ADMIN

Memo

Agenda

Minutes

Hair Dyes

CIR EXPERT PANEL MEETING

DECEMBER 4-5, 2017

Commitment & Credibility since 1976

MEMORANDM

To: CIR Expert Panel Members and Liaisons
From: Bart Heldreth, PhD, Executive Director, CIR
Subject: 145th Meeting of the CIR Expert Panel — Monday and Tuesday, December 4-5, 2017
Date: November 10, 2017

Welcome to our December 2017 Panel meeting. We are working hard to hire some additional writers and backfill the toxicologist and chemist positions, so you may see some fresh faces at this meeting and at the next. However, we are all set and ready for our fourth and final meeting of the year.

Enclosed are the agenda and accompanying materials for the 145th CIR Expert Panel Meeting to be held on December 4-5, 2017. The location is (mostly) new – we are at the Darcy Hotel, 1515 Rhode Island Avenue, NW, Washington, District of Columbia, 20005-5595. Phone: (202) 232-7000. (We were here before – but it was the Doubletree then.)

The meeting agenda includes the consideration of 14 ingredient groups advancing in the review process, including 8 final reports, 3 tentative reports, and 3 draft reports. Following up on the Panel's continuing standardization of guidance language documents, the agenda contains 3 items regarding Hair Dyes, comprising a presentation on hair dye chemistry, a presentation on hair dye patch testing, and an opportunity to finalize the updated CIR Guidance Document on hair dye epidemiology. We have two great speakers for this meeting, one who will present in person and one who present via web-conference.

The first speaker, Dr. Carsten Goebel, is a Senior Director of Toxicology at Coty, in Frankfurt, Germany. He previously presented to the Panel about the initial study design for the allergy alert test that we will hear more about from our second speaker today. This time around however, Dr. Goebel will refresh the Panel on the chemistry of hair coloring.

The second speaker, Dr. Maya Krasteva, is currently a Senior International Scientist for the Research and Innovation Division at L'Oréal. Dr. Krasteva will be updating the Panel on the progress of the proof of concept study regarding patch testing.

Schedule and hotel accommodations

We have reserved rooms for the nights of Sunday, December 3 and Monday December 4 at the Darcy Hotel. If you encounter travel problems, please contact Monice on her cell phone at 703-801-8156.

Team Meetings

Draft Reports - there are 3 draft reports for review.

1. *Ginkgo biloba*-Derived Ingredients (agenda and flash drive name – Ginkgo) – This is the first time that the Panel is seeing this report on 10 ingredients derived from *Ginkgo biloba*. In October 2017, a Scientific Literature Review (SLR) was issued with an invitation for submission of data on these ingredients. Concentration of use data and comments were received from the Council and addressed. According to the Dictionary, most of the *Ginkgo biloba*-derived ingredients

detailed in this safety assessment are reported to function as skin conditioning agents, while some are reported to function as antioxidants in cosmetics.

There are no publically available toxicity data that corresponds to any one of these cosmetic ingredients, specifically. For all of the endpoint results summarized in this report, the test article is a vaguely and variably described extract of *Ginkgo biloba* leaves, or some other non-cosmetic-ingredient source, such as "fruit pulp."

Because there may be differences in constituent levels of different *Ginkgo biloba*-derived extracts, specifically the leaves, CIR staff asked for additional data on the extraction methods and composition and impurities of the *Ginkgo biloba*-derived ingredients with the issuance of the SLR, as well as additional toxicological data specific to dermal and ocular irritation and sensitization data on these cosmetic ingredients at maximum use concentrations.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe Conclusion. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

2. *Eucalyptus globulus* (Eucalyptus)-Derived Ingredients (agenda and flash drive name – Eucalyptus). This is the first time that the Panel is seeing this report on 6 *Eucalyptus globulus*-derived ingredients. In September 2017, the SLR was posted for public comment with a request for additional data, including clarification of the ingredient definitions. Concentration of use data, comments, and characterization of the Eucalyptus Globulus (Eucalyptus) Leaf Oil were received from the Council and addressed.

   The plant part for these ingredients is the leaf or leaf/twig. The reported functions of the *Eucalyptus globulus*-derived ingredients include abrasive, fragrance ingredient, and skin-conditioning agent (miscellaneous and occlusive). A letter has been sent to RIFM asking their intentions towards the safety assessment of the fragrance-only ingredients recited in this report: Eucalyptus Globulus Leaf/Twig Oil and Eucalyptus Globulus Leaf Water.

   In most cases, the main component of Eucalyptus Globulus Leaf Oil is reported to be eucalyptol (54% to 95%; also called 1,8-cineole or simply, cineole). Eucalyptol is a cosmetic ingredient that has not been reviewed by CIR. Should this ingredient be added to this safety assessment?

   If no further data are needed, the Panel should formulate a Discussion and issue a Tentative Report. However, if additional data are required to formulate a conclusion of safety, the Panel should be prepared to identify those needs and issue an IDA.

3. Zinc Salt Ingredients (agenda and flash drive name – Zinc Salts). This is the first time that the Panel is seeing these 28 inorganic and organometallic zinc salts as used in cosmetic formulations. Five of the ingredients in this group have been reviewed previously by the Panel. In October 2017, the SLR was posted for public comment with a request for additional data. Concentration of use data, additional data, and comments were received from the Council and addressed.

   If the data included in this report adequately address the safety of the zinc salts, the Panel should be prepared to formulate a tentative conclusion, provide the rationale to be described in the Discussion, and issue a Tentative Report for public comment. If the data are not sufficient for making a determination of safety, then an IDA should be issued that provides a listing of the additional data that are needed.

Tentative Reports – there are 3 draft tentative reports.

1. Malic Acid and Sodium Malate (agenda and flash drive name – Malic Acid*)*. In June 2017, the CIR Expert Panel reopened this safety assessment that was originally published in 2001 to revise the conclusion based on the receipt of new data that address the insufficient data needs in the original report. Prior to determining the new conclusion, however, the Panel issued an IDA for Malic Acid and Sodium Malate. The data needs were:
   - an HRIPT, or other suitable sensitization studies, at the maximum reported leave-on use concentration of 2.1%

- information on which stereoisomer(s) are used as cosmetic ingredients. If D- or DL-isomers are used in cosmetics, the Panel wanted additional information on impurities and method of manufacturing for these ingredients

Since the June meeting, CIR has received a HRIPT of a sun protection product containing 1% Malic Acid (tested neat) and a HRIPT of a hair product containing 2% Malic Acid (3% dilution of product tested). No dermal sensitization was observed in either study. The new data have been incorporated in the report. Data concerning the other data requests were not received.

The Panel should consider and discuss the data and the draft Abstract and Discussion presented in this report and issue a Tentative Amended Report.

2. Alkyl Sultaines (agenda and flash drive name – Sultaines). In September 2017, the CIR Expert Panel issued an IDA for the 13 alkyl sultaine ingredients. The Panel's data needs were:

    a. method of manufacturing for all these ingredients
    b. impurities data for all these ingredients, except for Cocamidopropyl Hydroxysultaine, Lauramidopropyl Hydroxysultaine, and Lauryl Hydroxysultaine
    c. if impurities data indicate known sensitizing agents (e.g., 3,3-dimethylaminopropylamine (DMAPA)) are present, additional safety test data may be needed
    d. irritation and sensitization data for Capryl Sultaine, Lauryl Sultaine, or Myristyl Sultaine

    Comments provided by the Council prior to the September meeting on the draft report have been addressed. Since the September Panel meeting, CIR has received the following requested data, which have been incorporated into the report:

    a. method of manufacturing on Cocamidopropyl Hydroxysultaine
    b. composition data on Capryl Sultaine
    d. a rabbit skin irritation test of a product containing 0.25% Capryl Sultaine (maximum concentration reported in use)
    d. test results of a clinician's irritation studies on human subjects with cosmetic products containing 0.25% Capryl Sultaine (maximum concentration reported in use)

    CIR also received additional composition/impurities data on a trade name mixture containing Cocamidopropyl Hydroxysultaine.

    The Panel should carefully consider and discuss the data and the draft Abstract and Discussion presented in this report and issue a Tentative Report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion.

3. *Hamamelis virginiana* (Witch Hazel)-Derived Ingredients (agenda and flash drive name – Witch Hazel). In September 2017, the Panel issued an IDA asking for:

    - sensitization data on Hamamelis Virginiana (Witch Hazel) Extract at the highest concentration of use
    - clarification of the maximum concentration of use for Hamamelis Virginiana (Witch Hazel) Extract in cosmetic formulations.

    No new sensitization data have been submitted (although, there is sensitization data in the report for Hamamelis Virginiana (Witch Hazel) Leaf Extract at 0.45% and Hamamelis Virginiana (Witch Hazel) Water at up to 25.80%). However, updated concentration of use data have been submitted that indicate the maximum concentration of use for Hamamelis Virginiana (Witch Hazel) is 1.8% (down from 86%, which was an OTC product, not a cosmetic).

    It is expected that the Dictionary monographs for Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract, Hamamelis Virginiana (Witch Hazel) Leaf Water, and Hamamelis Virginiana (Witch Hazel) Flower Water will be proposed for deletion, and that these ingredients will be incorporated under remaining *Hamamelis virginiana*-derived ingredient names.

    RIFM has been contacted about Hamamelis Virginiana (Witch Hazel) Flower Water, which is reported to be only used as a fragrance ingredient. There has been no reply at the time of the

writing of this memo as to whether or not they have or are planning to review this ingredient.

The Panel should carefully consider and discuss the data and the draft Abstract and Discussion presented in this report and issue a Tentative Report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion.

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

1. Triglycerides (agenda and flash drive name – Triglycerides). At the September 2017 meeting, the Panel issued a Tentative Amended Report with a conclusion stating that the 51 triglyceride ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

   Prior to that meeting, CIR received information that Tripelargonin had been added to the wINCI Dictionary. The results of a literature search found ADME data, as well as acute and short-term toxicity information, for this ingredient. These data have been added to the report and are indicated by yellow highlighting.

   No new unpublished data have been received since the Tentative Amended Report was issued. Council comments on that report were received and have been addressed. Panel edits from the September 2017 meeting were also addressed.

   The Panel should carefully review the Abstract, Discussion, and Conclusion of this report. If these are satisfactory, the Panel should issue a Final Report.

2. Polysilsesquioxanes (agenda and flash drive name – Polysilsesquioxanes). In June 2017, the Panel issued a Tentative Report with the conclusion of safe as used. Concentration of use and other data, as well as comments were submitted by the Council and have been incorporated or otherwise addressed.

   If the new data warrant a change to the Conclusion of this report, the Panel should provide the rationale to be included in the Discussion. If the data do not warrant a change to the Conclusion, the Panel should review the Abstract, Conclusion, and Discussion, ensuring that each captures the Panel's thinking, and issue a Final Amended Report.

3. Polyaminopropyl Biguanide (agenda and flash drive name – Polyaminopropyl Biguanide). At the September, 2017 Panel meeting, the Panel issued a Tentative Report with a conclusion stating that the available data are insufficient to make a determination that Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride) is safe under the intended conditions of use in cosmetic formulations. The Panel also determined that the following data are needed:

   - HRIPT on Polyaminopropyl Biguanide involving a diverse population (i.e., with a range of Fitzpatrick skin types) of 100 subjects tested with a dose of 1000 µg/cm^2 (and recommend to test at 500 µg/cm^2 as well)
   - Consumer use data on pump and propellant hair sprays, for use in determining the extent of exposure to Polyaminopropyl Biguanide during product use.

   To date, the data stated above have not been received. Comments on the Tentative Report that were received from the Council have been addressed. One of the comments relates to the inhalation risk assessment. The Panel is being asked to review this comment and identify the information that needs to be added to the inhalation risk assessment section of the safety assessment.

   If the Panel is asked for additional time to submit the needed data, a timeframe should be agreed upon for return of this report to the Panel meeting table. However, if the progress of this report is not tabled, the Panel should carefully review the Abstract, Discussion, and Conclusion of this report, and issue a Final Report.

4. Persulfates (agenda and flash drive name – Persulfates). In June 2017, the Panel issued a

Tentative Amended Report with a conclusion stating that Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin. The Panel also concluded that the available data are insufficient for determining the safety of these persulfates in leave-on products and dentifrices. The Panel determined that the following data are needed in order to evaluate the safety of persulfates in leave-on and dentifrice products:

- no-Observed-Effect-Level (NOEL) for sensitization and urticaria
- maximum concentrations of use in leave-on products and dentifrices

To date, the data stated above have not been received. Comments on the Tentative Amended Report that were received from the Council have been addressed.

The Panel should carefully review the Abstract, Discussion, and Conclusion of this report. If these are satisfactory, the Panel should issue a Final Amended Report.

5. Panthenol, Pantothenic Acid, and Derivatives (agenda and flash drive name – Panthenol). In September 2017, the Panel issued a Tentative Report with the conclusion that these 7 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment. The Panel also noted that these ingredients may contain residual amines as impurities; and, thus cautioned that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds may be formed.

   No new data have been received since the Tentative Report was issued. Council comments on the Tentative Report were received and have been addressed. Panel edits from the September 2017 meeting were also addressed.

   The Panel should review the Discussion to ensure that it captures the rationale for the report Conclusion and review the Abstract and Conclusion to ensure that they capture the Panel's thinking. The Panel should be prepared to issue a Final Report.

6. *Mentha piperita* (Peppermint)-Derived Ingredients (agenda and flash drive name – Peppermint). In September 2017, the Panel issued a Tentative Amended Report for public comment with a conclusion stating that Mentha Piperita (Peppermint) Oil is safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing. However, the available data are insufficient to make a determination of safety for the other 9 *Mentha piperita* (peppermint)-derived ingredients. The Panel determined that the following data are needed:

   a. composition data on all ingredients except for Mentha Piperita (Peppermint) Oil.
      - depending on the composition data that are received, other toxicological endpoints may be needed
   b. skin irritation and sensitization data on all ingredients except Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, and Mentha Piperita (Peppermint) Leaf Water

   The following data were received in response to the insufficient data conclusion:
   a. composition, method of manufacturing, and physical properties data on Mentha Piperita (Peppermint) Leaf Extract
   b. human 48-h occlusive patch test, evaluating skin irritation potential, on a lipstick product containing 0.2961% Mentha Piperita (Peppermint) Leaf Extract

   Updated use concentration data on *Mentha piperita* (peppermint)-derived ingredients were also received. According to this updated data, use concentrations of Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract are no longer being reported and Mentha Piperita (Peppermint) Leaf Extract is being used at concentrations ranging from 0.3% to 0.5% in lipstick products. Comments that were received from the Council have been addressed.

   The Panel should determine whether the data are now sufficient to formulate a conclusion of safety for all of the *Mentha piperita*-derived ingredients. If the data needs are still unmet, the

Panel should review the Abstract, Discussion, and Conclusion to ensure that each captures the Panel's thinking, and issue a Final Report.

7. Ammonia and Ammonium Hydroxide (agenda and flash drive name – Ammonia). In September 2017, the Panel issued a Tentative Report with the conclusion that Ammonia and Ammonium Hydroxide are safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating. Comments were received from the Council. Specifically, the one comment suggested that the report conclusion should address the use in hair dyes and colors separately from products applied to the skin. Please review that comment carefully, and determine whether or not you agree with the suggestion. The other comments have been addressed.

   The Panel should review the Discussion to ensure that it captures the rationale for the report Conclusion. The Panel should also review the Abstract and Conclusion to ensure that they capture the Panel's thinking, and issue a Final Report.

8. Alkane Diols (agenda and flash drive name – Alkane Diols). At the September 2017 meeting, the Panel issued a Revised Tentative Report with a conclusion of safe in cosmetics in the present practices of use and concentration for 6 of the alkane diols, and insufficient data (for concentration of use and additional toxicity data) for 4 of the alkane diols, specifically, 1,4-Butanediol, 2,3-Butanediol, 1,5-Pentanediol, and Octanediol.

   No data have been submitted to address the noted insufficiencies. However, comments were submitted in response to the questions raised about 1,5-Pentanediol. If after considering these comments the Panel determines that the data on 1,5-Pentanediol are sufficient to determine safety, then the Conclusion should be revised to reflect that change.

   Conversely, if the Panel determines that the Conclusion is correct as currently stated, then the Panel should be prepared to verify the Abstract, Discussion, and Conclusion, and issue a Final Report with a mixed conclusion of safe in cosmetics in the present practices of use and concentration for 6 ingredients and insufficient data for 4 ingredients.

Other Item – there is 1 other item of business for consideration, comprising the finalization of the updated CIR Guidance Document on Hair Dye Epidemiology.

Guidance Document Update

1. Hair Dye (agenda and flash drive name – Hair Dye). This is the latest draft of the CIR Expert Panel Hair Dye Epidemiology document. The previous draft was reviewed by the Panel at the September 2017 meeting. Comments from the Panel have been addressed in the current draft. Furthermore, additional studies relating risks with the use of hair dyes have been proposed in this draft with highlighting, as well as a description of the differences between odds ratio (OR) and relative risk (RR) values as used in this document.

   The Panel should review this draft of the document and determine whether it is suitable for posting on the CIR website, to replace the version currently posted.

Full Panel Meeting

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

The Panel will consider the 8 reports to be issued as final safety assessments, followed by the remaining reports advancing in the process, including the tentative reports, draft reports, and guidance documents. It is likely that the full Panel session will conclude before lunch on day 2, so plan your travel accordingly.

Have a safe journey!

Agenda
145th Cosmetic Ingredient Review Expert Panel Meeting
December 4-5, 2017

The Darcy Hotel
1515 Rhode Island Avenue, NW,
Washington, District of Columbia, 20005-5595

Monday, December 4th

8:00 am	**CONTINENTAL BREAKFAST**	
8:30 am	**WELCOME TO THE 145th EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Heldreth**
8:40 am	**PRESENTATIONS – Hair Dye Chemistry and Patch Test Update** **→ *Title* Chemistry of Hair Coloring** **→ *Title* Allergy Alert Test: Proof of Concept Study**	**(via web-conference) Carsten Goebel, Ph.D., Coty** **Maya Krasteva, MD, Ph.D., L'Oreal**
10:50 am	**TEAM MEETINGS**	**Drs. Marks/Belsito**

Dr. Marks' Team*

FR (MF)	Triglycerides
FR (LS/MF)	Alkane Diols
FR (LS/MF)	Panthenol
DR (LS/MF)	Zinc Salts
FR (WJ)	Ammonia and Ammonium Hydroxide
FR (WJ)	Peppermint
FR (WJ)	Polyaminopropyl Biguanide
FR (WJ)	Persulfates
FR (LB)	Polysilsesquioxanes
TR (LB)	Witch Hazel
DR (LB)	Eucalyptus
TR (CB)	Sultaines
TR (CB)	Malic Acid
DR (CB)	Ginkgo
Admin (BH)	Hair Dye

Dr. Belsito's Team

Admin (BH)	Hair Dye
TR (CB)	Sultaines
TR (CB)	Malic Acid
DR (CB)	Ginkgo
FR (LB)	Polysilsesquioxanes
TR (LB)	Witch Hazel
DR (LB)	Eucalyptus
FR (LS/MF)	Alkane Diols
FR (LS/MF)	Panthenol
DR (LS/MF)	Zinc Salts
FR (MF)	Triglycerides
FR (WJ)	Ammonia and Ammonium Hydroxide
FR (WJ)	Peppermint
FR (WJ)	Polyaminopropyl Biguanide
FR (WJ)	Persulfates

FR: Final Report
TR: Tentative Report
DR: Draft Report

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

*Team moves to breakout room.

Tuesday, December 5th			
8:00 am	**CONTINENTAL BREAKFAST**		
8:30 am	**WELCOME TO THE 145th FULL CIR EXPERT PANEL MEETING**		**Dr. Bergfeld**
8:45 am	Admin	**MINUTES OF THE SEPTMBER 2017 EXPERT PANEL MEETING**	**Dr. Bergfeld**
9:00 am	**DIRECTOR'S REPORT**		**Dr. Heldreth**
9:10 am	**FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, OTHER ITEMS**		

Final Reports

FR (WJ)	Ammonia and Ammonium Hydroxide - Dr. Marks reports
FR (WJ)	Peppermint - Dr. Belsito reports
FR (WJ)	Polyaminopropyl Biguanide - Dr. Marks reports
FR (WJ)	Persulfates - Dr. Belsito reports
FR (LB)	Polysilsesquioxanes - Dr. Marks reports
FR (LS/MF)	Alkane Diols - Dr. Belsito reports
FR (LS/MF)	Panthenol - Dr. Marks reports
FR (MF)	Triglycerides - Dr. Belsito reports

Reports Advancing

DR (LS/MF)	Zinc Salts - Dr. Marks reports
DR (LB)	Eucalyptus - Dr. Belsito reports
TR (LB)	Witch Hazel - Dr. Marks reports
TR (CB)	Sultaines - Dr. Belsito reports
TR (CB)	Malic Acid - Dr. Marks reports
DR (CB)	Ginkgo - Dr. Belsito reports

Other Item

Admin (BH)	Hair Dyes - Dr. Marks reports

ADJOURN - Next meeting *Monday and Tuesday, March 5th – 6th, 2018,* at The Darcy Hotel, 1515 Rhode Island Avenue, NW, Washington, District of Columbia, 20005-5595

FR: Final Report
TR: Tentative Report
DR: Draft Report

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ONE HUNDRED FORTY-FOURTH MEETING

OF THE

EXPERT PANEL

September 11-12, 2017

Loews 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

Thomas Gremillion, J.D.

Industry

Beth A. Jonas, Ph.D.

Government

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

Adopted (Date)

Wilma F. Bergfeld, M.D.

1620 L Street, N.W., Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

Others Present at the Meeting

Robena Aziz	FDA
Lillian Becker	CIR
Don Bjerke	P & G
Ivan Boyer	CIR
Roshil Budhram	L-Brands
Kristen Buono	Presperse
Christina Burnett	CIR
Jamie Cacman	Kao USA
Kapal Dewa	FDA
Carol Eisenmann	PCPC
Monice Fiume	CIR
Kevin Fries	CIR
Dave Gossai	L'Oreal
Thomas Gremillion	CFA
Bart Heldreth	CIR
Duane Huggett	EAG
Carla Jackson	CIR
Wilbur Johnson, Jr.	CIR
David Jono	Lonza
Julia Linthicum	CIR
Tim McCarthy	J & J
Stanley R. Milstein	Milstein & Milstein Associates
Yergen Nazarenko	McGill
Goran Periz	FDA
Mark Pollak	PCPC
Thomas Re	TARE Consulting
Madhuri Singal	RB
David Steinberg	Steinberg and Associates

MINUTES FROM THE 144th CIR EXPERT PANEL MEETING

CHAIRMAN'S OPENING REMARKS

The 144th meeting of the CIR Expert Panel was called to order by Dr. Wilma Bergfeld on September 12, 2017 at 8:28 a.m., and all attendees were welcomed. She congratulated Dr. Bart Heldreth, new CIR Executive Director, and Mrs. Monice Fiume, CIR Senior Director, on their recent promotions, and stated that the Panel is looking forward to working with them and is willing to help whenever the need arises.

Dr. Bergfeld recalled that, at yesterday's Team meetings, the Panel heard two outstanding presentations relating to the inhalation of aerosols. Her impression is that the speakers were able to expand the Panel's thought process in evaluating the safety of ingredients in cosmetic products that are aerosolized or in powder form. Dr. Bergfeld noted that the presentations provided useful information that can be incorporated into the CIR Precedents – Aerosols Document (a guidance document). Additionally, the Team meetings agenda encompassed the review of 15 ingredient reports, including 8 final reports and 7 reports advancing to a higher level of review (many of which are re-reviews). Three re-review summaries that resulted from the Panel's decisions not to reopen the corresponding published final reports were also considered. Dr. Bergfeld thanked the CIR staff for their impressive productivity.

The following 3 CIR Precedent documents were also considered in Teams: CIR Precedents – Aerosols Document (mentioned earlier), CIR Precedents – Endocrine Activity Document, and the latest draft of the Hair Dye Epidemiology Document. Dr. Bergfeld stated that the Hair Dye Epidemiology Document will be reviewed at the December 2017 Panel meeting, where the Panel will hear related presentations.

Dr. Bergfeld noted that late unpublished data submissions and botanical constituents continue to be problem areas during the review process. She also mentioned that read-across predictions are being considered in safety assessments by the Panel, and that CIR has developed boilerplates that relate to read-across information.

APPROVAL OF MINUTES

The minutes of the June 12-13, 2017 CIR Expert Panel meeting were unanimously approved.

DIRECTOR'S REPORT

Dr. Heldreth expressed gratitude for the Panel's and other stakeholders' support of his promotion to Executive Director and that of Ms. Fiume to Senior Director.

Dr. Heldreth pointed out two cogent presentations made to the Panel at this meeting, and significant discussion involving Aerosols and the other two CIR Precedent Documents under review at this meeting. He also discussed the finalized status of the Preliminary Search Engines and Websites information resource document, including its public availability (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites) and the language therein approved for use in CIR reports going forward. This, and all other CIR Findings & Resources Documents, may be found on the dedicated page of the same name (http://www.cir-safety.org/cir-findings).

Dr. Heldreth reminded stakeholders about an impending change of status with regard to 3 ingredients, set for later this year. Specifically, Carrageenan and MEA-Hydrolyzed Silk will be moved to the "zero-use category," and Silkworm Cocoon Extract will be moved to the "use not supported" category, if data needs for assessing the safety of these ingredients are not met by the end of this year.

With regard to visibility of CIR, Dr. Heldreth mentioned that since the last Panel meeting, CIR staff made a presentation at a cosmetic science conference in Shanghai, sharing the structure of CIR and the safety assessment process performed herein, to members of the industry in Asia. Additionally, Ms. Fiume will be representing CIR at the upcoming 7th Cosmetic Compliance Conference, in New York, NY, on November 1st (https://cosmeticscompliance.iqpc.com/).

Final Safety Assessments

Bovine Milk Proteins and Protein Derivatives

The Cosmetic Ingredient Review Expert Panel (Panel) issued a final report with the conclusion that the 16 bovine milk protein and protein derivative ingredients listed below are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Ammonium Caseinate*
Calcium Caseinate*
Casein
Casein Extract*
Hydrolyzed Casein
Hydrolyzed Lactalbumin*
Hydrolyzed Milk Protein
Hydrolyzed Whey Protein
Hydrolyzed Yogurt Protein
Lactoglobulin
Milk Protein
Milk Protein Extract
Potassium Caseinate*
Sodium Caseinate
Sodium Hydrolyzed Casein*
Whey Protein

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

The Panel noted that Sodium Caseinate has use concentrations reported up to 96.9%; however, this concentration is in bath oils, tablets, and salts, which are diluted in water prior to use. In leave-on products, the maximum concentration of use reported in the casein-derived ingredients is 2%. Safety test data of Hydrolyzed Casein were negative at up to 30%. Because of these factors, the Panel was not concerned with the use of Sodium Caseinate at such a high concentration in diluted bath products.

The Panel noted that bovine milk proteins are known food allergens that can elicit Type I immediate hypersensitivity reactions when ingested by sensitized individuals. The Panel reviewed studies showing no relevant ocular irritation and no dermal irritation or sensitization in animals and human subjects. Additionally, according to their collective knowledge in treating patients with Type 1 hypersensitivity, the Panel clinicians have not experienced responses to bovine milk protein via dermal exposures. Thus, the Panel was not concerned that Type I reactions would be induced by dermal exposure to bovine milk proteins in cosmetics.

Plant-Derived Proteins and Peptides

The Panel issued a final report with the conclusion that the following 18 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Hydrolyzed Amaranth Protein
Hydrolyzed Avocado Protein*
Hydrolyzed Barley Protein
Hydrolyzed Brazil Nut Protein
Hydrolyzed Cottonseed Protein
Hydrolyzed Extensin
Hydrolyzed Hazelnut Protein
Hydrolyzed Hemp Seed Protein
Hydrolyzed Jojoba Protein
Hydrolyzed Lupine Protein
Hydrolyzed Pea Protein
Hydrolyzed Potato Protein
Hydrolyzed Sesame Protein
Hydrolyzed Sweet Almond Protein
Hydrolyzed Vegetable Protein
Hydrolyzed Zein*
Lupinus Albus Protein
Pisum Sativum (Pea) Protein

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

The Panel also concluded the data on Hydrolyzed Maple Sycamore Protein are insufficient to determine safety. This ingredient is not reported to be in use. The remaining data needs are:

- Method of manufacturing
- Chemical composition and impurities

- Clarification on food safety status, specifically if this ingredient is generally recognized as safe (GRAS). If this ingredient is not GRAS, then studies of systemic endpoints such as a 28-day dermal toxicity, reproductive and developmental toxicity, and genotoxicity are needed, as well as UV absorption spectra

The Panel acknowledged that Type I immediate hypersensitivity reactions could possibly occur following exposure to a protein-derived ingredient. Traditional human repeat insult patch tests (HRIPTs) and related tests do not detect Type I reactions. Thus, the Panel recommended that people with known allergies to tree nut, seed, and avocado proteins avoid using personal care products that contain these ingredients.

Skin and Connective Tissue-Derived Proteins and Peptides (previously "Ectodermal-Derived Proteins and Peptides")

The Panel issued a final report with the conclusion that the 19 skin and connective tissue-derived proteins and peptides listed below are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Ammonium Hydrolyzed Collagen
Atelocollagen
Calcium Hydrolyzed Collagen*
Collagen
Elastin
Fibronectin
Gelatin
Hydrolyzed Actin
Hydrolyzed Collagen
Hydrolyzed Collagen Extract*
Hydrolyzed Elastin
Hydrolyzed Fibronectin
Hydrolyzed Gelatin*
Hydrolyzed Reticulin
Hydrolyzed Spongin*
MEA-Hydrolyzed Collagen
Soluble Collagen
Soluble Elastin*
Zinc Hydrolyzed Collagen*

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

The Panel noted that there was a lack of systemic toxicity data (i.e. reproductive and developmental toxicity, genotoxicity, and carcinogenicity data); however, the Panel was not concerned that these proteins and peptides would cause adverse systemic effects in the general population. These proteins and peptides, similar to the other proteins and peptides reviewed by the Panel, are found in food, and daily exposures from the consumption of foods can be expected to yield much larger systemic exposures to these ingredients than those from use in cosmetic products. The Panel also found that the earlier assessments of Hydrolyzed Collagen supported the safety of these ingredients in cosmetic products.

The Panel noted that fish proteins are known food allergens that can elicit Type I immediate hypersensitivity reactions when ingested by sensitized individuals. The Panel expressed concern that sensitized individuals would not easily recognize cosmetic products containing fish-derived collagen based on the current naming conventions used in the ingredient lists on product labels (e.g., Collagen and Hydrolyzed Collagen may be sourced from fish, though "fish" is not in the ingredient name). In the absence of negative Type I immediate hypersensitization data for fish-derived protein ingredients (or other information supporting an inability of the supplied ingredient to elicit such sensitization (e.g., a maximum peptide length that is shorter than the minimum IgE-binding epitopes)), the Panel advised manufactures to label products containing these fish-derived ingredients as appropriate to inform individuals sensitized to fish proteins.

***Butyrospermum parkii* (Shea)-Derived Ingredients**

The Panel issued a final report with the conclusion that the following 13 ingredients are safe in cosmetics in the present practices of use and concentration as described in the safety assessment when formulated to be non-sensitizing.

Butyrospermum Parkii (Shea) Butter
Butyrospermum Parkii (Shea) Oil

Butyrospermum Parkii (Shea) Butter Extract
Butyrospermum Parkii (Shea) Butter Unsaponifiables
Butyrospermum Parkii (Shea) Nut Extract
Butyrospermum Parkii (Shea) Nut Shell Powder
Butyrospermum Parkii (Shea) Seedcake Extract
Hydrogenated Shea Butter
Hydrogenated Shea Oil*
Hydrolyzed Shea Seedcake Extract*
Shea Butter Glyceride
Shea Butter Glycerides
Shea Oleine

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

The Panel noted that, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients in one formulation may each contribute to the final concentration of a single constituent. Therefore, when formulating products, manufacturers should avoid reaching levels in final formulation of botanical constituents that may cause sensitization or other adverse effects.

There are no irritation or sensitization data for Butyrospermum Parkii (Shea) Nut Extract and Butyrospermum Parkii (Shea) Nut Shell Powder and no irritation or sensitization data for Butyrospermum Parkii (Shea) Seedcake Extract and Butyrospermum Parkii (Shea) Butter at maximum use concentrations (5.5% and 100% in leave-on products, respectively). HRIPTs for Butyrospermum Parkii (Shea) Seedcake Extract and Butyrospermum Parkii (Shea) Butter were negative when tested, although, these were tested at concentrations lower than the maximum use concentrations. However, based on the Panel's clinical experience, the absence of adverse event reports, and the available negative safety test data, the Panel does not expect dermal irritation or sensitization following exposure to these ingredients.

***Humulus lupulus* (Hops) Extract and Oil**

The Panel issued a final report with the conclusion that the following two ingredients are safe in cosmetics in the present practices of use and concentration as described in the safety assessment when formulated to be non-sensitizing.

Humulus Lupulus (Hops) Extract
Humulus Lupulus (Hops) Oil*

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

The Panel noted that, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients in one formulation may each contribute to the final concentration of a single shared constituent. Therefore, when formulating products, manufacturers should avoid reaching levels, in final formulations, of botanical constituents that may cause sensitization or other adverse effects.

Humulus Lupulus (Hops) Extract was reported to be used in 375 formulations, including 317 leave-on formulations and 54 rinse-off formulations. The highest reported maximum concentration of use was < 0.2% in hair conditioners; in products intended for dermal contact, the maximum concentration of use is 0.13% in eye lotions, deodorants, and other skin care preparations.

Monoalkylglycol Dialkyl Acid Esters

The Panel issued a final report with the conclusion that the following 28 monoalkylglycol dialkyl acid esters are safe in cosmetics in the present practices of use and concentration as described in the safety assessment.

Butylene Glycol Dicaprylate/Dicaprate
Butylene Glycol Diisononanoate*
Diethylpentanediol Dineopentanoate
Dioctadecanyl Didecyltetradecanoate*
Dioctadecanyl Ditetradecyloctadecanoate*
Glycol Dibehenate*
Glycol Diethylhexanoate
Glycol Dilaurate

Glycol Dioleate*
GlycolDipalmate/Palm Kernelate/Olivate/Macadamiate*
Glycol Dipalmate/Rapeseedate/Soyate*
Glycol Dipivalate*
Glycol Distearate
Glycol Ditallowate*
Hexanediol Distearate*
Neopentyl Glycol Dicaprate
Neopentyl Glycol Dicaprylate/Dicaprate
Neopentyl Glycol
Dicaprylate/Dipelargonate/Dicaprate*
Neopentyl Glycol Diethylhexanoate
Neopentyl Glycol Diheptanoate
Neopentyl Glycol Diisononanoate
Neopentyl Glycol Diisostearate
Neopentyl Glycol Dilaurate*
Propanediol Dicaprylate
Propanediol Dicaprylate/Caprate
Propanediol Diisostearate*
Propanediol Dipelargonate*
Trimethyl Pentanyl Diisobutyrate

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

The Panel noted that acute dermal toxicity tests of the smaller molecules (i.e., Neopentyl Glycol Diisononanoate and Trimethyl Pentanyl Diisobutyrate) revealed no concerns, and acute oral toxicity test results presented little concern. The Panel also considered the safety profile of potential hydrolysis products (e.g., resulting from esterases in the skin) of these ingredients, many of which were determined to be safe in previous CIR safety assessments. A concurrent report, Alkane Diols, also provided safety information about such hydrolysis products (or chemical surrogates thereof), 1,5-Pentanediol and Isopentyldiol, which the Panel considered in the overall weight of evidence. The Panel also noted that their lowered level of concern for the potential hydrolysis products of Diethylpentanediol Dineopentanoate was influenced in part by the maximum concentration of use of this ingredient of only up to 1% in rinse-off products.

Glycol Distearate was reported to be used in 1663 formulations, mostly in hair products (1041 formulations); Trimethyl Pentanyl Diisobutyrate is used in 399 formulations (all nail products), and Neopentyl Glycol Diheptanoate is used in 415 formulations (mostly in skin care products), respectively. The rest of the ingredients with reported uses were used in 102 or fewer formulations. Neopentyl Glycol Diethylhexanoate had the highest reported maximum concentration of use; it is used at up to 57% in leave-on products. Neopentyl Glycol Dicaprate had the next highest reported maximum concentration of use; it is used up to 50% in rinse-off products and 40% in leave-on products.

Polyurethanes

The Panel issued a final report on the following 66 polyurethane ingredients with the conclusion that these ingredients are safe in cosmetics in the present practices of use and concentration as described in the safety assessment.

Polyurethane-1
Polyurethane-2
Polyurethane-4*
Polyurethane-5*
Polyurethane-6
Polyurethane-7
Polyurethane-8
Polyurethane-9
Polyurethane-10
Polyurethane-11
Polyurethane-12*
Polyurethane-13*
Polyurethane-14
Polyurethane-15
Polyurethane-16
Polyurethane-17*
Polyurethane-18
Polyurethane-19*
Polyurethane-20*
Polyurethane-21*
Polyurethane-23*
Polyurethane-24
Polyurethane-25*
Polyurethane-26*
Polyurethane-27*
Polyurethane-28*
Polyurethane-29*
Polyurethane-32*
Polyurethane-33
Polyurethane-34
Polyurethane-35
Polyurethane-36*
Polyurethane-39
Polyurethane-40
Polyurethane-41*
Polyurethane-42*
Polyurethane-43*
Polyurethane-44*
Polyurethane-45*
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Polyurethane-60*
Polyurethane-61*
Polyurethane-62*
Polyurethane-63*
Polyurethane-64*
Polyurethane-65*
Polyurethane-66*
Polyurethane-67*
Polyurethane-68*
Polyurethane-69*
Polyurethane-70*

Polyurethane-71* Polyurethane-72*

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

The Panel reviewed the method of manufacturing information and the available data on impurities related to these ingredients, and determined that residual monomers would be expected to be either consumed in reaction or washed away in manufacturing and purification processes. Producers and formulators should continue to use good manufacturing principles to prevent conditions wherein monomers could be released from these polymeric ingredients.

Many of these ingredients are reported to be supplied (in pre-formulations or tradename mixtures) as emulsions or solutions with multiple components, sometimes including sensitizers such as methylisothiazolinone (MI; e.g., Polyurethane-60 and -61). Suppliers and formulators (finishing houses) should be aware of how these polymer ingredients are supplied, and should avoid reaching levels of components that may cause sensitization or other adverse health effects.

Polyurethane-11 was reported to be used in 315 formulations, including 303 leave-on formulations and 12 rinse-off formulations. The other ingredients were reported to have uses in 33 or fewer formulations. Polyurethane-1 has the highest reported maximum concentration of use, at up to 15% in nail products. The highest maximum concentration of use reported for products resulting in leave-on dermal exposure is 7.5% for Polyurethane-33 in the other skin care preparations category. The other reported maximum concentrations of use were at up to 9% (in nail, hair, or rinse-off dermal preparations).

Tentative Safety Assessments

Triglycerides

The Panel issued a tentative amended report for public comment with the conclusion that the 51 triglycerides listed below are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Acetic/Linoleic/Palmitic Triglyceride*
C12-18 Acid Triglyceride
C18-36 Acid Triglyceride
C8-12 Acid Triglyceride*
Capric/Lauric/Myristic/Oleic Triglyceride*
Caprylic/Capric Triglyceride
Caprylic/Capric/Lauric Triglyceride
Caprylic/Capric/Linoleic Triglyceride
Caprylic/Capric/Myristic/Stearic Triglyceride
Caprylic/Capric/Palmitic/Stearic Triglyceride*
Caprylic/Capric/Stearic Triglyceride
C10-40 Isoalkyl Acid Triglyceride
Cod Liver/Mink/Tallow Triglyceride*
C10-18 Triglycerides
Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride*
Glyceryl Stearate Diacetate*
Glyceryl Triacetyl Hydroxystearate
Glyceryl Triacetyl Ricinoleate
Glyceryl Tri-Hydrogenated Rosinate
Glyceryl Tripalmate/Palm
Kernelate/Olivate/Macadamiate/Rapeseedate*
Hydrogenated C12-18 Triglycerides
Isomerized Safflower Glycerides*
Jojoba Oil/Caprylic/Capric Triglyceride Esters*
Lauric/Palmitic/Oleic Triglyceride*
Oleic/Linoleic Triglyceride*
Oleic/Palmitic/Lauric/Myristic/Linoleic Triglyceride*
Palmitic/Stearic Triglyceride
Ricinoleic/Caproic/Caprylic/Capric Triglyceride*
Triarachidin*
Tribehenin
Tricaprin
Tricaprylin
Tierucin*
Triethylhexanoin
Triheptanoin
Triheptylundecanoin*
Trihydroxystearin
Triisononanoin
Triisopalmitin*
Triisostearin
Trilaurin
Trilinolein
Trilinolenin
Trimyristin
Triolein

Tripalmitin
Tripalmitolein*
Tripelargonin*
Triricinolein*
Tristearin
Triundecanoin

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

This amended report comprises 25 previously-reviewed ingredients, and 26 ingredients being reviewed for the first time. The Panel agreed that it was appropriate to remove Glyceryl Tribehenate/Isostearate/Eicosandioate from, and to add Tripelargonin to, the list of ingredients included in this report. Glyceryl Tribehenate/Isostearate/ Eicosandioate is actually a bis(triglyceride) and, therefore, not appropriate for inclusion in this family. Tripelargonin is a triglyceride that was added to the database of potential cosmetic ingredients (web version of the International Cosmetic Ingredient Dictionary and Handbook (wINCI)) after the inception of the safety assessment, and, therefore, it has been added to the report.

An insufficient data announcement (IDA) was issued at the April meeting, requesting irritation and/or sensitization data at maximum concentrations of use for several representative ingredients. Information was received to address some, but not all, of the requests. However, the Panel was confident that the weight of the evidence for safety was very strong, and that the available information was applicable to the entire group.

In the IDA from the April Panel meeting, the Panel also asked for clarification of the skin bleaching potential of Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride, including a dose-response for this action. These data were not received. However, the Panel stated that in the U.S., skin bleaching is not considered a cosmetic function, and, therefore, use in that manner is not being assessed in this report.

Finally, the Panel recognized that, reportedly, Triolein and Tricaprylin can enhance the skin penetration of other chemicals. Accordingly, the Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on a lack of dermal absorption, or wherein dermal absorption was a concern.

Alkane Diols

The Panel issued a revised tentative report for public comment with a split conclusion. The following 6 alkane diols are safe as used in cosmetics in the present practices of use and concentration as described in the safety assessment.

Propanediol
Hexanediol
1,10-Decanediol
Methylpropanediol
Butyl Ethyl Propanediol
Isopentyldiol

However, the Panel determined that the data on the following 4 ingredients are insufficient to determine safety.

1,4-Butanediol
1,5-Pentanediol*
2,3-Butanediol*
Octanediol

*Not reported to be in current use.

The data that are needed to evaluate the safety of 1,4-Butanediol; 1,5-Pentanediol; 2,3-Butanediol; and Octanediol comprise:

- Maximum concentration of use
- Short-term and chronic systemic toxicity data, specifically 28-day dermal toxicity studies
- Mammalian mutagenicity studies

The Panel highlighted the need for concentrations of use for the four ingredients listed above, especially for 1,4-Butanediol, as it can be metabolized into gamma-hydroxybutyric acid (GHB), a controlled substance in the United

States. The Panel also expressed concern that the toxicity data that do exist in this report cannot be confidently read across to the other ingredients that lack data. Toxicity data specific to 1,4- Butanediol; 1,5-Pentanediol; 2,3-Butanediol; and Octanediol are necessary to enable the Panel to assess the safety of this full group of ingredients.

The Panel noted that ocular irritation was observed for Butyl Ethyl Propanediol in rabbit studies. The ocular studies for the other alkane diols in this report largely indicated that these ingredients would not be ocular irritants. Given this weight of evidence, and in light of the exposure information that Butyl Ethyl Propanediol is not reported to be used in cosmetics that are used in the eye area, the Panel did not consider the use of the caveat, "formulated to be nonirritating," applicable to this conclusion.

Ammonia and Ammonium Hydroxide

The Panel issued a tentative report for public comment with a conclusion that Ammonia and Ammonium Hydroxide are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

It was noted that Ammonia and Ammonium Hydroxide, well-known skin irritants, are indistinguishable from each other in aqueous formulation. Furthermore, since the only cosmetic function of Ammonia applicable to this safety assessment is pH adjuster (which by default means aqueous formulations only) and Ammonium Hydroxide does not exist outside of water, regardless of which ingredient is added, the final formulations will contain an equilibrium of molecular Ammonia and the ions of Ammonium Hydroxide in water. Thus, whether toxicity data is reported for Ammonia or Ammonium Hydroxide, it is applicable to both (as the test articles would have had this same equilibrium).

The Panel agreed that the cosmetic ingredients Ammonium Chloride and Ammonium Sulfate, which, unlike Ammonia and Ammonium Hydroxide, would not function as pH adjusters in cosmetics, should not be counted in this safety assessment, though they agreed that the data on these other ingredients were useful as surrogates.

Panthenol, Pantothenic Acid, and Derivatives

The Panel issued a tentative report for public comment with the conclusion that the following 7 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Panthenol	Panthenyl Ethyl Ether Acetate*	Sodium Pantothenate*
Pantothenic Acid	Panthenyl Triacetate	
Panthenyl Ethyl Ether	Calcium Pantothenate	

*Not reported to be in current use. Were the ingredients in this group not currently in use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group. The Panel recognized that these ingredients, particularly Panthenol, can enhance the penetration of other ingredients through the skin. The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

The Panel also noted that these ingredients may contain residual amines as impurities. The Panel cautioned that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds may be formed.

***Mentha piperita* (Peppermint)-Derived Ingredients**

The Panel issued a tentative report for public comment with a conclusion stating that the available data are insufficient to make a determination of safety for 9 out of the 10 *Mentha piperita* (peppermint)-derived ingredients. These 9 ingredients, and the data that are needed to complete this safety assessment, are stated below.

Mentha Piperita (Peppermint) Leaf Extract	Mentha Piperita (Peppermint) Leaf Water
Mentha Piperita (Peppermint) Leaf	Mentha Piperita (Peppermint) Extract

Mentha Piperita (Peppermint) Flower/Leaf/Stem Extract
Mentha Piperita (Peppermint) Flower/Leaf/Stem Water*
Mentha Piperita (Peppermint) Leaf Cell Extract*
Mentha Piperita (Peppermint) Leaf Juice*
Mentha Piperita (Peppermint) Meristem Cell Culture*

*Not reported to be in use.

The data needed to formulate a conclusion of safety include:

- Composition data on each of the above ingredients.
    - ○Depending on the composition data that are received, other toxicological endpoints may be needed.
- Skin irritation and sensitization data on all of the above ingredients, except Mentha Piperita (Peppermint) Leaf Extract and Mentha Piperita (Peppermint) Leaf Water.

However, it was determined that Mentha Piperita (Peppermint) Oil is safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing.

The Panel noted that, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients in one formulation may each contribute to the final concentration of a single shared constituent. Therefore, when formulating products, manufacturers should avoid reaching levels, in final formulations, of botanical constituents that may cause sensitization or other adverse effects.

This group of ingredients was established at the April 2017 Expert Panel meeting, whereby the Panel agreed that the original final report (published in 2001) on Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water should be reopened to add 6 *Mentha piperita*-derived ingredients. Therein, the Panel also issued an IDA relating to all 10 ingredients, and composition, irritation, and sensitization data were requested.

Data were received in response to the IDA. The Panel agreed that the available composition data on Mentha Piperita (Peppermint) Oil are sufficient, but the data relating to composition of the other ingredients, are inadequate. After considering the available skin irritation and sensitization data, the Panel determined that skin sensitization data on all ingredients, except for the Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, and Mentha Piperita (Peppermint) Leaf Water, are still insufficient.

The Panel considered the positive effects that were observed in female rats, and in male and female mice, dosed with pulegone (component of Mentha Piperita (Peppermint) Oil) in the 2011 National Toxicology Program (NTP) oral carcinogenicity study. However, the Panel did not express concern over these findings relative to pulegone as a component of Mentha Piperita (Peppermint) Oil in cosmetic products, based on the understanding that the cytotoxic dose-response relationship (renal and liver toxicity) that was associated with cancer development would not be relevant to pulegone exposure from a cosmetic product. The Panel also reconsidered the 1% concentration limit on pulegone in the published final report on *Mentha piperita*-derived ingredients that appears to have been based on observations of brain lesions in rats. As the brain lesions were an artifact of the fixation method, the Panel determined that this study was not relevant to cosmetic safety. It was therefore agreed, that the 1% concentration limit and the carcinogenicity of pulegone should be addressed in the report discussion and not in the conclusion.

Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

The Panel issued a tentative report with a conclusion stating that the available data are insufficient to make a determination that Polyaminopropyl Biguanide is safe under the intended conditions of use in cosmetic formulations. The data that are needed to complete the safety assessment of this ingredient are:

- HRIPT on Polyaminopropyl Biguanide involving a diverse population (i.e., with a range of Fitzpatrick skin types) of 100 subjects tested with a dose of 1,000 μg/cm^2 (and recommend to test at 500 μg/cm^2 as well)

- Consumer use data on pump and propellant hair sprays, for use in estimating the extent of exposure to Polyaminopropyl Biguanide during spray product use

In response to a previous IDA, a spray model and a no observed adverse effect concentration (NOAEC) were used to calculate a margin of safety (MOS). MOS values for both pump hair sprays and propellant hair sprays were calculated. In reviewing this risk assessment, the Panel noted that the exposure scenario (e.g., sprayed over 6 hours) in one of the underlying experimental studies was not representative of pump and propellant hair spray product use. Thereby, consumer use data on these product types are needed to determine a dose, if the safe use of this ingredient is to be determined for products that are intended to be sprayed. However, this ingredient might not actually be in use in products that are intended to be sprayed. Indeed, one supplier submitted a comment that their company would not consider using this ingredient in such applications.

A quantitative risk assessment (QRA) yielded a no expected sensitization induction level (NESIL) of 1000 $\mu g/cm^2$, which theoretically supports the use of this ingredient at concentrations of $\leq 0.1\%$. However, the Panel noted that the HRIPT study utilized to support this NESIL may not be adequately diverse, and suggested that an HRIPT (> 100 subjects) on a more diverse study population at a dose of 500 and 1,000 $\mu g/cm^2$ is needed to derive an acceptable NESIL.

The Panel noted the contact urticaria potential of Polyaminopropyl Biguanide, but determined that this would not be an issue in relation to cosmetic product applications after considering that contact urticaria was observed under the conditions of burn dressings on severely damaged skin. It was also determined that the skin irritation potential of Polyaminopropyl Biguanide at cosmetic use concentrations is not a concern, based on the studies in the assessment.

Insufficient Data Announcements

***Hamamelis virginiana* (Witch Hazel)-Derived Ingredients**

The Panel issued an insufficient data announcement for the following 8 *Hamamelis virginiana* (witch hazel)-derived ingredients.

Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract*
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract
Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract*
Hamamelis Virginiana (Witch Hazel) Extract
Hamamelis Virginiana (Witch Hazel) Flower Water
Hamamelis Virginiana (Witch Hazel) Leaf Extract
Hamamelis Virginiana (Witch Hazel) Leaf Water
Hamamelis Virginiana (Witch Hazel) Water

* Not reported to be in current use.

The data needs are:

- Sensitization data on Hamamelis Virginiana (Witch Hazel) Extract at the highest concentration of use.
- Clarification of the maximum concentration of use for Hamamelis Virginiana (Witch Hazel) Extract in cosmetic formulations.

The Panel also requested confirmation that the only function of Hamamelis Virginiana (Witch Hazel) Flower Water is fragrance ingredient and whether the Research Institute for Fragrance Materials (RIFM) intends to perform a safety assessment thereon.

Alkyl Sultaines

The Panel issued an IDA for the following 13 alkyl sultaine ingredients.

Cocamidopropyl Hydroxysultaine
Capryl Sultaine
Cetyl/Lauryl/Myristyl Hydroxysultaine
Coco-Hydroxysultaine
Coco-Sultaine
Erucamidopropyl Hydroxysultaine

Lauramidopropyl Hydroxysultaine
Lauryl Hydroxysultaine
Lauryl Sultaine
Myristamidopropyl Hydroxysultaine
Myristyl Sultaine
Oleamidopropyl Hydroxysultaine
Tallowamidopropyl Hydroxysultaine

The additional data needed are:

- Method of manufacturing for all these ingredients.
- Impurities data for all these ingredients, except for Cocamidopropyl Hydroxysultaine, Lauramidopropyl Hydroxysultaine, and Lauryl Hydroxysultaine
    - If impurities data indicate known sensitizing agents (e.g., 3,3-dimethylaminopropylamine (DMAPA)) are present, additional safety test data may be needed
- Irritation and sensitization data for Capryl Sultaine, Lauryl Sultaine, or Myristyl Sultaine.

Re-Review Summaries:

Glyoxal

The Panel approved the re-review summary of Glyoxal with the conclusion that it is safe for use in products intended to be applied to the nail at concentrations ≤ 1.25%, and that the available data are insufficient to support the safety for other uses.

The Panel has now reviewed information that has become available since the year 2000 assessment, along with updated information regarding product types, and frequency and concentrations of use. The Panel determined to not reopen this safety assessment and reaffirmed the conclusion published in 2000. The Panel also noted that suppliers should take steps to limit the concentration of the free formalin impurity to 0.2% (0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol), which is consistent with the 2013 CIR safety assessment of Formaldehyde and Methylene Glycol.

Quaternium-26

The Panel approved the re-review summary of Quaternium-26 with the conclusion that it is safe as used in cosmetic products. Unlike the current exclusive use of Quaternium-26 in non-coloring hair products (16 rinse-off and 10 leave-on reported uses), data in the final report that was published in 2000 indicated use in this product type as well as in cleansing skin care preparations and bath soaps and detergents. The difference in Quaternium-26 use frequency is not significant when data in the published final report are compared with current data (i.e., 25 uses and 26 uses, respectively). According to the published final report from 2000, Quaternium-26 was being used at concentrations up to 5%. However, the results of a concentration of use survey that was conducted by the Council in 2015-2016 indicated that Quaterium-26 is being used at maximum concentrations up to 2% in rinse-off products (hair conditioners) and maximum concentrations up to 0.15% in leave-on products (tonics, dressings, and other hair grooming aids).

Biotin

The Panel approved the re-review summary of Biotin with the conclusion that it is safe as used in cosmetics.

Some new data were identified in the published literature; these data were similar to data that were included in the original assessment. The Panel reviewed updated information regarding product types and ingredient use frequencies provided by the FDA and maximum use concentrations provided by the Council. The Panel determined to not reopen this safety assessment and reaffirmed the original conclusion.

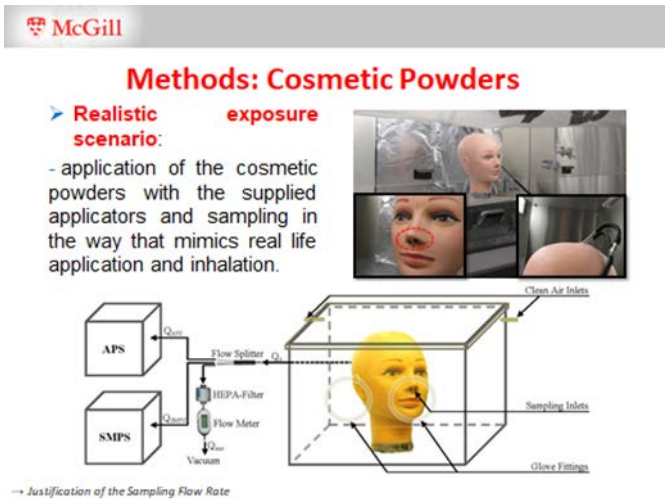
The reported frequency of use of Biotin in cosmetics has increased since its safety was originally reviewed; 71 uses were reported 1998, and 506 uses are reported in 2017. The reported maximum leave-on concentration of use has decreased from 0.6% to 0.1%. The number of uses in formulations with intentional application near the eye area increased from 2 to 54, and the maximum concentration of use reported for this type of exposure increased from 0.01% to 0.1%. However, this use concentration is still quite low, and did not raise any new concerns.

As in the original assessment, the Panel recognized that data on the irritation and sensitization potential of Biotin were absent. However, the Panel was of the opinion that if Biotin had a strong potential for irritation or sensitization, case reports would be available in the published literature.

The Panel also noted that there are reproductive studies of Biotin that show strong inhibition of spermatogenesis. However, these are oral studies at high levels which are irrelevant to uses in cosmetics. Therefore, it is the opinion of the Panel that the results of those studies are not pertinent to the safety of Biotin as a cosmetic ingredient.

Presentations

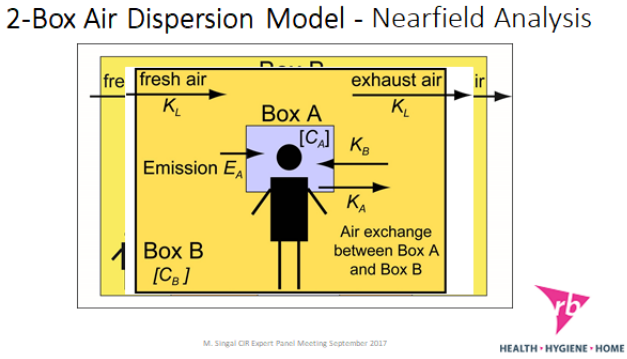
At the June 2017 meeting, the Panel requested further expert input on the topic of aerosols and otherwise incidentally inhalable particles. In response, two presentations were made at this meeting. Dr. Yevgen Nazarenko presented a briefing titled "Exposure Assessment of Nanomaterial-Containing Aerosols from Spray and Powder Products." Dr. Nazarenko is currently a Postdoctoral Fellow at McGill University in Montreal, QC, Canada. He presented research that he performed as a graduate student at Rutgers University.



Dr. Nazarenko emphasized the importance of knowing what techniques were used for collecting and preparing samples to characterize aerosols, because airborne particles can agglomerate, and the agglomeration state may be different from what is actually in the air when cosmetic products are used. He also noted the complexity of the dynamics of aerosols after spraying, emphasizing the importance of considering critical factors when evaluating inhalation exposures, including evaporation, condensation, coagulation, and precipitation of the constituents of the aerosolized particles or droplets, as well as temperature, relative humidity, how much is sprayed and how the product is applied.

In his research, Dr. Nazarenko found that nanoparticles can be found in, or released to the air from, cosmetic products, regardless of whether the products are marketed to contain such. He found that many nanoaggregates and nanoagglomerates were released even when energetic sprayers, such as nebulizers, were used to disperse the products to the air. Using a mannequin sampler, he determined that most (85% to 93%) of the mass of inhaled airborne nanoparticles released from powders deposit in the head airways. The inhaled dose of the aerosol fraction above 100 nm was 3 to 8 orders of magnitude greater than the dose of the fraction within the nano range.

Dr. Nazarenko noted that reducing incidental inhalation exposures to nanoparticles from cosmetic products can be accomplished by, for example, using spraying devices, ingredients, and formulations that enable minimizing aerosol generation and the size distributions of the particles released from these products. He emphasized that manufacturers should disclose information needed to ensure the safety of cosmetic products, including information characterizing the size distributions of the particles and droplets emanating from products, when used as intended, as well as factors such as the identities and concentrations of the ingredients in the cosmetic formulations.



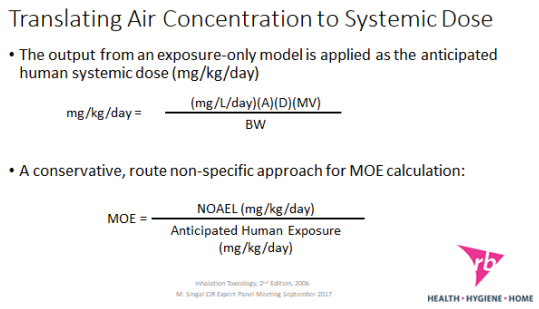
Dr. Madhuri Singal then presented a briefing titled "Considerations for Inhalation Safety Assessment: Approaches and Application." She is an Inhalation Toxicologist and Senior Consumer Safety Associate at Reckitt Benckiser, LLC, in Parsippany, NJ.

Dr. Singal opened her presentation with an example illustrating the importance of considering the scale of the data used to assess the safety of ingredients

in cosmetic products that may be incidentally inhaled. Data can easily be misinterpreted when evaluated without properly considering the critical context provided by the scale of the measurements used in the analysis.

Dr. Singal emphasized the need to understand the distinct characteristics of each product evaluated. She noted that integral factors in inhalation exposure and safety assessments include the concentrations of the ingredient of interest in the spray formulation and an understanding of the chemical and biological properties of the ingredient and how the spray device releases the formulation to the air, as well as the airborne concentration of the ingredient, the spray rate, the air exchange rate of the room in which the product is used, and physiological factors, including respiratory rate, tidal volume, and clearance mechanisms. She explained the importance of considering the solubility and surface charge and, especially, the chemical reactivity of the ingredient in safety assessments wherein inhalation is a potential route of exposure.

Dr. Singal described several computational tools available for assessing the exposure, deposition, and bioavailability of incidentally inhaled particles and and droplets, including the 2-Box Air Dispersion model, which is depicted, conceptually, in the figure above. She mentioned that the near-field analysis capability of this model would be most relevant in cosmetic ingredient safety assessments, centered on the head, but the model can be adjusted to evaluate, for example, whole-body near-field exposures and far-field exposures, as necessary. All of these models can be used to estimate exposures in defined conservative consumer or occupational exposure scenarios. In addition, all of them are amenable calculating refined estimates of exposures based on real-world measurements that reflect more accurately than the default assumptions the actual exposure scenarios of interest. And, once a modeled exposure concentration is obtained, it is necessary to calculate dose (mg/kg/day) to calculate an MOE.



Dr. Singal discussed the Multiple Path Particle Deposition (MPPD) Model, in particular, indicating that refinements of this model have enabled quantitatively estimating the amount of an ingredient that will be deposited in each of the three major regions of the respiratory tract, including the head airways, tracheobronchial region and alveolar region, when a cosmetic spray or powder product is used as intended. She emphasized that this model can estimate respiratory tract deposition in children as young as 3 months of age, as well as in older individuals.

CIR Precedents (Guidance Documents)

Aerosols

The CIR Precedents – Aerosols Document was updated to address some of the comments received on the previous draft, including the April 3, 2017 comments from Women's Voices for the Earth (WVE), and the revised document was submitted to the Panel in anticipation of presentations by Drs. Nazarenko and Singal. As noted above, the presentations at the September 2017 meeting addressed exposure assessment of nanomaterial-containing aerosols from cosmetic spray and powder products and considerations for inhalation safety assessments. The Panel concluded that the document must be revised to include information presented by these speakers and comments received on the document to date. In addition, the document should be corrected to replace the assumption that 5% of the particle-size distribution released from propellant deodorant sprays consist of respirable particles with the assumption that 50% of the particles are respirable. In addition, the Panel recommended that the cosmetics industry perform an empirical study to characterize the particle-size distributions released from an adequate number of representative cosmetic propellant and pump spray products using current tools and methods. The Panel emphasized Dr. Nazarenko's observation that there are substantial analytical-method platform-dependent differences in particle-size measurements, which the Panel will need to consider in the future when evaluating the nature and the quality of the data used to assess the safety of ingredients in cosmetic formulations that may be incidentally inhaled. Finally, the Panel noted that after all these data are collected and analyzed, and the precedents document finalized, the updated language is intended to apply to previous as well as future CIR safety assessments.

Endocrine Activity

The Panel reviewed the second draft of the CIR Expert Panel Endocrine Activity and Endocrine Disruption Background and Framework document, which was revised to address comments on the first draft received from the Council, the CIR Science and Support Committee (CIR SSC), and from Dr. Ellen Mihaich. (Dr. Mihaich briefed the Panel on the subject of endocrine activity and disruption at the December 2016 Panel meeting.) Overall, the Panel was pleased with the document. The final version of the CIR Precedents – Endocrine Activity Document is available on the CIR Findings & Resources Documents page (http://www.cir-safety.org/cir-findings).

Hair Dye Epidemiology

The Panel reviewed the latest draft of the Hair Dye Epidemiology document. The previous draft was reviewed by the Panel at the April 2017 meeting. Comments on the previous draft that were received from the Council Hair Coloring Technical Committee (HCTC) and from the Panel were addressed. The Panel noted that a presentation on hair dye self-testing and hair dye chemistry is scheduled for the December 2017 Panel meeting. The Panel approved the current revisions, but tabled the document pending the presentation in December. The Panel noted that summaries of two recently published epidemiological studies suggest an association between hair dye use and the incidence of breast carcinoma. The Panel concluded that summaries of other, older epidemiological studies that have examined this association should be included in the document as well.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Bart Heldreth, CIR Executive Director
Date: November 10, 2017
Subject: Revised Draft Hair Dye Epidemiology Document for Posting

Enclosed is the latest draft of the CIR Expert Panel Hair Dye Epidemiology document (Document). The enclosed draft is identified as *hdepi122017rep*. The previous draft was reviewed by the Panel at the September 2017 meeting. At the September meeting, the Panel requested the inclusion of additional studies regarding breast cancer incidences. Additionally, an additional study regarding hair dyes and the risk of leukemia was published since the September meeting, and incorporated herein. These additional studies are included in this draft for potential inclusion, and highlighted therein. Since both odds ratio (OR) and relative risk (RR) values are used in this document, a brief explanation of the differences therein has also been added to this Document for the Panel's consideration.

The Panel noted that the two presentations on the hair dyes scheduled for this meeting would possibly be informative to this Document, and tabled finalization until thereafter. The Panel should review this draft of the Document and determine whether it is suitable for posting on the CIR website, to replace the version currently posted.

1620 L Street NW, Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

142nd COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

Monday, April 10, 2017

DR. BERGFELD: Good morning, everyone. I think we'll begin. Welcome to the team meetings of the 142nd CIR Meeting. We have a busy day. I'd like to just bring your attention to the fact that we have 15 ingredients to review. Six of these are finals. The rest are in draft forms in one way or another.

But, a special attention has to be given to some of the documents that you've seen included, and that includes the hair dye update, the aerosol boilerplate and discussion, the endocrine activity and disruption document, and the search data document, because these are going to become final, I believe, at this meeting and will be posted on our website…

Dr. Marks' Team

DR. MARKS: Now we'll go back to hair dye. Something that Ivan and I are very interested in. Do you want any, you made, some, a few comments, changes in red. A lot of it has to do with obviously cancer, and after you make your comment, Ivan, I'd like obviously Tom to react and then anybody else. Ron and Ron. So, Ivan, do you want to bring us up to date on that? And that's administrative page 35.

DR. BOYER: So, for hair dye, we've been monitoring the literature, looking for papers that might be relevant for updating this particular document, which we have posted online, which we refer to through a link that's incorporated into our safety assessment reports when it's appropriate. And it's been awhile since we've updated anything. A few papers have shown up in the literature that seem to be relatively inconsequential, as far as the bottom line is concerned for this particular document. But we thought that, at this point, it'd be a good time to go ahead and incorporate those few papers that we have in this particular revision. And I guess to get the panel's feedback on whether or not simply accepting those changes is adequate, or if you see anything in there that might warrant some additional attention at this point.

DR. SHANK: I think you've done a great job. I don't have any change.

DR. SLAGA: I completely agree.

DR. MARKS: Okay. Sounds like we endorse the changes, Ivan…

DR. HILL: Yeah, I just had a couple of questions. When you mention, it's reference 15, it's the Chang et al, in cancer case control. Would it be appropriate to add any short sentence fragment on the nature of the association? When it says there's an association between this, that or the other, is there anything that can be? Do you know where I'm talking about here, it's exactly where the, search on associations. I usually highlight this sort of thing.

DR. SHANK: Is it page 41? On that table?

DR. HILL: Yes. I think that's it. That's exactly it. It's in the table where it's mentioned. I think that's the same reference where they re-analyzed what appeared to be the same data set. So it was more than 2007, is that the one? I'm not sure. Hold on. Yeah. John 2009 versus Morton 2007. I think it's the same data. Or that might be a different one. No that's a different one. That's a different one.

DR. BOYER: So, when you're asking for additional information on what the nature of the association, do you mean, for instance, the odds ratio that they may have calculated?

DR. HILL: It says an association between ever/never use of hair dyes, and the negative NHL was reported. That doesn't tell me anything. Just there was an association.

DR. BOYER: All of these studies have been summarized in a little bit more detail in the text of the document.

DR. HILL: Yeah

DR. BOYER: We try to keep it fairly short, and consistent as far as the information that we presented for each of the studies summarized. But I can take another look at it. The nature of the association is, at this point, you know, we've got these two different varieties of lymphomas. And one of them, there was a statistically-significant association that's probably represented by an odds ratio. None of the odds ratios exceed about two or so. So they're fairly small, and given the confounding factors typical in those types of studies, they're…

DR. HILL: I had been looking for something simpler, which was, it increased the odds of the cancer, or it decreased.

DR. BOYER: Oh, I see what you mean.

DR. HILL: Maybe that's implicitly obvious. That's so obvious, it couldn't have been that. It must have been a little more description but in there…

DR. BOYER: Okay

DR. HILL: But it sounds like there is no short encapsulation. From what you're saying. Sorry, I interrupted you. Didn't mean to…

DR. BOYER: That's fine. I'll take another look at it and see if we can include something a little more informative, without going into great detail.

DR. HILL: And similarly, just to enlighten, again, the reader can go out, but they have to go out and look at references, what the nature of the STAR 10 mutant of that N-acetyl transferase type one is the NAT 10. What exactly is the STAR 10? I actually had difficulty finding. But I think it's out there, I just didn't follow-up and finish before I got here. I was looking at this like two weeks ago. It was on my punch list, but I didn't get that far.

DR. BOYER: Mm hmm. Okay. I'll do that.

DR. MARKS: Okay. Any other comments about the hair dye boilerplate?

DR. BERGFELD: Was that to be an edit? And then it will go up on the website? Was that to be an edit?

DR. MARKS: Yeah. I think we'll have a discussion tomorrow.

DR. BERGFELD: Okay

DR. MARKS: And Ron Hill, you can bring it up. It sounds like Ivan, you'll take a look at it and see how it can be changed a little bit. But I didn't get a sense from Tom or Ron Shank that there was concern about this.

DR. SLAGA: My only comment about that would be, it's so weak, that you have to be careful how you state it. I mean you don't want it to come across like you're increasing cancer.

DR. HILL: Point well taken.

DR. SLAGA: So, the words, I like the way you have it.

DR. HILL: Okay. I mean, that's fine.

DR. MARKS: Okay. That's important, Tom. So it sounds like, Tom, as our cancer expert, would say leave it the way it is. Don't worry about smithing it. And we'll see what the Belsito team says tomorrow. Am I interpreting correct, Tom? Is that okay with you, Ron Hill?

DR. HILL: Yes. I still think a short description of what NAT 10 is belongs in there. And the STAR 10 allele. And also, similarly you've got arylamine acetyltransferases that can function to activate or de-activate arylamines. I've never encountered an instance of activating by acetyltransferases acetylation. And Ron Shank might have a thought on this, but acetylation, as far as I've seen, is always inactivating in terms of abolishing toxicity. So that's why you look at fast acetylaters versus slow acetylaters. In terms of certain drugs that have aniline-type nitrogens, or can have aniline-type nitrogens generated. That the acetylation, which is what the acetyltranferase is catalyzed, invariably deactivating.

DR. BOYER: So it sounds like what you're suggesting are basically some clarifications that wouldn't take much in terms of editing.

DR. HILL: No, in that particular case it's just function to activate or deactivate. I was sort of suggesting that we don't need activate, just deactivate. But I wanted to see if any of the others were aware of any cases where they saw that acetylation serve to activate. I've never encountered such.

DR. MARKS: I assume from a procedural point of view the Council, the Scientific Committee, will have some comments. And we're going to look at these documents again. Boilerplates with that in light.

DR. EISENMANN: Right, and this one is the Hair Color and Technical Committee that will look at it.

DR. MARKS: We'll have another look at this before it gets posted, I suspect. Unless that committee says everything looks fine and we can proceed.

DR. GILL: We were hoping to have a presentation at the June meeting from someone from that technical committee.

DR. MARKS: Okay.

DR. GILL: We've just decided to get this out earlier to get the thinking going.

DR. SADRIEH: I just have a question. So, I just want to understand that an increase in the arteries show two is not to be considered an increase in cancer? Is that what you're concluding? That an increase is not…

DR. SHANK: Statistically, it comes out so weakly, that most people I know consider it not to be a positive effect. It's a weak association is the only way I can describe it. It doesn't make it, I think if you use the word increase, it sounds like it's really increasing. That is questionable.

DR. SADRIEH: Okay. From one to two is not an increase. Is that? I mean, like a three would be an increase? What would be an increase then?

DR. SHANK: The change is insignificant.

DR. BOYER: You also want to look at the confidence interval. I mean if you have a two, and you have a confidence interval that doesn't include one, or the minimum is not far from one, then you would consider that to be a very weak association. On the other hand, if you have an odds ratio of 10, 11, 12 and so forth, and an odds ratio that does not include one, that exceeds one proportionally, then that would be a clear indication that there's an association. Generally, that's how epidemiological studies are interpreted. And there's good reason for that. There's a good argument that can be made to support that perspective, that way of interpreting those kinds of studies.

DR. MARKS: Thank you. That was helpful. Refreshed my memory on statistics 101. Any other comments on hair dye boilerplate? If not, then, tomorrow I'm just gonna mention that the format, the changes are fine with our team.

Dr. Belsito's Team

DR. BELSITO: Hair dye. What page, and this is in admin.

DR. LIEBLER: 36.

DR. BELSITO: So with the bladder cancer, I mean again there's so much with these epi studies. There was that women who were college grads were more likely among hair dye users to have bladder cancer. I mean when you broke them out. And, again, were these studies controlled for smoking and other contributing factors, do we know? In this study by Ross, et al, 2012, a population based study -- Oh, no that wasn't the one. It was the one in New Hampshire, Vermont, right? Yeah. So in the Koutros 2011 study, the study in Maine, Vermont, New Hampshire, the finding was an increase in bladder cancer with permanent hair dye use in a sub group of women with a college degree. But not dose response for color duration of use, or total lifetime uses.

And then the NAT2 phenotype was associated with a suggestive but not statistically-significant increase when college degreed women were stratified by education.

I mean I just point that out because, looking back at my childhood in the 50s and 60s, the mothers who went to college seemed more likely to be smokers, at that point in time, than the women who did not go to college in the 40s, because they were cool, educated, college women and sophisticated, and smoking was sophisticated. So, I mean, we know smoking is a risk for bladder cancer. So, in a lot of these epi studies, it just would be nice to get a sense of how well these were controlled. And then you have that whole issue of hair dye use pre 1980, post 1980, in terms of cancers.

Because there's no consistent trend, but then the data is also, it's the same with breast cancer. The Finnish study, there was an increase in odds of breast cancer in women who ever used hair dye, compared to those who never used hair dye. And it's a significant trend in the odds ratio for cumulative use of hair dyes. And that's coming out of Finland, where I would presume most women aren't using the same color hair dyes that the Italian women would be using. They're going to be much lighter colored hair dyes, if not blondish hair dyes.

It would be nice to see, and to report when we're doing this, whether they analyzed for other confounding factors between the control groups. What was the difference in bladder cancer among those who never used a hair dye? Did they smoke or not smoke? Did they even look at that? I mean otherwise I thought it was fine. I have no comments. We can continue to use it with the updates, but it's just that as I read through it, the idea of any confounding factors that might affect these cancers was never even mentioned.

DR. BOYER: It is pretty much standard practice for people who do epidemiological studies to at least do some sort of an analysis for the confounding variables. But they usually lump them together, so it's unlikely that smoking would be isolated as a single confounding factor in any one of these studies. But we can certainly bring forward --

DR. BELSITO: Just a brief statement as to whether confounding factors were looked at at all. They usually are, but not always.

DR. LIEBLER: I'm assuming these little paragraphs are mostly taking from the abstract from the papers.

DR. BOYER: No, actually they are our own.

DR. LIEBLER: I don't mean literally word for word, but you're distilling this from the main conclusions from the abstracts?

DR. BOYER: At least for the ones that I summarized, I've looked at the whole paper. And we rated the quality of the paper, let's put those plusses, double plusses, triple plusses.

DR. BELSITO: Right, four plusses.

DR. LIEBLER: The confounders are usually not mentioned in the abstract. But usually they are discussed in the discussion. And I'm sure you've looked at that. So that's there if you want it.

I took a very different approach to this document, maybe it was because I was near the end of my preparation, but I basically started with okay, for hair dyes, we basically take the position right now that there are no convincing data that support the causative relationship between hair dyes and cancers. So I'm looking at the new changes to see if any of those changed that conclusion. My assessment no. So we can update it, but doesn't change the conclusion.

DR. BELSITO: Yeah, fine. And I guess my point was a mention when we update it that confounding factors were or were not looked at in the report.

DR. SYNDER: Was that considered in your scoring scale, a one plus, two plus, three plus, whether they looked at confounding?

DR. BOYER: Whether they looked at confounding, no.

DR. SYNDER: Probably should. I have kind of a silly comment, but in the intro or something you should identify bladder cancer as urinary bladder cancer, not gall bladder cancer or something else.

Tuesday, April 11, 2017

DR. BERGFELD: Well, welcome everyone. We're going to begin the 142nd CIR Panel Meeting now… As the team members know, they had 15 ingredients to review yesterday… In addition, there was another discussion that was entertained. And that was, a number of position papers. One on hair dye update…..

DR. MARKS: The next is a draft update of the expert panel hair dye epidemiology. Findings and --. There are actually a number of changes in there. But our panel did like this also. So we'll mimic the Belsito team, at least in the previous drafts. We liked it.

DR. BERGFELD: Yeah. Belsito team. You liked it too?

DR. BELSITO: Yeah. I'm just trying to find out exactly where it is. Looking through dye and hair dye.

DR. MARKS: It's in page 35 in the Administrative tab there.

DR. BELSITO: Okay.

DR. MARKS: (inaudible)

DR. BELSITO: So, just off the top of my head, before I get to page 35. The one issue I had is, you know, yeah, the data is inconsistent. We say how we're looking at the data, yada yada yada. But, you know, there are some data coming out that are showing some linkages. So, for instance, in terms of, I believe it was bladder cancer in women in New Hampshire and Vermont, if they were college grads, that incidence was positive, if they weren't it wasn't. And just, you know, looking back at my own childhood in the 1950's and my parents. You know, my impression was that women who went to college smoked a lot more than women who didn't go to college in the 1950's. And I was just wondering how well these studies are controlled for other confounders that could influence the cancer's in question? And in our boilerplate, we never mention that. So, I mean, they are epi studies. They are very hard to control. But did they look at other confounding factors that might contribute to these cancers?

And so I'm fine with the document. I don't think that, in consumers, there's any strong evidence to suggest carcinogenicity of these hair dyes. I would just like, as we're going through the documents, a simple statement as to how well they looked at potential confounders in these studies that might contribute to the specific cancer endpoints in question. You know, like, for instance, even the relationship between cosmetologists and bladder cancer, you know, there are studies that show that cosmetologists smoke more than the general population. And then we know smoking is a risk for bladder cancer. So is it the hair dyes? Is it the other chemicals they use? Is it the smoking? Is it the combination of all of these? So, just a mention as to how well these studies were controlled for other confounders.

DR. BERGFELD: I'd like to make a comment. If you look at the references there, the references are in really strongly peer-reviewed journals.

DR. BELSITO: I understand.

DR. BERGFELD: I would think that those risk assessments, additional risk assessments, would have been made.

DR. BELSITO: Yeah. I mean, I think there should be --

DR. BERGFELD: A clarification would be well, but --

DR. BELSITO: -- at least a comment.

DR. BERGFELD: New England Journal, cancer. I mean, these are major.

DR. BELSITO: I'm not saying that they weren't.

DR. SLAGA: There's a lot of confounding issues and a good study that is peer reviewed, you know, that's one of the things they really look at. Are -- everything controlled for?

DR. BELSITO: Right. I understand. But we don't mention that in our --

DR. SLAGA: Yeah.

DR. BELSITO: -- reports. And I think just a one or two sentence mention that the following confounders were looked at.

DR. SLAGA: Yeah.

DR. LIEBLER: So, I think, even in the very best journals, the epidemiology is sometimes necessarily complicated by confounders. They can't be fully teased out and excluded, but need to be acknowledged, and are treated in their discussions.

DR. SLAGA: Right.

DR. LIEBLER: And this is going to be a case-by-case basis, where you might need to pull out something that appears interesting and potentially relevant from these discussions. And, Ivan indicated that he reviews the entire papers in preparing these. But I think it would be a good idea to consider, you know, looking at these carefully to see if there are any issues that were raised in a particular study that they said, you know, as possible confounder, we couldn't really resolve it. We think our conclusions are reasonably strong. But, and put the but in there for us.

DR. SLAGA: Right.

DR. BERGFELD: Good idea. I think that's a good editorial idea. Yeah. All right. Any further discussion. We have a next one?

144th COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

Monday, September 11, 2017

Dr. Belsito's Team

DR. BELSITO: Now we're on hair dye. And that's PDF what, Dan? You're our PDF page man.

DR. LIEBLER: Hair dye. Hang on.

DR. ANSELL: One twenty two.

DR. BELSITO: One twenty [sic]. So

SPEAKER: Yes.

DR. BELSITO: this was updated with new data and from my perspective we only really probably the new data we need to talk about is the breast cancer data. Two new reports, both linking, to some extent, hair dye use and breast cancer, although there are, of course, as always, caveats to the study.

SPEAKER: I'd ask that we skip hair dye until we get back.

DR. BELSITO: Oh, okay.

SPEAKER: And just (inaudible).

SPEAKER: Okay.

DR. BELSITO: Well, we can do that. Sure. That's fine. I didn't realize she was in here…

DR. BELSITO: … now we can go back to the hair dyes. So again, we've got some new data that's been incorporated and updated, which is good because it had been a while since we had done that. And the only two new reports that really bothered me were the ones on breast cancer. And, as I was saying before, they have their own little caveats. What page are we on, Jay? Is it 42?

DR. ANSELL: One twenty two.

DR. BELSITO: One twenty two?

JAY ANSELL: Is where we began.

SPEAKER: Yep.

DR. BELSITO: Okay. Because they both had that statistical length. So this is not my area of expertise, so I'll throw it out to my teammates to discuss.

DR. SNYDER: Obviously it's not mine because I have a comment. Anyone with expertise to ask for a review and comment?

DR. BELSITO: Well, should we have that woman back again?

DR. SNYDER: Well, I mean, I looked for these. You know, before it was always whether or not they evaluated contaminating factors and things. And there's no mention of compounding factors in here, in this paragraph, so I didn't go back and read the original.

DR. BELSITO: Well, the (inaudible) report, I mean, I think I actually sent that to Monice and Bart. I don't know if they had already seen it, but it's gotten a lot, a lot of play in the press.

SPEAKER: Yes.

DR. BELSITO: So it's not something that we can ignore.

DR. LORETZ: It's a (inaudible). I'll know the data there is (inaudible) American (inaudible) a very small study population of hair days and American women. So it kind of didn't fit and there's, you know, breast cancer has been looked at before and not found to be associated. So it's not a report in isolation.

DR. BELSITO: But then why don't we have those other reports where it's not been associated, because we only have two reports under breast cancer.

DR. LORETZ: It's the timing. (Inaudible) this epidemiology is not all inclusive. It's starting at certain time points moving

SPEAKER: That's right.

DR. LORETZ: forward.

DR. BELSITO: But we didn't have it in our prior document, did we? This is the first time I'm seeing any study looking

DR. BJERKE: Associating breast cancer?

DR. BELSITO: at breast cancer.

DR. LORETZ: Right, because

DR. BELSITO: Probably because all the other studies were negative

DR. LORETZ: Were

DR. BELSITO: but now that we have two positives, I think we need to go in and include all the reports and look at precedence. Because right now it looks like there have only been two or four and

DR. LORETZ: Yeah, yeah.

DR. BELSITO: it seemed they were both positive.

DR. LORETZ: And there were more. And there were ones that were looked at by IR for example. I (inaudible) correct that there's kind of a cut off when you're looking at more recent studies. Is that

DR. BOYER: Well, there was a cutoff, certainly a cutoff when with my search.

DR. LORETZ: In the original, right.

DR. BOYER: Right.

DR. LORETZ: Exactly.

DR. BOYER: Because I started where we left off last time (inaudible).

DR. BELSITO: 2014.

DR. LORETZ: Right, right.

DR. BOYER: 2014 prior. The history of the hair dye epidemiology precedence (inaudible) that actually precedes my

DR. LORETZ: Okay.

DR. BOYER: time that's

DR. LORETZ: Yeah.

DR. BOYER: (inaudible).

DR. LORETZ: Because I think it started at a certain time (inaudible) and that's

DR. BELSITO: Well, I think

DR. LORETZ: what (inaudible).

DR. BELSITO: we need to go back and capture all the documents

DR. LORETZ: Yeah.

DR. BELSITO: for

DR. LORETZ: No, I

DR. BELSITO: breast cancer and that because otherwise it looks like we have two that are highly suggestive in association and we're just blowing it away, saying, well, you know, all of the reports are equivocal. Well, it doesn't look terribly equivocal to me for breast cancer.

DR. LORETZ: Yeah, I

DR. BELSITO: Okay.

DR. LIEBLER: That's fine.

DR. BELSITO: So we'll add in those reports and everything will still look very equivocal so that we'll continue to monitor. But right now there's no clear cut risk that we can identify that's associated with any specific hair dye. That's what we're saying, right, folks?

DR. LIEBLER: Right. And we had asked for inclusion in all the other studies, the confounding factors that were controlled for, and those were all added. There's lots of yellow.

DR. BELSITO: Yeah, those

DR. LIEBLER: And that's good.

DR. BELSITO: Really good. (Inaudible 0:12:53.)

DR. LIEBLER: And, in fact, the study, the Yanis one we just mentioned, that does it's in the middle. It says, final multivariant model included age, education, BMI, family history, oral contraceptives. So (inaudible).

SPEAKER: And not alcohol and not smoking and the bigger ones.

DR. LIEBLER: Yeah.

SPEAKER: Yeah.

DR. LIEBLER: Anyway, okay.

DR. BELSITO: Okay. Any other comments on this?

MS. FIUME: And just so you're aware, we wanted to bring this so you could see the language that Ivan had been developing. We will have two speakers, correct, Ivan? At the

DR. BOYER: Mm hmm.

MS. FIUME: December meeting on hair dyes and hair dye chemistry.

DR. BELSITO: Two presentations?

MS. FIUME: Two presentations.

DR. BELSITO: Okay. And will one of them include

SPEAKER: No.

DR. BELSITO: re looking at these newer epi data?

DR. BOYER: That was not. What was planned, but I guess we can (inaudible) talk to the counsel about that. Basically one of them is going to be (inaudible) patch testing.

SPEAKER: Yes.

DR. BOYER: A patch testing study that was initiated several years ago. The final report has come out over I believe just a few months ago. I'm not sure if there's going to be a presentation on that final report and its results and conclusions and so on. And then the (inaudible) topic will be the hair dye (inaudible) issue. And there's been some requests lately from several panels to that we get an updated presentation on that topic….

Marks' Team

DR. MARKS: … next is hair dyes, still in the administrative. And

DR. SLAGE: Aren't we suppose to have...

DR. MARKS: Yes, so we expect a presentation in December on this, so in the draft there were lots of revisions in yellow but I think basically, we're going to table this until after we their presentation. If you want to comment about all the revisions, please. And then a lot of if obviously Tom is in your area of expertise, in terms of cancer.

DR. BOYER: We're talking about hair dye.

DR. MARKS: Hair dyes.

DR. BOYER: Okay.

DR. MARKS: That's what I have, is that correct? That's next on the agenda?

SPEAKER: Yes.

DR. BOYER: Okay. So we got some comments from the industries hair dye committee, you know, the council's hair dye committee. We got some comments from the other council, I got a few comments also from the panelist and that's been incorporated here. One of the major comments that this particular version addresses, is the comment that Dr. Belsito made the last time that we reviewed this document. Which was he wanted to have some idea of to what extent each of these epidemiology papers had addressed confounding variables. Smoking in particular, in relation to bladder cancer and so forth.

And so, what I did was to go back through all of the original published research epidemiological papers and to pull some of that out and summarize it. So, what you see highlighted in yellow is basically that information. And the presentations in December will address at least two topics one of which is the um, a self testing. The results of the testing report that was conducting in Europe and is completed sometime ago.

There's apparently a final report of that study, so we're going to hear some of that. And also, there's been over the last several panel meetings, it has been a request to hear again, about hair dye chemistry. So, we're hoping that topic will also be addressed in December. And then it will be up to panel to decide whether or not those two topics would be incorporated into the what's now simply the hair dye epidemiology background paper.

DR. MARKS: Ron, Ron and Tom did you like the yellow highlights in this draft?

DR. SHANK: Yes.

DR. SLAGA: Yes.

DR. MARKS: Okay.

DR. BERGFELD: I have a question. It was sort of hard for me to believe that some of the lymphoprolifer diseases had no relationship to some of the environmental issues, such as smoking. When lung cancer in women is about the third cancer and number one, I think in males. And has been related to smoking.

DR. MARKS: Well, that might be it. This is basically what they're showing in these particular pages. I mean, this is a subset of all of that research. Of all the epidemiological studies that have been performed on these sorts of topics. This is the subset that represent epidemiological studies that included hair dye exposure as one of the variables.

So if you were to expand a search to the full range of epidemiological studies that address these kinds of associations, then um, they wouldn't necessarily say a whole lot about hair dyes. But you would get the kind of information I think that you were looking for.

Tuesday, September 12, 2017

DR. BERGFELD: … then Dr. Marks, on the hair dyes.

DR. MARKS: We're told that a presentation on the hair dyes will occur in December. There are lots of revisions highlighted in yellow in this draft. We felt those revisions were okay. But obviously, we'll table the final document until after the presentation an update on hair dyes.

DR. BERGFELD: All right. I think we can agree to do that since we are anticipating this presentation, rather than to vote on it.

DR. BELSITO: Right. The only other point that our team made was that with the update in data from 2014, obviously, we now have two reports where there is some indication of a linkage between hair dye use and breast carcinoma. And what we failed to do is to bring in the multiple negative studies that had been existing in literature before 2014.

So based upon this new information about a potential link with breast cancer, we need to go back and recapture all of the data that looked at use of hair dyes and breast cancer, which was not done.

DR. BERGFELD: Excellent addition. Thank you.

HAIR DYE EPIDEMIOLOGY – through October, 2017

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

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

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

Conclusion

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

Background

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

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

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

The studies herein result in either an odds ratio or a relative risk, two similar but not synonymous terms. An odds ratio (OR) represents the odds that an outcome (e.g. cancer) will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure; whereas a relative risk (RR) is a measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group.[4,5] In cancer research, ORs are most often used in case-control (backward looking) studies, and RRs are used in prospective (forward looking) studies, such as cohort studies and clinical trials. An OR of 1 means that an exposure does not affects the odds of an outcome (i.e. does not increase the risk of cancer), while a RR of 1 means there is no difference between two groups in terms of risk following a particular exposure. However, either an OR or RR > 1 means the exposure may increase the risk of disease.

Bladder Cancer

Turati et al. (2014) performed a meta-analysis of 15 case-control and 2 cohort studies.[6] The abstracted information included the variables adjusted and/or used to match control subjects with cases. For example, 12 of the studies clearly adjusted for smoking; adjustment for smoking was not clear in 1 study. The pooled RR of bladder cancer incidence/mortality was 0.93 (95% confidence interval (CI) 0.83-1.05) for personal use of any type of hair dye, compared with no use, and similar results were obtained when the subjects were stratified by sex. The RR for personal use of permanent hair dyes from 7 of the studies was 0.92 (95% CI 0.77-1.09). Similarly, no association was found between bladder cancer and the duration or lifetime frequency of use of any type of hair dye or use of permanent hair dyes, compared with never used hair dyes. The RR for the use of dark-color hair dyes was 1.29 (95% CI 0.98-1.71).

Ros et al. (2012) performed a population-based case-control study of hair dye use and bladder cancer in the Netherlands.[7] The subjects were 246 cases and 2587 controls; all of the subjects for which the analyses were performed were women (less than 5% of the men selected for the study reported ever using hair dyes). The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale. All analyses were adjusted for age and smoking status, duration and intensity. Additional adjustment for education level and other variables considered were not included in the final model because they did not change the standardized regression coefficient (β) by more than 10%. No association was found between bladder cancer and ever use of permanent hair dyes (OR 0.87; 95% CI 0.65-1.18) or temporary hair dyes (OR 0.77; 95% CI 0.58-1.02). Similarly, no association was observed when hair dye use was defined by type, duration or frequency of use, dye color, or extent of use or when the patients were stratified by aggressive and non-aggressive bladder cancers.

Koutros et al. (2011) conducted a population-based case-control study in Maine, Vermont, and New Hampshire.[8] The subjects were 1,193 cases of urinary bladder cancer diagnosed from 2001 to 2004 (911 male and 282 female), and 1418 controls (1,039 male and 379 female). The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale. The hair dye models were adjusted for age, race, sex, and smoking status.

No association was found between ever/never use of hair dyes and bladder cancer – the OR and associated 95% CI for women was 0.7 (95% CI 0.5-1.0), and for men 0.7 (95% CI 0.4-1.0). Because of the excellent exposure assessment, the authors were able to examine subsets of the population studied. Women who used red hair colors, for example, exhibited an OR of 0.4 (95% CI 0.2- 0.8), suggesting a significantly lower risk of bladder cancer associated with the use of such hair dyes. A similar lower risk of bladder cancer was reported for women who used hair dyes for a duration between 10 and 19 years (OR 0.5; 95% CI 0.27-0.79). As the data were further analyzed, the authors considered women with and without college degrees. Women without college degrees who used permanent hair dyes exclusively, for example, had a significantly lower risk of bladder cancer (OR 0.5; 95% CI 0.4- 0.7). Exclusive use of permanent hair dyes by women with college degrees was associated with a significantly higher risk of bladder cancer (OR 4.9; 95% CI 1.7-14.6). No statistically-significant interactions with hair-dye use were found when the data were stratified by state of residence, hair-dye product type, smoking, age at diagnosis/interview, or disease aggressiveness in the female subjects.

Shakhssalim et al. (2010) reported a population-based case-control study of several likely risk factors for bladder cancer in Iran with 692 cases and 692 controls.[9] Cases were identified using the Iranian cancer registry. The hair dye exposure assessment was a + on the Rollison et al. (2006) scale. The OR for hair dye use and bladder cancer was 1.81 (95% CI 1.08-3.06). After adjustment for cigarette smoking, the OR was 1.99 (95% CI 1.02-3.82). When women and men were analyzed separately, no significant association with hair dye use and bladder cancer was found.

Lymphoma and Leukemia

Towle et al. conducted a meta-analysis of 20 case-control studies of leukemia.[10] The RRs for the associated risk of leukemia were: with permanent hair dye use RR = 1.19 (95% CI 1.07–1.33), with dark hair dye use RR = 1.29 (95% CI 1.11–1.50), with hair dye use among males RR = 1.42 (95% CI: 1.01–2.00), with hair dye use pre-1980 RR = 1.49 (95% CI: 1.21–1.83), and with hair dye use for longer than 15 years RR = 1.35 (95% CI: 1.13–1.62). Overall, findings suggest that ever use of hair dye is not a significant risk factor for leukemia.

Parodi et al. (2016) performed a population-based case-control study of leukemia and non-Hodgkin's lymphoma (NHL) in Italy.[11] The analysis was restricted to women in the population studies because too few of the men reported any

hair dye use. There were 161 cases (120 lymphoid and 41 myeloid) and 84 controls among the women. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale, because only duration of hair dye use < 15 years vs. ≥ 15 years was evaluated. In a multivariate analysis, the OR was 2.3 (95% CI 1.0-4.9), with p = 0.036 for a trend, for NHL in women using hair dye for at least 15 years. No association was found between lymphoid malignancies and tobacco smoking or the consumption of alcoholic beverages in this study.

Linet et al (2014) conducted a meta-analysis of 19 case-control studies of NHL subtypes, focusing on follicular lymphoma (FL).[12] No associations between FL and hair dye use type, duration, or frequency were found in this study, except for a modest increase in women who used hair dyes before 1980 (OR = 1.4; 95% CI 1.10-1.78). Many oxidative hair dye products were reformulated in the early 1980s in the U.S. to eliminate ingredients that produced tumors in animal bioassays.[13] In comparison, the risk of FL in women was associated with current cigarette smoking, trending higher with increasing duration of smoking.

Cerhan et al. (2014) performed a meta-analysis of 19 case-control studies of NHL subtypes, focusing on diffuse large B-cell lymphoma (DLBCL).[14] There were no overall and sex- or age-specific associations between DLBCL and hair dye use, based on the basic adjusted model results of this study. The OR for mediastinal DLBCL was 4.97 (95% CI 1.63-15.15) for use of hair dyes for at least 20 years, compared with never used hair dyes. Using hair dyes for at least 20 years was not associated with DCBCL at other anatomical sites, including the central nervous system (CNS), testis, gastrointestinal tract, and skin. Use of hair dyes for less than 20 years was not associated with DLBCL at any site. In comparison, smoking was associated with CNS, testicular and cutaneous DLBCLs in this study.

Salem et al. (2014) conducted a hospital-based case-control study of leukemia and lymphoma in Egypt.[15] There were 130 cases, including 23 cases of chronic lymphocytic leukemia (CLL) and 107 cases of NHL, and 130 age- and sex-matched controls. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale. In a univariate analysis, no statistically significant association was found between these lymphoproliferative disorders and history of using hair dyes, family history of cancer, exposure to X-rays, or smoking (χ^2, $p>0.05$).

Lv et al. (2010) conducted a hospital-based case-control study of myelodysplastic syndromes (MDSs) in China.[16] There were 403 cases and 806 controls, and the evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. In a univariate analysis, the OR for hair dye use (≥ 2 times per year) and all MDSs was 1.46 (95% CI 1.03-2.07). In a multivariate analysis performed to adjust for potential confounding factors, the OR was not statistically significant (OR 1.31; 95% CI 0.88-1.93). In comparison, smoking was associated with the development of MDSs in the univariate analysis and with refractory anemia with excess blasts (RAEB) in both the univariate and multivariate analyses.

Wong et al. (2010) conducted a hospital-based case-control study of NHL in Shanghai.[17] There were 649 cases and 1,298 controls, and the evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. No increased risk of NHL was reported (OR 0.93; 95% CI 0.75-1.16). For CLL and small lymphocytic lymphoma (SLL), the authors reported a significantly lower risk associated with hair dye use (OR 0.37; 95% CI 0.18-0.76). In comparison, alcohol consumption and cigarette smoking were not associated with NHL in this study, although smoking ≤ 20 years (but not > 20 years) was associated with precursor B-cell neoplasms.

Chang et al. (2010) re-evaluated tissue samples from a NHL case-control study in males from Iowa and Minnesota using FISH (fluorescence *in situ* hybridization) cytogenetic technique to evaluate both *t*(14;18)-positive and *t*(14;18)-negative NHL subtypes and IHC (immunohistochemistry) assays to evaluate expression of the anti-apoptotic protein bcl-2.[18] There were 8 *t*(14;18)-positive, 12 *t*(14;18)-negative, 20 bcl-2 positive, and 4 bcl-2 negative NHL cases and 58 control subjects in the subpopulation tested (i.e., men having used hair dye at least once a month for at least one year, or occupational exposure to hair dyes on any job held for at least a year). The evaluation of hair dye exposure scored + on the Rollison et al. (2006) scale. Adjusting for age, state and proxy status (i.e., whether or not next-of-kin proxies were interviewed), a statistically-significant association between ever/never use of hair dyes and *t*(14;18)-negative NHL (OR 2.9; 95% CI 1.6-5.0) and bcl-2 positive NHL (R 2.2; 95% CI 1.4-3.4), but not with *t*(14;18)-positive NHL (OR 1.3; 95% CI 0.6-2.6) or bcl-2 negative NHL (OR 1.4; 95% CI 0.5-3.8). Similarly, smoking was associated with *t*(14;18)-negative NHL, but not clearly associated with *t*(14;18)-positive NHL, bcl-2 negative NHL, or bcl-2 positive NHL in this study.

Wong et al. (2009) reported a hospital-based case-control study of acute myeloid leukemia (AML) in Shanghai.[19] There were 722 cases and 1,444 age- and sex-matched controls. The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. The study found no increase in the risk of AML and personal use of hair dyes; The OR was

0.98 (95% CI 0.8-1.2). In contrast, there was an association between AML and smoking, particularly among the male subjects, as well as alcohol consumption and a low level of education in this study.

Glioma

Shao et al. (2013) performed a meta-analysis of 4 case-control and 2 cohort studies of personal hair dye use and the incidence of gliomas.[20] Matching or adjustment for age and sex was performed in all 6 studies included in this meta-analysis, and for smoking in 2 of the 6 studies. The most adjusted risk estimates were included, and the raw data were used when adjusted estimates were not available. Summary RRs for ever use of any hair dyes were 1.132 (95% CI 0.887-1.446) for all studies, 1.291 (95% CI 0.937-1.777) for case-control studies, and 0.903 (95% CI 0.774-1.054) for cohort studies. Similar results were obtained when the subjects were stratified by geographic regions and sex. No significant associations were found among the studies that evaluated permanent hair dye use and duration of any hair dye use.

Breast Cancer

Llanos et al. (2017) conducted a population-based case-control study of hair dye use and breast cancer in African American and European American women in the Women's Circle of Health Study (WCHS).[21] The subjects were 1508 African American and 772 European American cases (52±10.7 and 52.0±10.0 years old, respectively) and 1290 African American and 715 European American age- and county-matched control subjects (50.9±10.3 and 49.8±8.7 years old, respectively). The evaluation of hair dye exposure was ++++ on the Rollison et al. (2006) scale). The final multivariate model included age, education, body-mass index (BMI), family history of breast cancer, and oral contraceptive use; age at menarche, parity and hormone-replacement therapy were omitted based on statistical analysis ($p > 0.1$). In the multivariate analysis, the ORs for breast cancer were 1.52 (95% CI 1.21-1.91), 1.30 (95% CI 1.03-1.63), and 2.21 (95% CI 1.26-3.86), respectively, for African American women who reported using dark permanent hair dyes, African American women who typically had their hair dyed in a salon (rather than using a home kit), and European American women who had a history of both hair dyes and chemical hair relaxers, compared with matched controls who never used hair dyes. Use of dark dyes among both African American and European American women and dual use of hair dyes among European women were associated with estrogen-receptor positive (ER+) breast cancer (OR=1.72, 95% CI 1.30-2.26; 1.36, 95% CI 1.01-1.84), and 2.40, 95% CI 1.35-4.27, respectively). In this study, women who started using hair dyes before 1980 were not distinguished from women who started in 1980 or thereafter.

Heikkinen et al. (2015) performed a population-based case-control study of hair dye use and breast cancer in Finland.[22] The subjects were 6,567 breast cancer patients and 21,598 age-matched controls. The evaluation of hair dye exposure was a +++ on the Rollison et al. (2006) scale. The multivariate model was adjusted for parity, age at first birth, family history of breast cancer, menarche age, use of hormonal contraceptives, physical activity, alcohol use, BMI and education. The OR for breast cancer was 1.23 (95% CI 1.11-1.36) for women who ever used hair dyes, compared with those who never used hair dyes; the analogous ORs were 1.28 (95% CI 1.10-1.48) for women born before 1950 and 1.14 (95% CI 0.85-1.54) for women born in 1960 or later. Logistical regression analysis indicated that there was a statistically-significant trend ($p=0.005$) in the ORs calculated for number of hair dye episodes (1.07 for 1-2 episodes vs. 1.35 for 35-89 episodes). The ORs did not change when smoking was included in the multivariate analysis.

Takkouche et al. (2005) conducted a meta-analysis of epidemiological studies of hair dye use and cancer risks, including 12 case-control studies and 2 cohort studies of breast cancer.[23] The adjustment, matching and/or restriction factors included age in all 14 studies, smoking in 6 studies, education in 2 studies, and alcohol consumption in 1 study evaluated in this meta-analysis. The random-effects pooled RR estimated from all 14 studies for ever users was 1.06 (95% CI 0.95-1.18). Likewise, ORs calculated for ever used vs. never used hair dyes specifically from case-control studies, cohort studies, or permanent hair dye use only, or for intensive exposure (i.e., more than 200 lifetime exposures) were not statistically significantly.

Mendelsohn et al. (2009) conducted a prospective study of ever hair dye use and cancer risks of women in China, including a case-control breast cancer study with 234 hair dye users and 358 non-users.[24] The results were derived using Cox proportional hazards models, adjusted for age, and education. The average number of person years was 7.31. The RR for breast cancer was 0.93 (95% CI 0.78-1.09) for women who ever used hair dyes, compared with those who never used hair dyes. Stratification by menopausal status indicated no association between breast cancer and hair dye use in either pre- or post-menopausal women.

Kinlen et al. (1977) conducted a case-control study of 191 breast cancer patients interviewed in a hospital in 1975 -1976 in Oxford, UK, with 561 aged matched controls without cancer (within three years), marital status, and social class.[25] Seventy-three cases and 213 controls had used permanent or semi-permanent hair dyes, giving an OR of 1.01. There was no evidence of an increasing risk for breast cancer with increasing duration of use of hair dyes or with use beginning more than four or more than nine years before diagnosis.

Stavraky et al. (1979) conducted a case-control study of 50 breast cancer patients at a cancer treatment center with 100 hospitalized controls in London, Ontario, and 35 breast cancer cases with 70 neighborhood controls in Toronto, Ontario, with respect to hair-dye use.[26] The ORs for breast cancer from use of permanent hair dyes (at any time) were 1.3 (95% CI 0.6-2.5) in London and 1.1 (0.5-2.4) in Toronto. Further statistical analyses, allowing for smoking habits, family history of cancer and age at first birth, showed no significant relationship between hair-dye use and breast cancer incidence.

Koenig et al. (1991) conducted a case control study of 398 breast cancer patients at a screening center bwteeen 1977 and 1981 in New York City, with 90 randomly selected, age matched controls.[27] The OR for breast cancer from use of permanent hair dyes (at any time) was 0.8 (95% CI 0.6-1.1). There was also no evidence of a trend in risk with increasing number of hair dye uses (38% of the subjects had used hair dye at least 100 times, while 77% had used hair dyes at least once). An analysis of breast cancer risk from 5 or more years of work as a beautician was also compared. Although personal hair dye use was unrelated to breast cancer risk, the OR for beauticians was 3.0 (95% CI 1.1-7.8).

Genetic Polymorphisms

NAT1, NAT2, GSTM1, and GSTT1 Genotype/Phenotype

The study by Koutros et al. (2011) is the latest in a series of studies that have examined the influence of genotype and phenotype of liver enzymes that may activate or inactivate potential carcinogens.[8]

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

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

Koutros et al. (2011) performed genotyping for NAT2, NAT1, GSTM1, and GSTT1.[8] The hair dye models were adjusted for age, race, sex, and smoking status. An increased risk of bladder cancer was reported primarily among exclusive users of permanent dyes who had NAT2 slow-acetylation phenotypes, compared to never users of dye with NAT2 rapid/intermediate-acetylation phenotypes. This increase was observed in females with a college degree, but the difference was not statistically significant. The authors concluded that NAT1, GSTM1, and GSTT1 genotypes did not appear to be important modifiers of the association between ever, permanent, or exclusive permanent hair dye use and bladder cancer.

Gago-Dominguez et al. (2003) reported that individuals with the NAT2 slow-acetylator phenotype who exclusively used permanent hair dyes had an increased risk of bladder cancer (OR 2.9; 95% CI 1.3-7.5) after adjustment for cigarette smoking, compared to individuals with the NAT2 rapid-acetylator phenotypes (OR 1.3; 95% CI 0.6-2.8).[28] The NAT*10 allele contains an altered polyadenylation signal that has been associated with elevated DNA adduct levels and greater risk of bladder cancer in other studies. Individuals with a NAT1*10 genotype who were non-smokers and used permanent hair dyes exclusively had an OR of 1.0 (95% CI 0.2-4.3), and those with a non-NAT1*10 genotype had an OR of 6.8 (95% CI 1.7-27.4) in this study.

Kogevinas et al. (2006) evaluated the association of hair dye use with bladder cancer among females in a case-control study that also examined the effect of hair-dye use among genetic subgroups.[29] ORs were estimated after

adjustment for age, region, and smoking. No statistically significant differences in bladder cancer incidence were noted as a function of any of the genotypes examined, including those with slow- or intermediate/rapid-NAT2 acetylator phenotypes. For NAT2 slow-acetylator phenotypes, the OR was 0.6 (95% CI 0.3-1.4), and for NAT2 rapid/intermediate phenotypes, the OR was 0.9 (95% CI 0.3-2.6). Individuals with a NAT1*10 genotype had an OR of 2.9 (95% CI 0.7-11.6), and those with non-NAT1*10 had an OR of 0.6 (95% CI 0.2-1.6). These findings were directionally opposite to those of Gago-Dominguez et al. (2003).[28]

Morton et al. (2007) conducted a population-based case-control study of NHL.[30] Subjects were identified among residents of 4 Surveillance Epidemiology and End Results (SEER) registries (Iowa, Los Angeles County, and metropolitan Detroit and Seattle). There were 101 cases and 98 control subjects reporting no use of hair coloring products and 509 cases and 413 control subjects among the women reporting use of such products, in the population studied. There were 317 cases and 269 control subjects reporting the use of hair dyes before 1980 and 192 cases and 148 controls reporting hair dye use in 1980 or thereafter. The risk estimates were adjusted for age, sex, race and SEER area; education, smoking status, history of farming, having a first-degree relative with a history of NHL or lymphoproliferative malignancy were excluded from the final models because these factors did not materially alter (> 10%) the parameter estimates.

Among the women who started using permanent, intense-tone hair dyes before 1980, those with the NAT2 slow-acetylator phenotype (23 cases/14 controls) or who had no copies of the NAT1*10 allele (26 cases/16 controls) did not have an increased risk of NHL (OR 1.5; 95% CI 0.6-3.6 and OR 1.5; 95% CI 0.7-3.3, respectively). Likewise, women in this subpopulation with 1 or 2 copies of the NAT1*10 allele (22 cases/10 controls) did not have an increased NHL risk (OR 2.5; 95% CI 0.9-7.6, respectively). However, women with the NAT2 rapid/intermediate-acetylator phenotype who started using such dyes before 1980 (25 cases/11 controls) did exhibit a potentially increased NHL risk (OR 3.3; 95% CI 1.3-8.6). There was no evidence of increased risk among women who began using hair dyes after 1980.

Zhang et al. (2009) re-evaluated data from a case-control study of NHL in Connecticut (Zhang et al. 2004) to consider NAT1 and NAT2 genotype/phenotype and 17 other single nucleotide polymorphisms (SNPs).[31,32] The subjects, including 461 cases and 535 control subjects, were identified from the Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource (RCASR). Potentially confounding variables included in the final model were age and race. Adjustment for cigarette smoking, alcohol consumption, and farming history were not included in the final models because these factors did not materially alter the parameter estimates.

With the exception of FL, none of the different individual genes examined was associated with a statistically-significant change in the risk of NHL for any of the NHL subtypes considered. The exception was a statistically-significant increase in the risk of FL in women with rapid/intermediate NAT2 phenotypes who started to use hair dye before 1980, compared with women who never used hair dye (OR 2.8; 95% CI 1.1-7.2; 24 rapid/intermediate acetylator cases vs. 79 control subjects). In women who carried the CYP2C9 allele (TT or CT genotypes) and started to use hair dyes before 1980, there was an increased risk of NHL in general (OR 2.9; 95% CI 1.4-6.1; 58 cases, 43 control subjects) and the follicular lymphoma subtype specifically (OR 6.3; 95% CI 1.6-24.7; 20 cases, 43 control subjects), compared with women who never used hair dyes and women who started using hair dyes in 1980 or thereafter. No association evident in women who carried the CYP2C9 allele (TT or CT genotypes) and started using hair dyes in 1980 or thereafter (23 cases, 46 control subjects), compared with women who carried this allele and never used hair dyes (OR 1.0; 95% CI 0.4-2.3; 23 cases, 46 control subjects).

DNA Repair-Enzyme Genes

Guo et al. (2014) investigated the interaction between polymorphisms in DNA repair genes and hair dye use with NHL in a population-based case-control study in Connecticut.[33] The study population from which the subjects were drawn was the same as that of Zhang et al. (2009)[32] study summarized above, including 461 cases and 535 control subjects identified from the Yale Comprehensive Cancer Center's RCASR. The subjects included 518 NHL cases and 597 age-matched controls. All subjects were genotyped for 24 single nucleotide polymorphisms (SNPs) in 16 DNA repair-enzyme gene polymorhisms. The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale. All of the models were adjusted for age, race, and smoking status. The risk of FL, but not DLBCL, was statistically-significantly elevated in women with any one of 10 of the 24 SNPs and who used hair dye before 1980, compared to those who never used hair dyes; the ORs ranged from 1.93 (95% CI 1.00-3.72; 15 cases and 70 control subjects with EECC1rs3212961 CC) to 3.28 (95% CI 1.27-8.50; 7 cases and 110 control subjects with BRCA2rs144848 AC+CC). In addition, there was a statistically-significant interaction between hair dye use before 1980 and NHL in

women with one of these 10 SNPs (1.88 (95% CI 1.26-2.80; 146 cases and 100 control subjects with WRNrs1346044 TT). There was no association between NHL, FL, or DLBCL in women who began using hair dyes after 1980.

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

Study Type/Methodology	Results	Reference
Bladder Cancer		
Population-based case-control study in the Netherlands. Cases diagnosed between 1975 and 2009 for a total of 246 female cases with 2587 female controls; Analyses were not performed for the men selected for the study because less than 5% reported ever using hair dyes.	No association between bladder cancer and ever/never use of permanent hair dyes – permanent OR 0.87 (95% CI 0.65-1.18); temporary OR 0.7 (95% CI 0.58-1.02) No association between bladder cancer and duration of use, number of times used per year, total number of times used over a lifetime, dying all the hair or only part of the hair, or dye color (none of the subjects reported use of black dye). No association found when patients stratified by aggressiveness of the cancer.	Ros et al (2012)[7]
Population-based case-control study in Maine, Vermont, and New Hampshire. Cases diagnosed 2001 to 2004 for a total of 1193 cases (911 male and 282 female) with 1418 controls (1039 male and 378 female). Genotyping done for NAT2, NAT1, GSTM1, and GSTT1.	No association between ever/never use of hair dyes and bladder cancer – women OR 0.7 (95% CI 0.5-1.0); men OR 0.7 (95% CI 0.4-1.0). No association between hair dye use, NAT2 phenotype or NAT1 genotype and bladder cancer risk. Increased risk of bladder cancer with permanent hair dye use in a subgroup of women with a college degree, but no dose-response for color, duration of use, or total lifetime uses. NAT2 phenotype was associated with a suggestive, but not statistically significant, increased risk when college-degreed women were stratified by education – this was based on 15 cases and 6 controls.	Koutros, et al. (2011)[8]
Population-based case-control study of bladder cancer in Iran with 692 cases and 692 controls (identified using the Iranian cancer registry).	Overall (male and female) OR for hair dye use and bladder cancer was 1.99 (95% CI 1.02-3.82). When women and men were analyzed separately, no significant association with hair dye use and bladder cancer was reported.	Shakhssalim et al. (2010)[9]
Lymphoma and Leukemia		
Cohort or case-control study of leukemia in North America, Europe and Asia.	Mutivariate analysis: Based on 20 studies, ever use of any type of personal hair dye was associated with a non-statistically significant increased risk of leukemia, when compared to no use of hair dye (RR=1.09; 95% CI 0.97–1.22). A model restricted to case-control studies yielded a statistically significant increased RR of 1.13 (95% CI 1.00–1.28), while a model including cohort studies yielded an RR of 1.00 (95% CI 0.85–1.19). When restricted to studies that adjusted for smoking history, use of any hair dye was not associated with leukemia (RR= 0.99; 95% CI 0.76–1.29).	Towle et al. (2017)[10]
Population-based case-control study of leukemia and non-Hodgkin's lymphoma (NHL) in Italy. There were 161 cases (120 lymphoid and 41 myeloid) and 84 randomly-selected controls among women in the population studied.	Multivariate analysis: Hair dye use for at least 15 years was associated with NHL (OR=2.3; 95% CI 1.0-4.9), but hair dye use for less than 15 years was not associated with NHL (OR=1.4; 95% CI 0.6-3.1). Leukemia was not associated with using hair dye for at least 15 years (OR=2.7; CI 0.9-7.9) or for less than 15 years (OR=2.7; CI 0.9-8.4).	Parodi et al. (2016)[11]

Hospital-based case-control study of lymphoproliferative cancers in Egypt. There were 130 cases (107 NHL and 23 chronic lymphocytic leukemia) and 130 age- and sex-matched controls.	Multivariate analysis: No increase in the risk of lymphoproliferative disorders with history of using hair dyes (χ^2, $p>0.05$).	Salem et al. (2014)[15]
Hospital-based case-control study of myelodysplastic syndromes (MDS) in China. There were 403 cases and 806 controls.	Univariate analysis: OR for hair dye use (≥2 times per year) and all MDS was 1.46 (95% CI 1.03-2.07). Multivariate analysis: OR was 1.31 (95% CI 0.88-1.93).	Lv et al. (2010)[16]
Hospital-based case-control study in Shanghai of NHL. There were 649 cases and 1298 controls	No increased risk of NHL, with an OR of 0.93 (95% CI 0.75-1.16). For chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), the authors reported a significantly lower risk associated with hair dye use with an OR of 0.37 (95% CI 0.18-0.76).	Wong et al. (2010)[17]
Re-evaluated tissue samples from an NHL case-control study in males from Iowa and Minnesota using FISH (fluorescence *in situ* hybridization) cytogenetic technique to evaluate both *t*-positive and *t*-negative NHL subtypes.	An association between ever/never use of hair dyes and t(14;18)-negative NHL (OR 2.9; 95% CI 1.6-5.0) and bcl-2 positive NHL (R 2.2; 95% CI 1.4-3.4), but not with t(14;18)-positive NHL (OR 1.3; 95% CI 0.6-2.6) or bcl-2 negative NHL (OR 1.4; 95% CI 0.5-3.8).	Chang et al. (2010)[18]
Hospital-based case-control study of acute myeloid leukemia (AML) in Shanghai, China. There were 722 cases and 1,444 controls.	No increase in the risk of AML with personal use of hair dyes; OR = 0.98 (95% CI 0.8-1.2).	Wong et al. (2009)[19]
Breast Cancer		
Population-based case-control study of breast cancer in African American and European American women in New York city and 10 counties in New Jersey. There were 1508 African American and 772 European American cases and 1290 African American and 715 European American frequency-matched (by age and county of residence) control subjects.	Increase in the odds of breast cancer in African American women who reported using dark permanent hair dyes (1.52; 95% CI 1.21-1.91), African American women who typically had their hair dyed in a salon (1.30; 95% CI 1.03-1.63), and European American women who had a history of both hair dyes and chemical hair relaxers (2.21; 95% CI 1.26-3.86). Women who started using hair dyes before 1980 were not distinguished from women who started in 1980 or thereafter.	Llanos et al. (2017)[21]
Population-based case-control study of breast cancer in Finland. There were 6,567 cases and 21,598 age-matched controls.	Increase in the odds of breast cancer in women who ever used hair dyes, compared with those who never used hair dyes (OR=1.28; 95% CI 1.10-1.48). Statistically significant trend in ORs for cumulative use of hair dyes (1.07 and 1.31 for 1-2 episodes and 35-89 episodes, respectively).	Heikkinen et al. (2015)[22]
Population-based case-control study of breast cancer in China. There were 234 cases and 358 age and education matched controls.	No increase in the odds of breast cancer in women who ever used hair dyes, compared with never used hair dyes (RR=0.93; 95% CI 0.78-1.09). Stratification by menopausal status indicated no association between breast cancer and hair dye use in either pre- or post-menopausal women.	Mendelsohn et al. (2009)[24]
Hospital based case-control study in the UK. There were 191 cases and 561 age matched controls. 73 cases and 213 controls had ever used hair dyes.	A non-statistically significant increase in the odds of breast cancer in women who ever used hair dyes, compared with never used hair dyes (OR=1.01). There was no evidence of an increasing risk for breast cancer with increasing duration of use of hair dyes or with use beginning more than four or more than nine years before diagnosis.	Kinlen et al. (1977)[25]

Hospital based case-control study in Canada. There were 85 cases and 170 controls, both over two locations.	A non-statistically significant increase in the odds of breast cancer in women who ever used hair dyes, compared with never used hair dyes (London, Ontario: OR=1.3; 95% CI, 0.6-2.50 and Toronto, Ontario: OR=1.1; 95% CI, 0.5-2.4). Further statistical analyses, allowing for smoking habits, family history of cancer and age at first birth, showed no significant relationship between hair-dye use and breast cancer incidence.	Stavraky et al. (1979)[26]
Hospital based case-control study based in New York City.	No increase in the odds of breast cancer in women who ever used hair dyes, compared with never used hair dyes (OR=0.8; 95% CI 0.6-1.1). There was also no statistically significant difference between those who report using hair dyes at least once and those who reported more than 100 uses.	Koenig et al. (1991)[27]

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