to a policy book on boilerplates, or would they be included both places? I mean obviously these will be the current boilerplates, these options, these three options.

DR. BELSITO: Right.

DR. BERGFELD: And what you're saying is that you want to handle aerosols like we did the hair dyes, have a place on the website for whoever wants to look at it. But we need to make sure that if we don't include these options that they occur in the boilerplate -- I'm not sure what you're calling it, but Policy Book. Is that a Policy Book or Administrative --

DR. ANDERSEN: Precedents.

DR. BERGFELD: Precedents Book.

DR. BELSITO: So I guess the question is what would appear on the website, just the background or would the boilerplate options be there as well?

DR. ANDERSEN: We haven't had that discussion yet. I would lean towards giving the public everything.

DR. BERGFELD: I would, too.

DR. ANDERSEN: I don't see why they couldn't read the whole thing.

DR. BERGFELD: I would lean towards having someone look over it as 60 days.

DR. ANDERSEN: But certainly the background is the part that it makes no sense to repeat in safety assessment after safety assessment. So for every hair dye safety assessment, we reference our shorthand for the hair dye epidemiology position established by the Panel. And we cite the website so if anybody wants to read the whole nine yards, they can go to the website and read it all. We would take the same approach here. We would -- it's less clean because it isn't one approach. It's several, but they all should reference the background. And that's what's --

DR. BELSITO: And they do.

DR. ANDERSEN: -- equivalent to how we've handled hair dye epidemiology.

DR. BELSITO: Uh-huh.

DR. KLAASSEN: And you'd put these three after the background, not in front of the background the way we have it now.

DR. ANDERSEN: It could easily be done.

DR. BELSITO: Yeah, it would make more sense.

DR. BERGFELD: Did we go and have a public review of our hair epidemiology statement prior to putting it on the website? Did it -- was it ever sort of publicized?

DR. ANDERSEN: Yes, initially it was. As we've tweaked it going along, we've not done that. But we've just been tweaking it as opposed to making a wholesale change. The minutes of each meeting -- for example, after the presentation in June of the latest hair dye epidemiology, the minutes of the meeting said, "We heard about all of the recent studies and the Panel reaffirmed its position," yadda, yadda, yadda. That offers any interested party the opportunity to say, say what? But we've gotten nothing back. So there is at least an opportunity for input, but we've not formally solicited input each time we make a change in the hair dye epidemiology material on the website.

DR. KLAASSEN: Okay, on these suggested discussions, there's a word here I'd like to change, but I think it's significant. Like on this -- in the middle of the page where it says "level" --

DR. BELSITO: Which discussion point?

DR. KLAASSEN: The one right in the middle of the page.

DR. BELSITO: Under "Tentative reports for which the expert Panel has not requested" --

DR. KLAASSEN: Yeah, third line from the bottom where we have the word "level." I'd rather have the word "amount."

DR. ANDERSEN: Gotcha.

DR. BELSITO: Oh, it's the fourth line up, "aerosols would not be respirable to any appreciable amount."

DR. KLAASSEN: Right.

DR. BELSITO: Okay.

DR. KLAASSEN: And it's in both of these paragraphs.

DR. ANDERSEN: Yeah, so lose "level" and put in "amount."

DR. SNYDER: I had a couple of comments. One is I think -- one thing that's kind of I think confusing and why I kind of agree with Wilma maybe having somebody outside the box review this terminology that we use because when we

talk about inhaled, we're talking about limited only to the level of nasopharynx. And when we talk about respirable, we're talking all the way down into the lungs. But then when we throw in -- sometimes we're using inhalation. When you do inhalation studies, you're basically evaluating safety at all levels of the respiratory tract. So I think there's a blurring in the document. It's not real clear of when we're talking about inhaled versus respirable. I think we need to be very, very careful there in that regard.

And then I would like to propose using -- instead of saying "inhalation toxicity" or "inhalation exposure," that we use the term "potential for incidental exposure" because this really is an incidental exposure; it's not an intended target or an intended consequence of the ingredients, an incidental exposure. And so I think we should emphasize the incidental aspect of that.

DR. BOYER: So just add the word "incidental."

DR. SNYDER: Yeah, yeah.

DR. BOYER: Incidental inhalation.

DR. SNYDER: Yeah because that's really what it is because it's not a -- lungs or the respiratory system is not an intended target for that cosmetic product or ingredient. It's an incidental exposure, emphasizing that.

DR. BOYER: We did also, to your other point, we did try to make it clear the distinctions between inhalation and respirable -- inhalable versus respirable -- and, in fact, respirable particles are inhalable. So we're basically covering the entire respiratory tract with inhalable. And if you have some specific suggestions as to --

DR. SNYDER: I've tagged some in my book. And then on the background, the first paragraph on the background --

DR. BELSITO: If I could just interrupt. In that regard then wouldn't you want to incorporate these exposure calculations?

DR. SNYDER: Yes, I think it would be useful.

DR. BELSITO: I said, with that in mind, consider including the sample exposure calculations that were received from PCPC.

DR. BOYER: So that would go toward building an argument that exposure, in fact, tends to be very small, will be very small, and will not be of concern depending on other factors.

DR. SNYDER: Correct.

DR. ANDERSEN: I'm a little bit concerned with taking the monkey back on us. If the reported use is in a category that we know is a spray, then I have absolutely no trouble with the very straightforward recommendations from the Council. I'm just having a hard time going through all of that effort, and I don't know whether it's used in a spray or not. It's just in a category that includes sprays, but I don't know whether it's used in a spray. We're not getting always that data. In some cases we have them. And if we have the data that says it's in an aerosol deodorant, then this is a wonderful addition to that particular safety assessment. And the existence of the ability to make these calculations probably has to go in this master document someplace so that the public sees what this is like. But I can't see putting it in a safety assessment if I don't know that it's used in that product.

DR. BELSITO: I'm not talking about putting these in the safety assessment. I'm talking about putting it in the aerosol

background.

DR. ANDERSEN: Either way the question is of what utility is it, if you don't know that it's true?

DR. BELSITO: Because I think that if all we know is it may be used in a product that could be aerosolized, and we don't know whether that product would be a pump or a spray, my approach would be to take the worse-case scenario -- i.e., that it's used in a spray -- and we'll have the smallest droplet size. I mean I think the --

DR. ANDERSEN: So if it were, this is what you get, and it's really small.

DR. BELSITO: Right.

DR. ANDERSEN: Okay.

DR. BELSITO: And if we don't know, we assume that it is, and we still get a very small -- I think this is -- because we're not going to get that information. We went out and said yes, when you tell us it's used in a product where there could be incidental inhalation, we want to know is it a pump or is it a spray. Right. We're not going to get it, I mean let's fess up. So I think from my standpoint, I'm just going to assume it's a spray, worst-case scenario.

DR. ANDERSEN: And then these calculations put some boundaries on well, how bad could it be.

DR. BELSITO: Right.

DR. ANDERSEN: Okay.

DR. SNYDER: I have a question for Curt. On the first sentence of the background -- or actually the first two sentences -- shouldn't it really state, "Inhalation toxicity is an important consideration," not safety; and, "Inhalation toxicity of ingredients such as products," not inhalation safety? Shouldn't that be the other way around?

DR. KLAASSEN: I think so.

DR. ANSELL: Yeah, we have the same comment. The Panel requested safety data to evaluate the endpoint. They're requesting inhalation data because otherwise it contradicts the next sentence, which says "in the absence of inhalation data, the Panel will consider other data that may be pertinent." So we agree that other pertinent data can address the safety even if you don't have inhalation.

DR. BERGFELD: What will happen to this particular document? Tomorrow we'll discuss it as a Panel and make recommendations? But are there some automatic things that will happen?

DR. ANDERSEN: I think several things have to happen. To the extent that this is a model for boilerplate language that gets used in individual reports, it has to have that impact. We've made some tweaks to add the concept of incidental, changed "level" to "amount," but not much else. We had almost a reverse argument from what was just made between Paul and Curt. Curt earlier reacted to the use of the word "safety" -- maybe it's the same point. "Absence of sufficient toxicity data" -- okay, so that does work. Never mind, I withdraw that. So that's the same point both places. I'm looking back at citric acid where it started, so the issue is toxicity and always has been.

Then those boilerplate paragraphs get used in the discussion section on the reports for which they're applicable. Now you raised the issue, Wilma, that there is an opportunity here -- Paul as well -- for letting interested parties know that this is going to be posted for comment. Why not? I mean we've had it in the books, so arguably anybody that wanted

to make comments -- the CIR Science and Support Committee certainly did -- but anybody else that wants to provide input could do so. And then we could finalize it in either March or June, depending on your pleasure.

DR. SNYDER: So DR. Rothe has reviewed this?

DR. ANDERSEN: Yes.

DR. LIEBLER: I have a question based on the document we received this morning, the memo from the Science and Support Committee. One point that they raise is the definition of pulmonary overload. This appears on document page 3, which we report page 53, top of the page. The term pulmonary overload, for example, "suggests little potential for pulmonary overload or other respiratory effects." That phrase is used twice. And I suppose it's not immediately clear to me what you mean by pulmonary overload, and is this something that needs to be there or could we just delete that and just include that as respiratory effects?

DR. BOYER: Actually, the definition of pulmonary overload -- it appears in the background discussion, and it's basically the result of overloading the alveoli with inert particles, insoluble inert particles essentially, that can result in respiratory distress. In fact, the standards, the occupational standards, are -- for respirable particles -- are based on that effect. So it's a fairly specific type of effect to look at, but that many different substances would be capable, would have the potential, of causing.

I think that the comment that the Science and Support Committee is making is related to another one. They would like us to remove the example language in the boilerplate itself, the formula that appears in the blue font in the Panel Books. And I think their comment on the use of the term overload on page 3 is simply that there's no explanation of what overload is. But I didn't put it in there because this was just an example.

DR. LIEBLER: So you could envision a situation perhaps separate from the use of a cosmetic product where pulmonary overload might happen.

DR. BOYER: Absolutely.

DR. LIEBLER: Somebody working around heavy concentrations of dust or other things like that. I'm not sure if the focus on pulmonary overload is really relevant to the scope of what we're considering on this Panel, though.

DR. BOYER: Well, it also is relevant when you examine the results of animal studies because, again, you use -- typically they use respirable, large proportions of respirable particles in those studies, and that may be the only effect that they see. So it may appear -- if you take one of these examples, it may appear in our report simply to acknowledge that, in fact, the animal studies reported pulmonary overload, but not necessarily applicable and probably not applicable to anything that anybody would be exposed to through cosmetics.

DR. LIEBLER: Yeah, I see. So it's there to follow off the animal study where there was literally pulmonary overload relative to the nature of the animal study, and that in itself being really irrelevant to evaluating the effects under conditions of use of a cosmetic product.

DR. BOYER: Right.

DR. LIEBLER: So I get that point, but I'm just wondering if that occurs frequently enough to merit highlighting that as opposed to any other respiratory effects in that sense --

DR. BOYER: It occurs frequently in the context --

DR. LIEBLER: -- dealing with animal study data, for example.

DR. BOYER: I would say it occurs frequently. It's something that is often reported.

DR. ANSELL: It goes to I think the potential as an effect. It's entirely dose related, doses which are irrelevant to cosmetics.

DR. BOYER: Irrelevant to cosmetics, yes, but maybe relevant to occupational exposures.

DR. ANSELL: Yeah, typically very large -- or the animal data also whopping great doses. So it's the tying it with a respiratory effect as if there's irritation or sensitization or some type of physiologic effect versus the overload, which is directly related to dose, and I think is pretty well understood for insoluble inert particles.

DR. BOYER: Right.

DR. ANSELL: So I think that's kind of why they were looking to perhaps get it out of here.

DR. BOYER: Yeah, and I think it also -- maybe part of the reason why they would like to see these examples go away in this part of the boilerplate, these examples.

DR. KLAASSEN: I think we have these different paragraphs here, but I think this last paragraph where we do this explanation on the bottom of page 2 and the top of page 3 is probably not necessary to put in this. I mean there's so many different -- I mean as you can see, it's mainly blue rather than black and, therefore, becomes very complicated, I think. I just wonder if this -- I guess I could see just not putting this third explanation in there, just kind of these first two.

DR. ANDERSEN: Where it's turned out to be important is internal to CIR. Not all the technical writers have the same background in inhalation toxicity and part of writing this is to explain that this is complex and that if we're going to be dealing with this, we're going to be dealing with a number of factors. Now this alternatively could be written "see Ivan," but it would be considerably less informative. So it's -- I was looking at this as we understand that this is complex. I think to some extent shifting the language to after the background helps immensely. As Ivan went through, the reality is when you get the odd inhalation toxicity study that is reporting pulmonary overload, now you've got to deal with it because that sounds bad. Well, this is a way of -- the background goes into it, and the opportunity to put in something that says "and you know, that's just not an issue with cosmetics" is comforting somehow.

DR. ANSELL: Well, could we suggest then that that's what the sentence actually would say? I mean what it's looking like is pulmonary overload is a property of a product and not the exposure, so I think what you said is quite correct. I just don't think that this sentence says what you just meant to say.

DR. BELSITO: But that sentence is all in blue, so it's subject to change depending upon what the dataset is.

DR. ANSELL: To the extent its instruction to staff as Alan was suggesting.

DR. BELSITO: Right, but I think -- I don't know, I liked it. So here we've got data. It's like the silylates. When we developed all that, the granuloma formation because they sheared them down to 4 microns and suddenly they were respirable, whereas in real life they're not.

DR. ANDERSEN: They're not.

DR. BELSITO: I mean -- so that would be something where okay, we have the data and now it needs to be based on the data crafted into this paragraph, and it's a guide to the writers as to how to craft it. In that case it wasn't pulmonary overload. It was simply making a molecule that really wasn't pertinent to the cosmetic molecule.

DR. ANDERSEN: So I think the idea that we can further tweak this is a given. But I do like the idea of providing guidance, a maximum amount of guidance, on how to interpret all of this because sooner or later -- and, in fact, we already have run into circumstances where the data seem to be suggesting pulmonary overload. Now what do we do? Well, relax, that's not the end of the world. That's a particular endpoint and here's how it fits into the cosmetics milieu -- and, again, especially going back to the use of the word "incidental exposure" as opposed to an occupational exposure, as opposed to purposefully making the particles so small that they are actually respirable. I mean those are all different circumstances, but -- so I think it adds some explanation in here that will help everybody.

DR. BELSITO: Well, I -- go ahead, Dan.

DR. LIEBLER: I'm sorry. So basically if it's in blue here, that means it might be used verbatim by staff in a draft of a report. And then we see it and we decide pulmonary overload doesn't fit in this case. We can take it out, no problem, right?

DR. BELSITO: Right.

DR. LIEBLER: I'm good with that.

DR. BELSITO: But I think -- I mean that third paragraph obviously needs to be reworked. For the purpose of this meeting, we have two boilerplates that do need to be worked because we have one ingredient where we ask for inhalation toxicity and did not receive it. So we have to use boilerplate number one. And then we have several ingredients where we didn't ask, but they are potentially respirable, so we need to use boilerplate number two. So I think the real question that needs to be finalized at this meeting is are we comfortable with Curt's change of "level" to "amount" -- with the exception of that change, are we comfortable with what those first two boilerplates state? Because that's what we said we're going to put into the reports of today's meeting.

DR. BERGFELD: Like all boilerplates, though, as we use them we will hone them --

DR. BELSITO: Right.

DR. BERGFELD: -- improve them, but right now I think these are great.

DR. BELSITO: Right now.

DR. SNYDER: I agree. I think they're a good basis to move forward and test. And so we'll see how it works.

DR. BELSITO: Okay.

DR. ANSELL: I would hope in those small modifications that the sentence, "The Panel requested safety data," be changed to, "The Panel requested inhalation data."

DR. BELSITO: Okay, so --

DR. ANDERSEN: I was thinking, Jay, of just deleting safety test Panel requested data.

DR. ANSELL: And then you'd have to also then remove "in the absence of." I mean we're arguing that all this other data is relevant for assessing the inhalation safety; that in the absence of an inhalation study, other data can help us assess the safety. And so I think that was the suggested changes. "The Panel requested inhalation data that may be available to evaluate this endpoint directly. In the absence of such data, the Panel will consider other data that may be pertinent, including data available," et cetera, et cetera. So I think that the piece is great, and we fully support it.

DR. ANDERSEN: I hadn't caught that nuance.

DR. BELSITO: Okay. So I --

DR. ANDERSEN: So add inhalation back in.

DR. BELSITO: So for discussion one, for the chemical group where we ask for inhalation because there was an indication in the MSDS sheet that it was there and we did not get it. Because yadda "can be used in products that may be sprayed, the Panel discussed the issue of potential inhalation toxicity. It requested inhalation data that may be available to evaluate this endpoint directly. In the absence of such data, the Panel considered" -- not will consider -- "other data that may be pertinent, including data available to characterize the potential for the ingredient to cause systemic toxicity, ocular, and other effects. The Panel noted," yadda, yadda, yadda, to Curt's correction, changing "level" to "amount," "coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used. This information suggested the inhalation would not be a significant root of exposure that might lead to local respiratory or systemic toxic effects."

DR. SNYDER: "Incidental inhalation."

DR. BELSITO: Suggested that incidental inhalation?

DR. SNYDER: Yes.

DR. BELSITO: Everyone happy with that?

DR. KLAASSEN: Yes.

DR. BELSITO: Okay.

DR. BERGFELD: And those corrections would be made in the second and third options as well, correct?

DR. BELSITO: Well, let's go through the second option because we're going to use that even more than the first option because there was only one ingredient we asked for data and didn't get it. So "because these ingredients could be used in products that may be sprayed, the Panel discussed the issue of potential inhalation toxicity -- in the absence of sufficient inhalation data" instead of safety data.

DR. BERGFELD: Don't you want to say "issue of incidental inhalation toxicity?" Did you want to put "incidental" there rather than "potential?"

DR. BELSITO: Well, I think "incidental" went down lower.

DR. BERGFELD: Okay, you want to keep potential.

DR. BELSITO: So, "The absence of sufficient inhalation data to evaluate this endpoint directly, the Panel considered other data that were evaluated to characterize the potential for it to cause this toxicity evaluated."

DR. BERGFELD: So use "potential" twice?

DR. BELSITO: Well, the --

DR. ANDERSEN: Okay, go ahead, Don.

DR. BELSITO: That goes back to my comment on the first ingredient or second that we reviewed that I didn't like the idea of the potential for it to cause toxicities. I had changed that word "available" to "characterize the safety" -- I forget exactly what I said.

DR. BERGFELD: How about "the Panel discussed the issue of incidental inhalation exposure" for that second sentence? Better? It's a little less damning.

DR. ANDERSEN: Well, it certainly focuses the discussion from the "because they can be used in products that may be sprayed" we talked about incidental inhalation exposure. So it does --

DR. BELSITO: What I had done for the alkyl glucosides, I said, "In the absence of sufficient safety data to evaluate this endpoint directly, the Panel considered other data that were available to characterize the safety of the alkyl glucosides, including repeated -- in this case, "repeated dose toxicity, ocular, dermal irritation and sensitization studies and other facts." I just -- I mean you want to emphasize -- I think you want to emphasize other data to characterize the safety, other toxicity endpoints. I mean I guess --

DR. BERGFELD: That's a given.

DR. BELSITO: But to my ear when I read it, it was like, okay, we're looking at other toxicity and we're assuming? So it causes cancer, but inhalation is going to be miniscule, so we don't care about the fact that it causes cancer. I mean what we're looking at are other toxicologic endpoints that are negative, i.e., safe.

DR. LIEBLER: So it's a very fine point, but I think I agree with Don on this. I think the process that we're going through is when we don't have the information on potential incidental inhalation toxicity, we're looking at other data to provide us reassurance of safety. There probably would be some data for toxicity, that's not the best way to put it --

DR. SNYDER: We may have other routes of exposure that give us tremendous confidence that systemic toxicity is not going to be an issue. It doesn't matter whether it comes through the respiratory route or the oral route. And so I think that's alleviated -- that dataset helps to alleviate any systemic exposure even if it is potentially inhaled. And then we have other aspects of whether or not it's respirable and has any bearing on causing respiratory toxicity. So I kind of understand what you're saying, but again, we're entrenched into this discussion and everything, and I'd really like an outside person to read it to make sure that it's clear -- what we're stating is what we think we're stating.

DR. BELSITO: I just -- again, is this to characterize the potential for the ingredients for toxicity? Again, I just -- we're trying to characterize the safety.

DR. SNYDER: I actually like Wilma's point because it is inhalation exposure. That's the first sentence -- should be inhalation exposure, which could then lead to respiratory problems or it could lead to systemic probleMS. So I do like that because it has the route of exposure.

DR. ANSELL: Right, and then in the absence of inhalation data, we rely on all of these other data points to assess the safety.

DR. ANDERSEN: So let's just be clear then. Paul, what you're saying is in that very first sentence, the Panel discussed the issue of potential inhalation exposure as opposed to toxicity.

DR. SNYDER: Correct.

DR. BELSITO: So that would be for both, the first and the second.

DR. SNYDER: Correct.

DR. ANDERSEN: Correct.

DR. BERGFELD: We had changed the first one to incidental inhalation.

DR. BELSITO: No, incidental down at the bottom. We're talking about the second line of each. Instead of saying potential inhalation toxicity --

DR. BERGFELD: Yeah, I said that. I wrote down incidental on both, though.

DR. LIEBLER: So I like that change.

DR. BELSITO: So you think incidental should be in both areas?

DR. BERGFELD: Yeah. Well, I think in the first two sentences of the first option and the second, we're talking about incidental inhalation exposure. I think it's the same.

DR. BELSITO: Discuss the issue of potential --

DR. SNYDER: No.

DR. BELSITO: Incidental? That seems --

DR. KLAASSEN: Take out the potential then.

DR. ANSELL: Because potential and incidental are the same modifier.

DR. BELSITO: Right.

DR. ANSELL: So it's one or the other. The potential doesn't suggest amount, and incidental suggests it's not potential anymore, it's actual.

DR. ANDERSEN: I think potential has to come out, and in both places incidental inhalation exposure is the right phrase.

DR. BELSITO: Okay.

DR. BOYER: I was using the word "potential" thinking like a toxicologist. You have dose response. You have dose

makes the poison basically. So you may have a good deal of data that shows toxicity, but it's at very high doses and that would be something that would enter the discussion. But I understand what you're trying to do in terms of looking at it from a different perspective.

DR. SNYDER: I think in this case we're agreeing that there's going to be incidental exposure, and it's a matter of how we're going to interpret that.

DR. BELSITO: Okay. I mean quite honestly I don't know why we need to have a different opinion or a different statement when we requested data and when we didn't request data because in the end, we're making a decision without the data. So I actually like the first paragraph for both situations because it says, "In the absence of such data, the Panel considered other data that may be," in this case I think we considered the data that were pertinent, "including data available to characterize the potential" for whatever the ingredients to cause yadda, yadda, yadda. And then -- so there are two conclusions: One when we requested data and didn't get it, or we didn't request data and it's used in an inhalation product, and it's the same discussion. I don't see why we need to have two different boilerplates.

DR. LIEBLER: I agree because in both situations, you're dealing with the absence of data.

DR. BELSITO: Right.

DR. KLAASSEN: Right.

DR. BELSITO: And just because we asked for it doesn't mean --

DR. LIEBLER: It's not a difference in --

DR. BELSITO: In many cases we don't ask for it because we're going to use the boilerplate. I mean the only reason that last go-around we asked for it is we had a material safety data sheet that said there was some inhalation tox data. We thought we could get it.

DR. LIEBLER: So I agree with your suggestion of just using the refined first paragraph as our boilerplate for both scenarios.

DR. ANDERSEN: I'm just thinking ahead to the March meeting, and somebody on the Panel raises their hand and says I want inhalation tox data. And I'm going to ask why because you aren't going to use it. You've already told me you don't care. And if you're not -- if you're going to back off, why ask? Devil's advocating --

DR. BELSITO: Well, but even that second option is we asked, and we're backing off. So that already admits it. I mean I think that there may be a particular issue, for instance, with benzyl alcohol where we weren't so much concerned about what was -- well, we were concerned about what was going on in the alveoli because the studies -- we got inhalation studies where there was alveolitis, and we couldn't understand it. And then they repeated the study, and we saw it again or saw something going on down there. So there may be chemicals where we're not going to back off.

DR. ANDERSEN: Yeah, that could be. I think that's going to end up being few and far between, but I'll agree it's non-zero. I think then there is a duality, though, of paragraphs that get written because whether you want it or not, for some ingredients there are going to be inhalation toxicity data.

DR. BELSITO: And that's the second -- well, what now is the third option, when we have inhalation data.

DR. ANDERSEN: Yeah, and that then, either you have it or you don't, are the two relevant situations.

DR. BELSITO: Right.

DR. ANDERSEN: Not this whether you asked for it or not.

DR. BELSITO: Right.

DR. ANSELL: And one would hope, indeed, that if there was sufficient data to respond to the inhalation without an actual inhalation study, that it would be addressed in the same way carcinogenicity is without a cancer study or a liver toxicity is without any particular study.

DR. ANDERSEN: I think I'm getting it.

DR. BERGFELD: So what happened?

DR. BELSITO: So the second paragraph, the second potential discussion point where we asked for data and didn't receive it, disappears. And we use the first one, "The tentative reports for which the expert Panel has requested available inhalation toxicity," that's the one we use for both. So the tentative discussion when we didn't ask for data, we're not reworking that anymore. We're going to use the same discussion when we do not have inhalation data, whether we asked for it or not, and that's the one that is currently in the book under, "for tentative reports for which the expert Panel has requested available inhalation toxicity data."

DR. ANDERSEN: Okay, the part of that first paragraph that says, "The Panel requested" --

DR. KLAASSEN: That goes.

DR. ANDERSEN: Goes.

DR. BELSITO: Right.

DR. ANDERSEN: "In the absence of inhalation toxicity data, the Panel considered other data that may be pertinent," as such has to be explained now.

DR. BELSITO: Okay.

DR. KLAASSEN: Right.

DR. ANDERSEN: Do we even need toxicity there in the absence of inhalation data?

DR. BELSITO: "In the absence of inhalation data," right, "the Panel considered other data" --

DR. ANDERSEN: "That may be pertinent."

DR. ANSELL: What's other pertinent data here?

DR. ANDERSEN: That would shorten it and be to the point, yes.

DR. BELSITO: "Other pertinent data" --

DR. ANSELL: Don't need impertinent data.

DR. BELSITO: "Other pertinent data, including data available to characterize the potential" --

DR. SNYDER: I think we just quit with "other data." I'm sorry, just quit with "other data" because some of the data may be physical chemical properties, right?

DR. BELSITO: True.

DR. SNYDER: Do we need to specify? How about we just leave "data" open- ended?

DR. BELSITO: Yeah, like clays and --

DR. KLAASSEN: Gums.

DR. BELSITO: Gums.

DR. ANDERSEN: I thought the utility of mentioning systemic toxicity ocular, dermal, et cetera, was that we recognized that that's true, but it wouldn't necessarily be immediately obvious to the reader that that's true. So we're telling them, we're pretty smart here. Snyder's looked at this all along. We're just telling you.

DR. BELSITO: Well, then shouldn't we -- I mean shouldn't that be like a blue? "In the absence of inhalation data, the Panel considered other pertinent data, including size, lack of systemic toxicity," yadda, yadda, yadda.

DR. ANDERSEN: And then tailor it to whichever --

DR. BOYER: And that's how it's written in that next paragraph.

DR. BELSITO: Right.

DR. ANDERSEN: So we'll pull that up from the bottom paragraph as this depends on what's actually in the report.

DR. KLAASSEN: Right.

DR. BERGFELD: In what scenario then would you use "that it cannot be used in aerosols," because we have several of those conclusions? It doesn't seem to fit any of these.

DR. ANDERSEN: If it's formaldehyde --

DR. BERGFELD: No, I mean you don't have -- any of these would fit that. That's just a statement, "should not be used in aerosol products."

DR. BELSITO: Well, that's where we asked for toxicity data and we're actually really concerned about lung toxicity and it's a volatile substance. It's used in a spray and could be respirable.

DR. BERGFELD: No, no, no, I know, but it isn't really approached by this because it's a flat-out statement. "It should not be used in aerosol products."

DR. BELSITO: We wouldn't be using these boilerplates. If we're banning it --

DR. BERGFELD: This is only used when we're giving a reason why we're okaying it for aerosols.

DR. BELSITO: Right, exactly.

DR. BERGFELD: So I just don't see that other piece.

DR. SNYDER: This is the gray zone. If it's safe, it's fine, and if we have inhalation data, it's fine. And if it's not, if it's toxic, then clearly we've got to ban it. But this is for the gray zone when we don't have the full dataset that --

DR. BERGFELD: This is when we have lack of data.

DR. BELSITO: We have lack of data and lack of concern, that we don't --

DR. BERGFELD: Well, I think it ought to be the topic or the title should be that then.

DR. ANDERSEN: But we could -- and it never occurred to me until you brought it up, Wilma -- there's no reason we couldn't add a paragraph, maybe it takes two, to explain that under some circumstances, i.e., formaldehyde, the toxicity to the respiratory tract and were it to get to the -- be respirable is sufficient for the Panel to say this is unsafe. So we do have the possibility that you can get over that line. We've done it. This is to talk about that other area where it's not over the line and we want to be able to say something.

DR. ANSELL: When we first opened these discussions, I mentioned that it's something that we're likely to have to work on over a period of time. And I think that's what we're learning now is that we felt the report language that says it's nonrespirable was not sufficiently accurate, but we're going perhaps way over in the other direction. I mean when we look at -- do we have a cancer boilerplate? Do we have a 90-day boilerplate? Do we have a boilerplate that could be applicable for any single data point which may not be available? We tend -- as I think Wilma was pointing out -- if it's an issue we'll write something specific to that. I think the important part that came out of this exercise in my mind is not so much the boilerplate, which I think is a great piece, but the fact that it isn't a significant route in almost all cases. So we don't need to raise it with every single product. Maybe that's where we're struggling. Is this the equivalent to a pesticide boilerplate or is this something, a truly unique endpoint that needs to be treated differently than all the other endpoints we assess?

DR. BERGFELD: Can I ask a question? Logistically tomorrow, how would you like this handled? Is it going to just have team reports? And it will be brought up the next time when all these adjustments have been made? Are we going to redo this conversation?

DR. SNYDER: Don's got it.

DR. ANDERSEN: I think the question is which report does the boilerplate appear in first, and I'm not sure I know the answer to that. It probably isn't in the anisole final report. What about sodium lauriminodipropionate? Is anybody spraying this crap?

DR. LIEBLER: The boilerplate appears near the end of the agenda tomorrow.

DR. BERGFELD: But in a way it's being said that there are ingredients that have inhalation studies.

DR. LIEBLER: I understand. So the rationale --

DR. BELSITO: So we really should probably move the boilerplate up to first because that's a whole discussion in and of itself. And once we have that resolved --

DR. LIEBLER: Because that could prevent us getting tied in knots during the ingredient reviews. We could resolve it --

DR. BERGFELD: I'll do it. I would like an abbreviated discussion.

DR. BELSITO: They usually are.

DR. ANDERSEN: He said that with a straight face. Right now it's assigned to Don. There's no reason, Wilma, you can't do it as a chair prerogative --

DR. BERGFELD: I just moved it. I moved it.

DR. ANDERSEN: Done.

DR. BELSITO: Good, I think that's critical. Otherwise we end up with this argument mixed in with other arguments about an ingredient. We should have this clarified before we move.

DR. SNYDER: Are we going to need a motion from the floor to amend the agenda?

DR. BELSITO: Okay.

DR. BERGFELD: I'm taking the chairman's prerogative.

DR. ANDERSEN: So she who has the gavel rules.

DR. BELSITO: So from our standpoint, we're making one conclusion for whether we have or have not asked for respiratory toxicity and did not receive it. We have a conclusion where we do have some respiratory tox, and are you serious about writing a one- or two-page paragraph when we ban it from inhalation or --

DR. ANDERSEN: No, I take Jay's point that the target for this piece is the acknowledgment that cosmetic sprays, while we're not entirely taking the monkey on our back, we're acknowledging that this is -- to use that wonderful phrase -- incidental inhalation exposure, and this is to explain what the heck all that means.

DR. BELSITO: Okay.

DR. ANDERSEN: It's not done to the extent that these are ever done. DR. Rothe's presentation, this background document acknowledged, that the powder part of this is pretty much on the short side. And as more of such data become available, we will better understand and maybe be rewriting that. And that's going to come to a head next year because one of the ingredients on our radar screen is talc.

DR. BELSITO: Well, that will be fun…

…DR. BELSITO: … Pentaerythrityl tetraesters. So we tabled this report back in September. It had been ready to go final, but there was a question about concentration of use to 45, 50 percent in toilet waters and perfumes, respectively, and we weren't sure whether they might be spays or not. We've received information now that, no, they're not sprays. The highest concentration in a spray product is 21 percent. We also have now the boilerplate, which I think we've

agreed to, and the other available tox data…

DR. SNYDER: I like the new table format. This is, I think, the first instance where you used the new terminology regarding the incidental inhalation sprays, incidental inhalation powders, et cetera, except for under Deodorant we still didn't specify if we knew whether it was roll-on or spray. And so can we -- were we not going to try to elicit that difference?

DR. BELSITO: We were going to try, but, you know, my point is, we're not going to get it. So, I think that's why I liked including PCPC's calculation on exposure, because I think we're always going to have to knee jerk to the assumption that it's a spray with the lowest aerodynamic particle size, you know. And then if it becomes an issue, you know, we'll simply say, you know, should not be used in sprays at whatever concentration we're concerned about.

DR. Marks' Team Discussion 12 December 2011

DR. MARKS: We're back to the Buff Books and the aerosol inhalation toxicity. The boilerplate which, actually, Ron, you referred to multiple times. And there were comments about that back and forth on the e-mail. Any other -- anything else in terms of -- and this was, yeah, Ivan, you're here. Good…

DR. SHANK: Just where there was a lack of inhalation data, we said we would use the boilerplate (inaudible) because it was variations from one report to another as to how the lack of inhalation data was handled. Now we're going to have a formal boilerplate statement for that.

DR. BOYER: We do have some suggested verbiage for the cosmetic use section. And then there's some variation depending on whether the report is tentative versus a final -- tentative with a request for any available inhalation data versus tentative without that request. And then the final, suggested language gives a lot of examples. And those -- that kind of language would be captured in a final report, at least that's the intent…

Dr. SHANK: It seems to me there's more detail than is necessary and basically what we could say is that these particular issues would be handled on an ingredient by ingredient basis or case by case basis rather than trying to have so many fill-ins, I guess, whatever you call these.

DR. HILL: Fill in the blanks.

DR. SHANK: Yeah, probably having all of this fill in the blanks. This would be handled on a discussion of a particular ingredient rather than trying to create something that's applicable to everything.

The second comment I had was it's still, I have a feeling, we talk a lot about the effects of inhaled -- pardon me, respired particles and the effects on the lungs. And I get the feeling that we are not giving proper attention to the nasopharyngeal tissue --

SPEAKER: Or the bronchial.

DR. SHANK: Or the bronchial tissue. They are susceptible to adverse effects. Case in point, formaldehyde. All right. Very serious effects on the nasal pharyngeal tissue. So maybe you pair back at least a couple of sentences saying that just because a particular deposits in the nasal pharyngeal area doesn't mean there's no problem that's going to be sneezed or coughed or swallowed. Now, there may be a local reaction.

And I don't know where to put it but when we keep talking about the particles, we tend not to think of the chemistry of the particles. And it's more than just a particle of a certain size or aerodynamic property. Of course, that's very

important for a deposition, but then once there's a deposit, the chemistry of the particle is important and I would like to see a little more emphasis on that. But it's a great document in coverage… of the importance of inhalation toxicology. Very well done.

DR. MARKS: How do you want to proceed tomorrow with this? Do we want to just say, Ivan, you've captured DR. Shank's comments here today and we'll incorporate that in the next revision?

DR. SLAGA: I think we have to discuss it.

DR. SHANK: Is this going to be a panel discussion, Ivan?

DR. MARKS: It's in my notes here.

DR. BOYER: It's actually going to be brought forward to the beginning (inaudible). And the chairman --

DR. MARKS: No, it's actually -- well, if I'm looking at the right Tuesday, it's other discussion iteMS. That's the first one. It's the second to the last.

DR. BOYER: There's going to be a motion to move it up to… 1st. And also there's going to be a suggestion to keep things very brief.

DR. MARKS: Motion to move it up. I think Wilma and Alan can do that without a motion. Let's see.

MS. BURNETT: It was discussed as the chairwoman's prerogative…

MS. EISENMANN: One comment we're going to bring up on page 55 of the Panel Book. It's about this paragraph. It says however characterizing a particle distribution from finished powder products that are sprays. It comes from one of DR. Rothe's slides. It really did not concern about powder products in general and the methods of measuring sizes of powders, changes to powder, so it doesn't really reflect what the powder is. That's what the (inaudible) trying to get across. So if you disperse -- to measure a powder you have to just burst in a solvent or you disperse it through a nozzle to measure it, so that changes it. That was the point. It did not concern spray powder products. Was that useful?

DR. BOYER: That was my misinterpretation of what [she] said.

DR. MARKS: So are you going to mention that tomorrow?

MS. EISENMANN: Yeah, it's in his comments, so I don't know if that means we mention it when we provide comments this morning.

DR. MARKS: Okay.

MS. EISENMANN: I gave them to Ivan. And so -- I don't know how much they have to be considered. And then the other concern that was mentioned is that in the first paragraph in the boilerplate in the U section, it doesn't really distinguish -- I don't know if you want to distinguish -- you're asking me at times to collect is it a pump spray or is it an aerosol spray? Well, maybe you should distinguish that the pump spray has a smaller tail versus the aerosol spray. If you want me to collect that information. I can distinguish. Maybe I should just be collecting spray products. But it would be nice if, you know, it might be useful to distinguish between the two types of sprays. Right now it doesn't in that paragraph.

DR. HILL: It seems to me we should because a manufacturer might choose in a case where there was some problem with inhalation, they might be able to get around that by using a pump spray where you didn't have droplets that could penetrate deep into the lungs even though it would be a small amount. I don't know.

MS. EISENMANN: That's what the committee suggested in our comments that it would be good to distinguish between. To let them know that there is a difference between the two types of sprays.

DR. HILL: Oh, yes.

MS. FIUME: Are you going to bring that up tomorrow then, Carol?

MS. EISENMANN: If you want me to. I mean, it's in our comments, written comments.

DR. MARKS: As long as it's captured. Thank you, Ivan. Well done…

Full Panel Session 13 December 2011

DR. BERGFELD: I think we are going to begin. This is, again, the 35th year of the CIR, and this is our 121st meeting. And the panel had an unusual number of ingredients to go through this time, 18, five of which were new. And I'm going to take as the chair the opportunity to move the agenda slightly and put aerosols first as the first discussant ingredient or precedent, I should say… I'd like to move then to the changed agenda and take up the discussion of the aerosols, the precedent setting aerosol document. And for the reason we're putting this first is that there are many ingredients that have an inhalation portion to them. We'd like to settle that and what we are going to include in those as we proceed through.

And, Don, you were slated to discuss first the aerosols, so if you don't mind starting.

DR. BELSITO: Okay. Sure. We obviously spent a good amount of time on this since it's going to impact so many reports that we will issue at this meeting and in a future meeting.

You know, first of all, we're very appreciative of Ivan for putting this together. We thought the background section was excellently written, made one minor change in terms of some wording. We appreciated the input that we got from the PCPC and CIR Science and Support Committee. We thought that we would include in the background their sample exposure calculation since our group felt that in all reality when we ask for, is it in a pump or is it in a spray, we're not going to know, and we're not going to get that information. So, the conservative estimate in terms of particle size would be that it's in a spray, and this is a very nice calculation of safety and exposure in the breathing zone, so we felt that that could be incorporated into the background.

The background section would go first, and then the options that the technical writers would have for putting in the cosmetic use section, we had no comments.

The options for the discussion, we felt that in the discussion it didn't really matter whether we had asked for inhalation toxicity, and it didn't come, and we felt we didn't need it, or whether we never asked for it at all. Obviously in the end, we felt that the other safety data supported it. So that the first two paragraphs under "options for discussion," whether the tentative report had requested inhalation toxicity and we didn't get it, or whether we had not requested it, we thought those paragraphs could be the same.

And we sort of blended the two paragraphs to go something like this: “because this ingredient, or these ingredients, or some of these ingredients, can be used in products that may in inhalation -- or in products that may be sprayed, the

panel discussed the issue of incidental inhalation exposure. In the absence of inhalation data, the panel considered other pertinent data that were available, including," and then it would be open to whatever data that we had looked at. And we would list that data; it would vary from compound to compound, and then, the rest of that paragraph pretty much as written.

"The panel noted that 95 to 99 percent of droplet particles producing cosmetic aerosols would not be respirable to any appreciable amount." We changed "level" to "amount" at Curt's suggestion.

Going on with the next sentence, pretty much as written, except that when we get to "this information suggested that," again we inserted "incidental inhalation." Since none of these products are designed to be inhaled, the inhalation would all be incidental. And then, the rest of the paragraph as is.

For final reports and re-review summaries, we thought that was fine. I mean, we had asked for data or we got data, I mean, really how you write it is going to be dependent upon the data you get and how you interpret the data. So, there are many options.

One of the issues that Alan raised is, if we collapse those first two paragraphs, we're pretty much saying that we don't need inhalation toxicity. And there the panel really felt, no, that's not what we're saying, because if we need inhalation toxicity, and we don't get it, and we still feel we need it, we're not going to fall back on these boilerplates. We're going to issue an insufficient or whatever. These are boilerplates for when we get data and it's still safe. We don't have data, and we feel it's still safe, not for when we don't have data and we're concerned, or we have data and we're concerned. So, that's where we're at.

We also thought that this document, just like the hair dye epidemiology document, should be out on the website, and perhaps should go out for public comment.

DR. BERGFELD: Jim -- DR. Marks?

DR. MARKS: Yes. I'm going to let Ron Shank go over the comments go over the comments that he and our team had.

DR. SHANK: I would just like to add a little bit to the report. One is the -- what's here is fine, but it gives the impression that if something lodges in the nasopharyngeal region, the respiratory system, that's okay because it's going to be coughed or sneezed or swallowed.

That tissue is also very responsive to chemical intoxicants, and I think we need to actually say that. The case in point, formaldehyde, okay? It gives the impression that if it goes into the nasopharyngeal region, that's okay. It doesn't say that, but it gives that impression. So, I would like to be explicit and say there is a potential for toxicants, so even if it lodges in the nasopharynx.

The other is we talk all the time about particles. We should mention the chemistry of the particle and the surface chemistry. What's on the surface of the particle is important in determining the toxicity potential, not just the aerodynamic part. That's good for distribution, but we should say that it's the chemistry ultimately that's going to probably be responsible for toxic insult.

So, it's not a change; it's just maybe adding one or two sentences to give the correct impression or the correct feeling that nasopharyngeal tissue is sensitive and responsive, and particle size is extremely important for distribution, but chemistry is also important for toxic response.

DR. BERGFELD: Where are you asking to put that in this document, in the background materials or in the --

DR. SHANK: Well, the first time -- the first --

DR. BERGFELD: -- options of --

DR. SHANK: Good point.

DR. BERGFELD: In the decision making tree.

DR. SHANK: The first time we mentioned that the larger particles are lodged in the nasopharyngeal region, and they are removed ultimately by, I think it says sniff, cough, and swallow. That's where I would put the statement that that tissue is responsive and can be the sign of a toxic insult.

DR. BELSITO: And would you put it in the discussion again as well, or just in the background?

DR. BERGFELD: Probably case dependent or ingredient dependent, is it not?

DR. SHANK: Probably it is, yes. It should be in here someplace because right now it gives the impression that it's not a problem if it's only in the nasopharyngeal region, and that's not the impression I think we should give.

DR. LIEBLER: I think, Ron, the place where it looks like it might logically fit is in the boilerplate for the Cosmetic Use Section where you actually have this -- the language that, you know, "Therefore, most droplets/particles incidentally inhaled would be deposited in the nasopharyngeal region and would not be… respirable to any appreciable level." But then, you come in with your point about the particles in this region -- in the nasopharyngeal region could still have their own effects there.

DR. SHANK: Correct. That's fine.

DR. BERGFELD: It looks like that's -- everyone's agreeable --

DR. SHANK: The tracheobronchial --

DR. BERGFELD: -- that that should occur? It looks it. That's done. We'll do that.

DR. SHANK: Okay.

DR. BERGFELD: Now, that is in the -- there are two issues: Merging the two tentative boilerplates that you see on page 2 or Panel Book 52, and leaving stand the final one, the final reports and re-review summaries with the addition of this piece of the chemistry. Is that what we're hearing? Is that agreeable to merging the first two options?

Okay. I'm not sure we have to discuss anything further then. It looks like we've done that, at least this is a document from which we will work from. I don't need a vote on this. And obviously there'll be adjustments along the way with this. So, thank you very much…

COSMETIC INGREDIENT REVIEW

CIR Precedents

Aerosols

Draft Revision

1/2012

This document is a compilation of issues discussed by the CIR Expert Panel along with precedent language used in CIR Reports to articulate the Panel's views. Standard formats used in Panel Reports are also addressed. This is intended to provide background on issues and serve as a reference explaining the reasoning behind previous Panel decisions.

Sprays/Powders

Update 1/2012

BACKGROUND

Inhalation toxicity is an important consideration for sprays and loose powders containing cosmetic ingredients. The inhalation toxicity of ingredients in such products depends, in part, on where the ingredients may contact tissues in the respiratory tract and whether they can cause local adverse effects in the respiratory tract tissues or systemic effects after absorption from the respiratory tract.[1]

The deposition and absorption of gases and vapors in the respiratory tract depend mainly on their water solubility and reactivity with the fluids or other components of the surfaces of the airways.[2-4] For example, absorption of an insoluble, non-reactive gas is negligible. A moderately soluble or reactive gas will be deposited throughout the respiratory tract. A highly soluble or reactive gas will be rapidly deposited or absorbed almost entirely in the nose and upper airways.

Aerosols are broadly defined as multiphase systems of particulate solids or liquids dispersed in air or other gases, including mists, fumes and dusts.[1] The deposition, absorption, clearance and, ultimately, the effects of ingredients in aerosols (liquid droplets or solid particles) in the respiratory tract depend on the solubility, reactivity, and toxicity of the ingredients. However, the size of the inhaled aerosol droplets/particles also plays an important role.[1,3,5]

The physical parameter most strongly associated with the deposition pattern of an aerosol in the respiratory tract is the aerodynamic equivalent diameter, d_{ae}.[6,7] The d_{ae} of a droplet/particle is defined as the diameter of a hypothetical, smooth sphere of unit density (1 g/cm^3) that has the same gravitational settling velocity as the droplet/particle in calm air, regardless of its actual geometric size, shape and density.[5,8]

The droplets/particles of an aerosol can be divided into three mass fractions, based on the depth to which they will penetrate the respiratory tract. These fractions include the inhalable fraction (median d_{ae} =100 µm), which can enter the nasopharyngeal region through the nose or mouth, the thoracic fraction (median d_{ae} =10 µm), which can pass through the larynx to enter the trachea, bronchi and bronchioles, and the respirable fraction (median d_{ae} =4 µm), which can enter the alveolar region of the lungs.[1-3,9] In the nasopharyngeal and thoracic regions of the respiratory tract, mucus-secreting and ciliated cells form a protective mucociliary blanket that carries deposited droplets/particles to the throat. Thus, droplets/particles deposited in these regions can be sneezed or spit out or swallowed.[10] In the pulmonary region, the clearance of inert, poorly soluble particles is mediated primarily by alveolar macrophages, and is slow and limited by comparison. However, the potential for toxic effects is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and tracheobronchial regions of the respiratory tract may cause toxic effects in these regions depending on their chemical and physical properties.

There is broad scientific consensus that the probability of penetration of droplets/particles with d_{ae} >10 µm into the pulmonary region is essentially zero.[1,5,11-15] Thus, only droplets/particles with d_{ae} <10 µm are considered to be respirable. This is a conservative assumption because a d_{ae} of 5 µm is often reported in the scientific literature as the threshold below which droplets/particles can reach the alveoli.[1] In addition, there is consensus that droplets/particles with d_{ae} >15 µm are deposited almost exclusively in the nasopharyngeal and thoracic regions of the respiratory tract, and that healthy people will clear particles with d_{ae} >7 µm from these regions within 24 hours through mucociliary action.[1]

Particle size distributions are product specific. Numerous factors determine the initial size distribution of droplets or particles released from a spray product, including the product formulation (e.g., volatile or nonvolatile solvent), propellant, can size, and differential pressure through the nozzle for propellant sprays, and formulation and nozzle characteristics for pump sprays.[616] After release to the air, the particle size distribution can change rapidly through aggregation, agglomeration, sedimentation, evaporation of volatile components, or hygroscopic absorption of water.[1,7,9,12,17,18] For example, all of the

water and other volatile solvents and propellants in droplets with d_{ae} <40 µm will evaporate within 1 second of release from a spray can, so that the remaining particles will contain non- or low-volatile constituents (e.g., polymers with little or no biological activity in hairs sprays).[1,17,19,20] Accordingly, a wide spectrum of particle size distributions can be released from cosmetic sprays.

Both pump sprays and propellant sprays (also called "aerosol sprays") produce aerosols, but the aerosols from propellant sprays have larger fractions of respirable droplets/particles than aerosols from pump sprays.[1] For example, the median d_{ae} of the airborne droplets/particles of pump hair sprays range from 60 µm to 80 µm.[1,16,17] Typically, <1% of the airborne droplets/particles released from pump sprays are in the range considered to be respirable (i.e., d_{ae} <10 µm).[16] In comparison, the median d_{ae} of the airborne droplets/particles of propellant hair sprays range from 25 µm to 50 µm.[1,16,17] Usually, 1% to 2.5% but no more than 5% of the droplets/particles emitted from propellant hair sprays are within the respirable range.[16]

Further, different types of propellant-spray products may yield substantially different particle size distributions. For example, conservative estimates indicate that propellant hair-spray aerosols have a median d_{ae} of 35 µm with a coefficient of variation of 0.3.[12,17] Thus, the insoluble aerosol particles inhaled during hair-spray use will be deposited primarily in the nasopharyngeal region, where they can be trapped and cleared from the respiratory tract through mucociliary action. In contrast, analogous estimates indicate that the tested deodorant-spray aerosols have a median d_{ae} of 10 µm with a coefficient of variation of 0.3, suggesting that half of these particles are within the range considered to be respirable.[12,17]

These differences in droplet/particle size distributions between pump and propellant spray products, and between the few hair spray and deodorant spray products tested, are important considerations for evaluating the safety of cosmetics ingredients that may be respired during use. This is because they suggest that the margin of safety may be lower for propellant sprays compared to pump sprays, and for propellant deodorant sprays compared to propellant hair sprays. The inhalation of respirable droplets/particles from cosmetic products, including pump and propellant hair sprays and deodorant sprays, is likely to be very small, even negligible, compared with dermal contact and other exposure routes associated with the use of these products. Further, products like underarm deodorant and foot sprays are not usually sprayed in the direction of the face, so less of these products will likely be sprayed directly into the users breathing zone compared with hair sprays, for example. However, the limited evidence currently available does not provide adequate support for these assumptions.

The droplets/particles released from a propellant hair spray are distributed within a 1 to 2 m^3 space in the breathing zone during the first 2 minutes after spraying, which expands to form an homogenous 10-m^3 cloud (about the size of a bathroom) over the subsequent 18 minutes.[1,16] Simulation studies revealed that all of the droplets/particles released from both pump sprays and propellant sprays settle quickly after spraying, including the respirable and inhalable fractions, which substantially reduces the overall potential for inhalation exposure.[5,8,16-18] Specifically, about 35% of the airborne droplets/particles drop away from the breathing zone in the first minute, 60% in the second minute, 90% in six minutes, and 95% in eight minutes after spraying.[16] The droplets/particles are likely to be undetectable in the breathing zone within 10 minutes after spraying.

Pulmonary overload is a condition in which the accumulation of any inert, poorly soluble particulate material in the lungs overwhelms the capacity of the alveolar macrophages to clear the material from the lungs. Chronic pulmonary overload can cause persistent inflammatory responses, fibrosis and tumors,[21] although the mechanism(s) of overload-induced tumor formation is not completely understood.[21-24] The European Union's current threshold for protecting workers from pulmonary overload during occupational exposure to respirable dust particles is 1.5 mg/m^3 8-hour time-weighted average. In comparison, inhalation exposures to aerosols from cosmetic sprays will be much lower than this threshold, primarily because of the much shorter exposure duration associated with cosmetic spray use (i.e., only a few minutes).[1,16]

Industry can ensure that inhalation exposures to cosmetic sprays and powders are minimized.[16] For example, particle size distributions can be characterized and exposures estimated each time a significant change is made in the formulation or spray mechanisms of spray products to ensure that potential inhalation exposures are very low.

Similarly, industry can minimize airborne particles from cosmetic powder products by controlling the milling of the ingredients and adding binding materials, such as oils, waxes or hygroscopic ingredients, in the formulations.[25] The binding materials foster the agglomeration of the ingredients and substantially increase their cohesivity. These measures increase the size of the particles in the product.

However, characterizing the particle size distributions released from finished powder products under use conditions is difficult. This is because the methods used to measure the particle sizes of powder products involve dispersing the powder in a solvent or applying a pressure differential to break up the agglomerated particles.[25] Thus, these measurements do not correlate well with the size distributions of the particles released from the product under use conditions. Some photographic methods are being developed to characterize the actual sizes and shapes of the particles released from powder products during use. However, it is not clear whether these methods are amenable to characterizing the aerodynamic equivalent diameters of such particles.

The CIR Expert Panel noted that, in practice, 95% to 99 % of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters greater than 10 µm. Thus, most aerosol droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal region of the respiratory tract and would not be respirable to any appreciable amount. However, some of the droplets/particles are respirable, including up to 5% of the particle size distribution during the use of some products. Such information should be included in each safety assessment for which the ingredient(s) may be used in a pump or propellant spray. Information will continue to be sought from suppliers and formulators to specifically identify such spray uses.

The Panel recognized that aerosols from propellant sprays are distinct from aerosols from pump sprays. For each ingredient or ingredient group assessed, the Panel would like to know whether the current practices of use include propellant sprays, pump sprays, or both, when appropriate and the information is available. Identifying the use of ingredients in deodorant spray products may be especially important, because they potentially release the largest amount of respirable droplets/particulates among the products evaluated. However, better information about particle size distributions and their variability (within and across product types) that can be reasonably expected, generally, from a broad range of products (e.g., hair, sunscreen, indoor suntanning, foot and deodorant sprays, and cosmetic powders) would substantially increase confidence in safety assessments of ingredients in products that may be aerosolized.

The Panel recognizes that the distribution of aerodynamic equivalent diameters of cosmetic aerosol droplets/particles is an important parameter determining where the inhaled particles/droplets will be deposited in the respiratory tract. However, the Panel also emphasizes that the chemical properties of the particles/droplets will be critical factors determining whether they will cause inhalation toxicity where they are deposited.

The Panel will continue to review all of the relevant inhalation toxicity, use, and other data to determine the safety of cosmetic ingredients. The Panel will evaluate the importance of the inhalation route for assessing the safety of an ingredient or group of ingredients, and evaluate data that may be available to estimate potential respiratory doses from aerosolized products. Factors to consider include whether or how much of the spray products enter the breathing zone, the likely droplet/particle size distributions in the breathing zone, and the exposure durations that can be expected during product use. The Panel agreed that, generally, inhalation exposure to ingredients in aerosolized cosmetic products is unlikely to be significant compared to the dermal or other exposure routes associated with the use of cosmetic products. For example, conservative estimates indicate that inhalation exposures for once-a-day application of a propellant deodorant spray, pump hair spray, or propellant hair spray would be no more than 3, 7, and 20 µg/kg/day.[26] These estimates were based on the following conservative assumptions:

- All of the spray enters the breathing zone (i.e., 100% is available for inhalation)
- Exposure duration: 20 minutes
- The droplets/particles:
    - Form a 1-m^3 cloud in the first 2 minutes after spraying
    - Dissipate to fill 10-m^3 space around the user in the next 18 minutes
- 25% of the inhaled droplets/particles are exhaled
- Breathing rate: 0.01 m^3/minute
- Body weight: 60 kg
- Amount of product used: 1.43, 15.6 and 9.89 g/day deodorant, pump-hair, and propellant-hair spray, respectively
- Respirable fraction: 5%, 1%, 5% for deodorant, pump-hair, and propellant-hair spray, respectively

However, even such small inhalation exposures may be significant for an ingredient that has the potential to act as a potent systemic or local respiratory tract toxicant or to accumulate in the body.

The Panel noted that inhalation toxicity studies on test animals are often conducted using high concentrations of droplets/particles with size distributions well within the respirable range and long exposure durations to ensure that the potential for pulmonary or systemic toxicity will be detected. In contrast, the concentrations of respirable droplets/particles and the inhalation exposure durations from the use of cosmetic products will be much less than those of the animal studies. Thus, the adverse effects reported in such studies may have little or no relevance for evaluating the inhalation safety of cosmetic ingredients.

For example, the Panel noted studies that reported pulmonary granulomas in animals exposed to high concentrations of inhaled silylates sheared to form particles with aerodynamic equivalent diameters ranging from 1 to 4 µm, which is well within the range considered to be respirable. However, this ingredient, as supplied to formulators, has an average aerodynamic equivalent diameter of about 20 µm, and the ingredient aggregates and agglomerates to form clusters and chains with d_{ae} >125 µm and none <90 µm. Thus, the formation of granulomas in the animals was not considered to be relevant for evaluating the inhalation safety of this ingredient as used in cosmetic products.

If inhalation toxicity data are absent or provide an insufficient basis to support the safety of an ingredient used in products that may be aerosolized, the Panel will evaluate the sufficiency of other data that may be available on a case-by-case basis. Such data would include, for example, the potential for the ingredient to cause systemic toxicity, ocular or dermal irritation or sensitization, or other effects after repeated exposures. Other factors to consider include whether the ingredient belongs to a class of toxicants recognized to have the potential to cause lung injury after exposure via inhalation or other routes, possesses structural alerts based on known structure-activity relationships, or has a noteworthy potential to yield reactive intermediates or other metabolites of concern in the lungs.

Precedent language for specific report sections:

Cosmetic Use Section

[INGREDIENT(S) is OR are] used in [LIST TYPE(S) OF PRODUCT(S), e.g., cosmetic sprays, including hair, deodorant, foot, and other propellant and pump spray products], and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm [IF PRODUCT(S) MAY INCLUDE BOTH PROPELLANT AND PUMP SPRAYS, ADD: ,with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump sprays.[16,27]] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the

nasopharyngeal region and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[1,12] However, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. [IF PRODUCT(S) MAY INCLUDE DEODORANT SPRAY(S), ADD: There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[28] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.]

Discussion Section

For **Tentative Reports**

Because [this ingredient OR these ingredients OR some of these ingredients] can be used in products that may be sprayed, the Panel discussed the issue of incidental inhalation exposure. In the absence of inhalation data, the Panel considered other pertinent data that were available, including [list whatever data the Panel deemed to support the conclusion; this will vary from ingredient (group) to ingredient (group); e.g., data characterizing the potential for [INGREDIENT(S)] to cause systemic toxicity, ocular or dermal irritation or sensitization, and other effects]. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information suggested that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

For **Final Reports** and **Re-Review Summaries**

Because these ingredients can be used in products that may be aerosolized, including [SPECIFY PRODUCT TYPE(s), e.g., cosmetic powders and sprays], the Panel discussed the issue of incidental inhalation exposure. [NOTE INHALATION TOXICITY DATA, e.g., The limited data available from inhalation studies, including acute and chronic exposure data, suggest little potential for respiratory effects at relevant doses OR The data available from multiple inhalation studies, including acute and chronic exposure data, indicate little potential for respiratory effects at relevant doses.] [ADDRESS PARTICLE SIZES TESTED, e.g., Although particles appear to have reached the lungs in these animal studies, the sizes of the particles used were either clearly within the respirable range (ie, ≤10 µm) or were not reported. The Expert Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. Thus, the adverse effects reported using high doses of respirable particles in the inhalation studies do not indicate risks posed by use in cosmetics.] The Panel considered other data available to characterize the potential for [INGREDIENT(S)] to cause [LIST PERTINENT TOXICITIES EVALUATED, e.g., systemic toxicity, irritation, sensitization], or other effects. [SUM UP PERTINENT TOXICOLOGY RESULTS, e.g., They noted the lack of systemic toxicity at high doses in several acute and subchronic oral exposure studies and one chronic oral exposure study, little or no irritation or sensitization in multiple tests of dermal and ocular exposure, the absence of genotoxicity in multiple Ames tests and a Chinese hamster ovary test, and lack of carcinogenicity in a lifetime oral exposure study.] [SUM UP PERTINANT PHYSICOCHEMICAL PROPERTIES, e.g., In addition, these ingredients are large macromolecules, insoluble in water, and chemically inert under physiological conditions or conditions of use, which supports the view that they are unlikely to be absorbed or cause local effects in the respiratory tract.] Further, these ingredients are reportedly used at concentrations [MAXIMUM PERTINENT CONCENTRATION OF USE, e.g., ≤4%] in cosmetic products that may be aerosolized. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any

appreciable amount. [NOTE OTHER PERTINENT INFORMATION, e.g., Furthermore, several of these ingredients are used for viscosity increasing functions, indicating that they tend to swell and aggregate in water and other solvents and would, thus, be too large to be inhaled or respired.] Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

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Cosmetic Ingredient Review
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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Alan Andersen, Director, CIR

Date: February 10, 2012

Subject: Re-Review Summaries

At the September 2011 meeting, the Panel determined to not re-open the safety assessment of Methyldibromo Glutaronitrile and Polyvinyl Acetate.

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

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Phone 202.331.0651 FAX 202.331.0088 http://www.cir-safety.org

Methyldibromo Glutaronitrile

CONCLUSION: In the1996 safety assessment of methyldibromo glutaronitrile, the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient is safe as used in rinse-off products and safe at ≤ 0.025% in leave-on products.[1] The Expert Panel reviewed newly available studies since that assessment along with updated frequency and concentration of use information.[2-4950-65] The Expert Panel determined to not reopen this safety assessment and confirmed the original conclusion of methyldibromo glutaronitrile.

DISCUSSION: The Expert Panel reviewed a large number of dermal irritation and sensitization studies. The Panel noted that the European Commission had banned the ingredient from both leave-on and rinse-off products due to increased reports of sensitivity. However, the Panel was of the opinion that many, if not most, reports of sensitization in patch test studies likely are due to testing at high concentrations such that the reactions observed are actually irritation responses.

Table 1. Historic and current uses and concentrations of methyldibromo glutaronitrile.[1,37,38]

	# of Uses		*Max. Conc. of Use (%)*	
	Methyldibromo Glutaronitrile			
data year	*1996*	*2011*	*1996*	*2011*
Totals	**35**	**36**	**0.0075-0.06***	**0.005-0.04**
Duration of Use				
Leave-On	*23*	*22*	*	*0.012*
Rinse Off	*12*	*11*	*	*0.04*
Diluted for(bath) use	*NR*	*3*	*	*NR*
Exposure Type				
Eye Area	5	NR	*	NR
Incidental Ingestion	NR	NR	*	NR
Incidental Inhalation - Sprays	4	NR	*	0.01
Incidental Inhalation – Powders	5	NR	*	NR
Dermal Contact	22	22	*	0.04
Deodorant (underarm)	NR	NR	*	NR
Hair - Non-Coloring	12	14	*	0.016
Hair-Coloring	NR	NR	*	NR
Nail	1	NR	*	NR
Mucous Membrane	NR	9	*	NR
Baby Products	NR	NR	*	NR

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

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Polyvinyl Acetate

CONCLUSION: In the1996 amended safety assessment of polyvinyl acetate, the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient is safe as a cosmetic ingredient in the present practice of use.[1] The Expert Panel reviewed newly available studies since that assessment along with updated frequency and concentration of use information.[2-11] The Expert Panel determined to not reopen this safety assessment and confirmed that polyvinyl acetate is safe in the present practices of use and concentration.

DISCUSSION: The CIR Expert Panel noted that for polyvinyl acetate the number of uses had increased and that the use concentration had increased. Current data indicate uses at concentrations up to 47%. The original safety assessment, however, details a human repeat insult patch study in which polyvinyl acetate was tested at a concentration of 50% with no allergic or irritation responses.

Table 1. Historic and current uses and concentrations of polyvinyl acetate.[1-3]

	# of Uses		*Max. Conc. of Use (%)*	
	Polyvinyl Acetate			
data year	*1996*	*2011*	*1996*	*2011*
Totals	**7***	**50**	**<25***	**0.4-47**
Duration of Use				
Leave-On	*	*49*	*	*0.4-47*
Rinse Off	*	*1*	*	*11*
Diluted for(bath) use	*NR*	*NR*		*NR*
Exposure Type				
Eye Area	7	49	*	2-47
Incidental Ingestion	NR	NR	*	NR
Incidental Inhalation - Sprays	NR	NR	*	NR
Incidental Inhalation – Powders	NR	NR	*	NR
Dermal Contact	*	7	*	0.4-15
Deodorant (underarm)	NR	NR	*	NR
Hair - Non-Coloring	NR	NR	*	NR
Hair-Coloring	NR	NR	*	NR
Nail	NR	NR	*	NR
Mucous Membrane	NR	NR	*	11
Baby Products	NR	NR	*	NR

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

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