

ADMIN

Memo

Agenda

Minutes

RRsum Glyoxal

RRsum Quaternium-26

RRsum Biotin

Aerosols

Endocrine Activity

Hair Dyes

CIR EXPERT PANEL MEETING

SEPTEMBER 11 – 12, 2017



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MEMORANDM

To: CIR Expert Panel Members and Liaisons
From: Bart Heldreth, PhD, Interim Director, CIR
Subject: 144th Meeting of the CIR Expert Panel — Monday and Tuesday, September 11-12, 2017
Date: August 18, 2017

Welcome to our September 2017 Panel meeting. CIR is still in an interim leadership phase, but we are all set and ready for our third meeting of the year.

Enclosed are the agenda and accompanying materials for the 144th CIR Expert Panel Meeting to be held on September 11-12, 2017. The location again is the Loews Madison Hotel, 1177 Fifteenth Street, NW, Washington, DC 20005. Phone: (202) 862-1600. Fax: (202) 785-1255.

The meeting agenda includes the consideration of 15 ingredient groups advancing in the review process and 3 re-review summaries. Following up on the Panel's continuing standardization of guidance language documents, the agenda also includes 3 items for discussion. These 3 very cogent documents include the topics of Endocrine Activity, Hair Dyes, and Incidentally Respirable Particles. Through Ivan's efforts, the culmination of input from the Panel, stakeholders, and Dr. Mihaich, has resulted in a new draft of the Endocrine Activity Guidance document for the Panel's review. Additionally, a synopsis of the current state of the CIR guidance documentation for dealing with hair dyes is available for review. We are expecting a presentation on this topic in December, and this review presents an opportunity for the Panel to prefigure what they expect to see and hear in that presentation. And, with regard to how we handle aerosols, or otherwise incidentally inhalable particles, we have two great speakers to present on this topic, and to help inform a redrafting of the CIR Aerosols guidance document.

The first speaker, Dr. Yevgen Nazarenko, is a Fellow at McGill University and is the first author of the two papers of which there was much discussion at the last Panel meeting, specifically, those titled:

- *Potential for Inhalation Exposure to Engineered Nanoparticles from Nanotechnology-Based Cosmetic Powders*
- and
- *Nanomaterial Inhalation Exposure from Nanotechnology-Based Cosmetic Powders: a Quantitative Assessment*

The second speaker, Dr. Madhuri Singal, is currently a Senior Consumer Safety Associate Inhalation Toxicologist at Reckitt-Benckiser, and a Clinical Instructor at Rutgers University. Those here who have worked closely with RIFM over the years may remember Dr. Singal from her tenure there as Respiratory Science Program Manager from 2007-2013.

Schedule and hotel accommodations

We have reserved rooms for the nights of Sunday, September 10 and Monday September 11, at the Loews Madison 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. Ammonia and Ammonium Hydroxide (agenda and flash drive name – Ammonia and Ammonium Hydroxide) – This is the first time that the Panel is seeing this report on these 2 nitrogenous ingredients. In July 2017, an SLR was issued with an invitation for submission of data on these ingredients. Concentration of use data and comments were received from the Council. The CIR final report on Phosphoric Acid and Its Salts is included, as the Panel may find the data on ammonium phosphate supportive to the safety of Ammonia and/or Ammonium Hydroxide, as a surrogate. In addition, data from the European Chemicals Agency (ECHA) registration dossier on Ammonia on potential surrogate chemicals have been included in this report. The Panel should determine whether data on these surrogate chemicals are relevant to this safety assessment. One of the comments received from the Council suggests that two of these proposed surrogate chemicals, which are also cosmetic ingredients, should be added to this ingredient family. Ammonia and Ammonium Hydroxide, however, were proposed as a grouping during the priorities-setting process last year, and these additional ingredients were not recommended for inclusion until now. Ammonia and Ammonium Hydroxide constitute a perfect grouping because these ingredients are exactly the same thing in cosmetic products, existing with each other in equilibrium. The Panel should determine whether or not this change is warranted.

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. Alkyl Sultaines (agenda and flash drive name – Sultaines). This is the first time that the Panel is seeing this report on 13 alkyl sultaine ingredients. The sultaines/alkyl sultaines are structurally related to betaines/alkyl betaines (which the Panel has assessed the safety of), and are sometimes referred to as sulfobetaines. Each of the ingredients named in this report is a sulfopropyl quaternary ammonium salt. The structures of these ingredients are so similar that certain toxicological data, on a given endpoint, for one ingredient may be informative about the toxicity of one or more of the other ingredients in this report. Indeed, in the ECHA assessment, data on Cocamidopropyl Hydroxysultaine was used to read-across data to Lauramidopropyl Hydroxysultaine. The Council has provided concentration of use survey data and comments on the SLR that was issued on June 30th. The concentration of use survey conducted in 2017 reported the highest reported maximum concentrations of use of 11.5% in rinse-off products and up to 2.5% in leave-ons.

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

3. *Hamamelis virginiana* (Witch Hazel) (agenda and flash drive name – Witch Hazel). This is the first time that the Panel is seeing these 8 ingredients derived from part(s) of the *Hamamelis virginiana* (Witch Hazel) plant. In July 2017, an SLR was issued with an invitation for data on these ingredients. Data regarding concentration of use, method of manufacture, impurities, *in vitro* dermal and ocular irritation, and human dermal sensitization were submitted. “Witch hazel” is a ubiquitous term and is used generically, along with other terms (e.g., “hamamelis water,” “witch hazel extract,” “witch hazel oil,” and other variations) in the literature. Much of the information in the literature does not clarify the source plant part(s), the solvent(s), and/or the extraction method(s).

If no further data are needed to formulate a Conclusion of safety, the Panel should develop the basis for the Discussion and issue a Tentative Report. If more data are required, the Panel should list the data that are needed for a Conclusion of safety, and issue an IDA.

Tentative Reports – there are 4 draft tentative reports.

1. Panthenol, Pantothenic Acid, and Derivatives (agenda and flash drive name – Panthenol and Derivatives). At the April 2017 meeting, the Panel issued an Insufficient Data Announcement with requested data needs as follows:
 - Method of Manufacturing for Panthenyl Ethyl Ether, Panthenyl Ethyl Ether Acetate, and Panthenyl Triacetate
 - Impurities of data for Panthenyl Ethyl Ether, Panthenyl Ethyl Ether Acetate, and Panthenyl Triacetate
 - Sensitization data, specifically an HRIPT or a guinea pig maximization test for Panthenol at a concentration $\geq 5\%$

A supplementary request from the Panel was for chronic toxicity data on Panthenyl Ethyl Ether.

Council comments and Industry data have been submitted and have been incorporated into the report as appropriate. Panel edits from the April 2017 Meeting were addressed; the Abstract and Discussion were added to the report. The Panel should consider whether or not the data are now sufficient for making a determination of safety for all of the ingredients, and whether the *N*-nitrosation boilerplate language should be included in the Discussion in regards to the presence of possible residual amines as impurities for Panthenol.

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 sufficient for all, then a safe (or safe with qualifications) Conclusion should be issued. If the data are not sufficient for some or all of the ingredients, then that decision should be reflected in the Conclusion.

2. Polyaminopropyl Biguanide (agenda and flash drive name – Polyaminopropyl Biguanide). Given the inclusion of two chemical names in the title of this safety assessment, the report introduction contains a fair amount of detail relating to the use of the INCI name Polyaminopropyl Biguanide to represent the chemical polyhexamethylene biguanide hydrochloride throughout the report text. An Insufficient Data Announcement with the following data requests was issued at the June 2017 Expert Panel meeting (this was the second IDA issued for this ingredient):
 - a) Calculation of a margin of safety (MoS) for Polyaminopropyl Biguanide inhalation exposure, using toxicity data from a short-term (28-day) rat inhalation-exposure study and use concentration data on Polyaminopropyl Biguanide in hair sprays, both of which were included in the CIR safety assessment.
 - b) Further clarification of urticarial reactions reported in SCCS assessment of Polyaminopropyl Biguanide.
 - c) Raw data sheets (i.e., individual scores obtained during the induction and challenge phases) on subjects evaluated in the HRIPT on a product containing 0.2% Polyaminopropyl Biguanide submitted (HRIPT with raw data sheets) by the Council on May 2, 2017.
 - d) A dermal sensitization quantitative risk assessment (QRA) for Polyaminopropyl Biguanide.

Additionally, industry was encouraged to provide any available HRIPT data that could yield a more refined no-expected-sensitization-induction-level (NESIL); the current NESIL of $25\mu\text{g}/\text{cm}^2$ was considered likely to be overly conservative for use in the QRA. Furthermore, at the meeting, the Council informed the Panel that they would provide CIR with a corrected HRIPT summary and a corrected concentration of use table.

In response to this IDA:

- a) MoSs for Polyaminopropyl Biguanide inhalation were calculated by the CIR staff. The Panel should determine whether the safety assessment report presents the modelling effort adequately.

- b) Given the Panel's concern about contact urticaria, the 3 case reports in the published literature that were identified as relevant are summarized under the Contact Urticaria subheading in the section on Case Reports. The Panel should also determine whether case reports relating to anaphylaxis should be added to the Case Reports, Contact Urticaria section of the safety assessment report.
- c) The updated use data corrected the previously reported highest maximum use concentration of 0.5% in suntan products; the highest maximum use concentration in a leave-on product is now 0.2% in eye lotions. A corrected summary of the HRIPT on a leave-on product containing 0.5% Polyaminopropyl Biguanide (provided by the Council on 6-15-2017) was also received.
- d) To date, a dermal sensitization QRA has not been received from the Council, and the same is true for any additional available HRIPT data that might yield a more refined NESIL.

The Panel should decide if all of the needs defined in the IDA have been met, or are otherwise deemed moot. Other comments from Council were received and addressed. In addition, comments relating to the inhalation toxicity of polyhexamethylene guanidine phosphate (PHMG) were received from Women's Voices for the Earth. In these comments, the "discrepancy of professional opinion" with respect to how similar PHMG and Polyaminopropyl Biguanide are to each other was noted and publications were provided. The papers cited by WVE applied a no observed adverse effect concentration (NOAEC) from a 28-day inhalation-exposure study of Polyaminopropyl Biguanide (0.024 mg/m³) to read-across to the risks associated with inhalation exposure to PHMG. The Panel should consider this issue and determine whether or not the publications relating to PHMG-induced lung injury that are summarized in the Other Clinical Reports section of the Draft Tentative Report are relevant to this safety assessment.

The Panel expressed concern about the irritation and sensitization potential of Polyaminopropyl Biguanide and discussed the likely recommendation that products containing Polyaminopropyl Biguanide be formulated to be non-irritating and non-sensitizing using the QRA or a similar risk assessment method.

After reviewing the available data, the Panel should determine whether a Tentative Report with a safe as used, safe with qualifications, insufficient data, or unsafe Conclusion should be issued at this meeting. With respect specifically to the potential for incidental inhalation exposure, the Panel should determine whether a safe Conclusion with inhalation-specific qualifications is warranted.

3. *Mentha piperita* (Peppermint) (agenda and flash drive name – Peppermint). At the April 2017 meeting, the Panel agreed that the safety assessment published in 2001 should be reopened to add 6 additional *Mentha piperita* (peppermint)-derived ingredients. At that meeting, the Panel issued an IDA with the following data requests for all ten ingredients:

- Skin irritation and sensitization data
- Composition, method of manufacture, and impurities data

The following data were received in response to the Panel's IDA: 1) use concentration data on the 6 ingredients that are being added; 2) method of manufacture, composition, and impurities data on Peppermint Leaf Extract (butylene glycol/water), Peppermint Leaf Extract (water/ethanol), peppermint leaf extract powder (not an INCI ingredient), and Peppermint Leaf Water; and 3) *in vitro* skin irritation data on Peppermint Leaf Extract (water/ethanol) (at concentrations of 10% and 100%) and an HRIPT on Peppermint Leaf Extract (water/ethanol) (at a concentration of 100%).

Regarding the statement in the prior final report Conclusion that the concentration of pulegone in these ingredients should not exceed 1%, the Panel considered whether, in hindsight, their concern should have been addressed using a non-sensitizing-qualification approach (which may be based on a QRA). Furthermore, it was noted that the 1% concentration limit on pulegone was based, in part, on maximum leave-on product concentrations of 0.2% - 2% *Mentha Piperita* (Peppermint) Oil, but that the oil is now being used at concentrations up to 5% in leave-on

products.

Taking into consideration that skin irritation was observed in subjects after application of a cleansing gel containing 50% *Mentha Piperita* (Peppermint) Leaf Water (diluted to 5% concentration of the leaf water) and that *Mentha Piperita* (Peppermint) Leaf Water is being used at concentrations up to 40% in leave-on products, the Panel considered the possibility of issuing a Conclusion stating that products containing *Mentha piperita* (peppermint)-derived ingredients should be formulated to be non-irritating. Furthermore, given the terpene content of these ingredients, addition of the safe when formulated to be non-sensitizing qualification to the Conclusion that will be developed was further considered.

The unpublished data, and received comments, have been incorporated into the report, as appropriate, and a draft Discussion has been added. The Panel should determine whether the data provided satisfy all of the data needs, and, if not, be prepared to state the additional needs that are needed to make a determination of safety, and issue a Tentative Amended Report with an insufficient data Conclusion. However, if the data that were received address all concerns, or those concerns are otherwise deemed moot, the Panel should determine whether a safe as used, safe with qualifications, or unsafe Conclusion should be issued.

4. Triglycerides (agenda and flash drive name – Triglycerides). This re-review was considered at the April 2017 meeting, and the Panel determined that it was appropriate to consolidate three previous reports on 25 triglyceride ingredients, and to include 26 triglycerides that had not yet been reviewed by the Panel. However, a question was raised about removing one of the ingredients, Glyceryl Tribehenate/Isostearate/Eicosandioate. The Panel should determine whether this ingredient should be removed from the report. Also at the April meeting, the Panel requested the following information in an IDA:

- sensitization data for Tribehenin at the reported maximum concentration of use (i.e., 15.6% in mascara);
- sensitization data for Caprylic/Capric Triglyceride at the reported maximum concentration of use (i.e., 95.6% in face and neck products);
- sensitization data for Triethylhexanoin at the reported maximum concentration of use (i.e., 100% in face and neck products);
- irritation and sensitization testing of C10-40 Isoalkyl Acid Triglyceride at the expected maximum concentration of use (no concentrations of use were reported);
- clarification of the skin bleaching potential of Docosahexenoic/Docosapentenoic/Oleic/Palmitic Triglyceride, including a dose-response for this action

The following were received in response to the IDA:

- TKL Research. (2000) Human repeated insult patch test: Moisturizer with 6% Tribehenin;
- Consumer Product Testing Co. (2000) Repeated insult patch test protocol of a material containing 20% Tribehenin;
- Anonymous. (2015) Clinical evaluation report: Human patch test (facial oil containing 95.51% Caprylic/Capric Triglyceride);
- Product Investigations, Inc. (2015) Determination of the sensitizing propensities of facial oil (containing 95.51% Caprylic/Capric Triglyceride) on human skin;
- KGL. Inc. (2015) Photocontact allergenicity potential of a facial oil containing 95.51% Caprylic/Capric Triglyceride.

Also received were concentration of use data for the additional (add-on) triglycerides, and concentration of use information that was an update to that which was reported in the re-review document that the Panel reviewed in April. The most significant change that was reported in the update is that the maximum concentration of use of Tribehenin in deodorants is 5.1%, not 50.6%. Therefore, the maximum concentration of use reported for Tribehenin is 15% in mascara.

After reviewing the available data, the Panel should determine whether a Tentative Amended Report with a safe as used, safe with qualifications, insufficient data, or mixed Conclusion should be issued at this meeting.

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. Bovine Milk Proteins (agenda and flash drive name – Milk Proteins). In April 2017, the Panel issued a Tentative Report with the Conclusion that the 16 bovine milk proteins and protein-derived ingredients are safe in the present practices of use and concentration. Data received since the April meeting include the results of the concentration of use survey on Lactoglobulin: no uses were reported. The 2017 FDA VCRP data indicate this ingredient has 1 reported use in a face and neck skin care preparation. Comments received from the Council prior to the April meeting, and on the tentative report, have been considered.

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. Plant Derived Proteins (agenda and flash drive name – Plant Proteins). In June 2017, the Panel issued a Tentative Report with the Conclusion that 18 of the 19 plant-derived protein and peptide ingredients are safe in cosmetics in the present practices of use and concentration. The Panel also concluded that the data on Hydrolyzed Maple Sycamore are insufficient to determine safety. No new unpublished data were received since the June meeting. The Council suggested expanding information regarding tree nut allergies with information from a review article. This, and all other comments received from the Council have been considered and incorporated in the report, as appropriate.

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

3. Ectodermal Derived Ingredients (agenda and flash drive name – Tissue Proteins). At the June 2017 meeting, the Panel issued a tentative report with the Conclusion that these 19 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment. Since the June meeting, CIR staff have received updated concentration of use data on Soluble Collagen and the results of the concentration of use survey on Atelocollagen. The maximum leave-on concentration for Atelocollagen is 0.005% in skin care products. The Council provided comments on the tentative report. Included in those comments was a recommendation to change the name of the report to the “Safety Assessment of Skin and Connective Tissue-Derived Proteins and Peptides.” Also, inclusion of information from the Hydrolyzed Wheat Protein (HWP) report regarding molecular weight size and Type 1 sensitivity reactions was suggested. The CIR Science and Support committee have also suggested incorporating this information in the Discussion section of the report. Included in the report are limited relevant information and supporting discussion language from the HWP report for the Panel’s review, but significant changes have been held in abeyance until the Panel has had the opportunity to confer at the meeting on whether the limitations applied in the HWP report are relevant to the ingredients in this report. The Panel will need to determine if these additions are appropriate for the ingredients in this report and if further language is needed. All other Council comments have been incorporated, as appropriate.

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

4. *Butyrospermum parkii* (Shea) (agenda and flash drive name – Shea). At the April 2017 meeting, the Panel issued a revised tentative report for the 13 *Butyrospermum parkii* (shea)-derived ingredients with the Conclusion that these are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing. Previously, the Panel had concluded that 9 of the ingredients were safe as used in the present practices of use and concentration and that the data were insufficient for *Butyrospermum Parkii* (Shea) Nut Extract, *Butyrospermum Parkii* (Shea) Nut Shell Powder, *Butyrospermum Parkii* (Shea) Seedcake Extract, and Hydrolyzed Shea Seedcake Extract. However, the data needs for these 4 ingredients were fulfilled. The Panel should review the minutes from the Full Panel meeting of April 2017 to see if the discussion in the report adequately captures the rationale for the revised Conclusion with the sensitization caveat. Since the April meeting, an HRIPT on *Butyrospermum Parkii* (Shea) Seedcake Extract at 0.42% was received. These data have been incorporated into the report, as have comments received from the Council, as appropriate.

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

5. *Humulus lupulus* (Hops) (agenda and flash drive name – Hops). In April 2017, the Panel issued a Tentative Report with the Conclusion that *Humulus Lupulus* (Hops) Extract and *Humulus Lupulus* (Hops) Oil are safe as used when formulated to be non-sensitizing. The Panel changed the name of the report to reflect the revision of the names of the ingredients being reviewed. Specifically, five INCI ingredient names were consolidated under the name *Humulus Lupulus* (Hops) Extract, and *humulus lupulus* (hops) cone oil is now named *Humulus Lupulus* (Hops) Oil. No new data have been submitted. Council comments have been 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. Monoalkylglycol Dialkyl Acid Esters (agenda and flash drive name – Monoalkylglycol Dialkyl Acid Esters). In June 2017, the Panel concluded that 25 of the 28 monoalkylglycol dialkyl acid ester ingredients are safe as used in cosmetics. The Panel also concluded that the data on 3 of the 28 ingredients are insufficient to come to a Conclusion of safety. The data needs, as described in the December 2016 Insufficient Data Announcement, were:
 - Dermal penetration for Diethylpentanediol Dineopentanoate, Dioctadecanyl Didecyltetradecanoate, and Dioctadecanyl Ditetradecyloctadecanoate
 - If there is dermal absorption for any of the three ingredients specified in the previous bullet, then: 28-day dermal toxicity, genotoxicity, and irritation and sensitization at maximum concentration of use or greater ($\geq 57\%$)
 - Because these ingredients can potentially form ester hydrolysis products, toxicity data on the hydrolysis products of these three ingredients including:
 - Diethylpentanediol Dineopentanoate
 - 2,4-diethyl-1,5-pentanediol
 - neopentanoic acid
 - Dioctadecanyl Didecyltetradecanoate
 - 9,10-dinonyl-1,18-octadecanediol
 - decyltetradecanoic acid
 - Dioctadecanyl Ditetradecyloctadecanoate
 - 9,10-dinonyl-1,18-octadecanediol (repeat from above)
 - tetradecyloctadecanoic acid

Of the requested data, acute oral, genotoxicity, irritation, and sensitization for Diethylpentanediol Dineopentanoate were submitted; dermal penetration and 28-day dermal toxicity data were not submitted. Council comments have been addressed. Additionally, since the last time the Panel examined this report, data were discovered for one of the two hydrolysis products of Diethylpentanediol Dineopentanoate, neopentanoic acid, but not the other, 2,4-diethyl-1,5-pentanediol. These data include: acute oral, dermal, and inhalation toxicity; oral and dermal repeated dose toxicity; genotoxicity; dermal (100%) and eye irritation (100%); and sensitization (guinea pig maximization study (intra-dermal induction at 0.05%, topical induction at 25%, challenge 10%). No other data have been submitted to address the IDA.

The Panel should consider whether the data that were received, in conjunction with the data on Diethylpentanediol Dineopentanoate already in the report, warrant a change in the Conclusion for this ingredient. 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, and issue a Final Report. If the data does not warrant a change to the Conclusion, the Panel should review the Abstract, Conclusion, and Discussion, ensuring that it captures the rationale for the current report Conclusion, and issue a Final Report.

7. Polyurethanes (agenda and flash drive name – Polyurethanes). In April 2017, the Panel issued a Tentative Report with the Conclusion that these ingredients are safe as used when formulated to be non-sensitizing. The Council has reported that the definitions of Polyurethane-60 and -61 were erroneously stated in the Web-Based Ingredient Dictionary (wINCI), but that the monographs have since been updated. Therein, dimethyl aminopropylamine (DMAPA) was erroneously stated instead of

dimethylolpropionic acid (DMPA). With these changes, there are now no ingredients in this report for which DMAPA was used as a monomer. Council comments have been addressed. No new toxicity data were submitted.

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 April 2017 Meeting, the Panel issued a Tentative Report with a safe Conclusion for 9 (out of 10) of the alkane diols and an insufficient data Conclusion for concentration of use for 1,4-Butanediol. A neurotoxicity study referring to 2,5-hexanedione has been added, Panel edits from the April 2017 Meeting were addressed, the Abstract and Discussion were updated, and the Conclusion was added to the report.

For the Panel's consideration with regard to 2,3-butanedione (aka diacetyl; a potential metabolite of the ingredient, 2,3-Butanediol), the Council has submitted a comment and accompanying article that refer to the toxicity of this metabolite; and, a draft report on 2,3-butanedione is now available from NTP with a Conclusion that indicates there is evidence of carcinogenicity in 2-year inhalation studies in rats exposed to 2,3-butanedione.

The Panel should be prepared to provide any additional rationale to be described in the Discussion; to verify the Abstract, Discussion, and Conclusion; and to issue a Final Report.

Other Items – there are 6 other items of business for consideration, comprising 3 re-review summaries, and 3 guidance document updates.

Re-Review Summaries - After reviewing these drafts the Panel should issue them as final summaries, as appropriate.

1. Glyoxal (agenda and flash drive name – Glyoxal). The Panel has 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 that Glyoxal is safe for use in products intended to be applied to the nail at concentrations $\leq 1.25\%$ and that the available data are insufficient to support the safety for other uses.
2. Quaternium-26 (agenda and flash drive name – Quaternium-26). New safety test data, since the final report was issued on Quaternium-26, were neither found in the published literature nor provided by the Council; however, the Panel reviewed updated information regarding product types and ingredient use frequencies provided by the FDA and use concentrations provided by the Council. The Panel determined to not reopen this safety assessment and reaffirmed the original Conclusion that Quaternium-26 is safe as used in cosmetic products.
3. Biotin – (agenda and flash drive name – Biotin). Some new safety test 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 that Biotin is safe as used in cosmetic products.

Guidance Document Updates

4. Aerosols and the CIR Particle Size Document (agenda and flash drive name – Aerosols). The Aerosols document has been updated to address some of the comments received to date. At the April 2017 meeting, the Panel noted that a few sentences could be added to this document to address the topic of incidental inhalation exposures to nano-size ingredients that may be added to cosmetic formulations and may be present in the droplets/particulates released to the air in the breathing zone during the use of cosmetic sprays and powders. The document has not yet been revised to address this topic.

The Panel should use the material presented by the speakers to inform such revision and issue an update guidance document.

5. Endocrine Activity (agenda and flash drive name – Endocrine Activity). This is the second draft of the CIR Expert Panel Endocrine Activity and Endocrine Disruption Background and Framework document. The first draft was reviewed by the Panel at the April 2017 meeting. Comments on the first draft received from the CIR Science and Support Committee and from Dr. Mihaich have been addressed in this draft.

The Panel should review the document for the adequacy of the content, scope, and detail, including the draft Framework for Discussion Sections that appears at the end of the Document and the adequacy of the revisions implemented in response to the comments received.

6. Hair Dyes (agenda and flash drive name – Hair Dyes). This is the latest draft of the CIR Expert Panel Hair Dye Epidemiology document. The previous draft was reviewed by the Panel at the April 2017 meeting. Comments on the previous draft received from the Council's Hair Coloring Technical Committee (HCTC) and from the Panel been addressed in the current draft.

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.

Please note that the Document may be revised again at the next few meetings, after the Panel receives the expected presentations on hair-dye chemistry and the recently completed European hair-dye self-testing study. Indeed, the Panel should consider review of these documents as an opportunity to prefigure any questions or concerns to be answered in those presentations.

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, re-review summaries, and guidance documents.

The agenda is split fairly evenly between reviewing the draft and tentative reports, and the final reports. 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

144th Cosmetic Ingredient Review Expert Panel Meeting

September 11 - 12, 2017

The Loews Madison Hotel
1177 15th Street, N.W.
Washington, D.C. 20005

Monday, September 11

8:00 am	CONTINENTAL BREAKFAST	
8:30 am	WELCOME TO THE 144th EXPERT PANEL TEAM MEETINGS	Drs. Bergfeld/Heldreth
8:40 am	PRESENTATIONS - Aerosols and the CIR Particle Size Guidance Document → <i>Exposure Assessment of Nanomaterial-Containing Aerosols from Spray and Powder Products</i> → Title TBD	Dr. Nazarenko Dr. Singal
10:00 am	TEAM MEETINGS	Drs. Marks/Belsito

Dr. Marks' Team

FR (CB)	Milk Proteins
FR (CB)	Plant Proteins
FR (CB)	Tissue Proteins
FR (CB)	Shea
DR (CB)	Sultaines
FR (LS)	Alkane Diols
TR (LS)	Panthenol and Derivatives
FR (LB)	Hops
FR (LB)	Monoalkylglycol Dialkyl Acid Esters
FR (LB)	Polyurethanes
DR (LB)	Witch Hazel
RRsum (LB)	Glyoxal
TR (MF)	Triglycerides
RRsum (MF)	Biotin
Admin (IB)	Endocrine Activity
Admin (IB)	Aerosols
Admin (IB)	Hair Dyes
TR (WJ)	Peppermint
TR (WJ)	Polyaminopropyl Biguanide
DR (WJ)	Ammonia and Ammonium Hydroxide
RRsum (WJ)	Quaternium-26

Dr. Belsito's Team*

FR (LB)	Hops
FR (LB)	Monoalkylglycol Dialkyl Acid Esters
FR (LB)	Polyurethanes
DR (LB)	Witch Hazel
RRsum (LB)	Glyoxal
Admin (IB)	Endocrine Activity
Admin (IB)	Aerosols
Admin (IB)	Hair Dyes
TR (MF)	Triglycerides
RRsum (MF)	Biotin
TR (WJ)	Peppermint
TR (WJ)	Polyaminopropyl Biguanide
DR (WJ)	Ammonia and Ammonium Hydroxide
RRsum (WJ)	Quaternium-26
FR (LS)	Alkane Diols
TR (LS)	Panthenol and Derivatives
FR (CB)	Milk Proteins
FR (CB)	Plant Proteins
FR (CB)	Tissue Proteins
FR (CB)	Shea
DR (CB)	Sultaines

Noon - 1:00pm **Lunch for Panel, liaisons, and staff**

5:00 pm **Adjourn Team Meetings**

FR: Final Report
TR: Tentative Report
DR: Draft Report
RRsum: Re-review summary

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

*Team moves to breakout room.

Tuesday, September 12

8:00 am	CONTINENTAL BREAKFAST	
8:30 am	WELCOME TO THE 144th FULL CIR EXPERT PANEL MEETING	Dr. Bergfeld
8:45 am	Admin MINUTES OF THE JUNE 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 (CB)	Milk Proteins – Dr. Marks reports
FR (CB)	Plant Proteins – Dr. Belsito reports
FR (CB)	Tissue Proteins – Dr. Marks reports
FR (CB)	Shea – Dr. Belsito reports
FR (LB)	Hops – Dr. Marks reports
FR (LB)	Monoalkylglycol Dialkyl Acid Esters – Dr. Belsito reports
FR (LB)	Polyurethanes – Dr. Marks reports
FR (LS)	Alkane Diols – Dr. Belsito reports

Reports Advancing

TR (LS)	Panthenol and Derivatives – Dr. Marks reports
TR (WJ)	Polyaminopropyl Biguanide – Dr. Belsito reports
TR (WJ)	Peppermint – Dr. Marks reports
DR (WJ)	Ammonia and Ammonium Hydroxide – Dr. Belsito reports
TR (MF)	Triglycerides – Dr. Marks reports
DR (CB)	Sultaines – Dr. Belsito reports
DR (LB)	Witch Hazel – Dr. Marks reports

Other Items

RRsum (LB)	Glyoxal – Dr. Belsito reports
RRsum (WJ)	Quaternium-26 – Dr. Marks reports
RRsum (MF)	Biotin – Dr. Belsito reports
Admin (IB)	Aerosols – Dr. Marks reports
Admin (IB)	Endocrine Activity – Dr. Belsito reports
Admin (IB)	Hair Dyes - Dr. Marks reports

ADJOURN - Next meeting *Monday and Tuesday, December 4-5, 2017* at The Darcy Hotel, 1515 Rhode Island Avenue, NW, Washington, District of Columbia, 20005-5595

FR: Final Report
TR: Tentative Report
DR: Draft Report
RRsum – Re-review summary



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ONE HUNDRED FORTY-THIRD MEETING

OF THE

EXPERT PANEL

June 12-13, 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

Jay Ansell, Ph.D.

Government

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

Adopted (Date)

Wilma F. Bergfeld, M.D.

Others Present at the Meeting

Robena Aziz	FDA
Lillian Becker	CIR
Don Bjerke	P & G
Ivan Boyer	CIR
Roshil Budhram	L-Brands
Christina Burnett	CIR
Kapal Dewan	FDA
Carol Eisenmann	PCPC
Monice Fiume	CIR
Kevin Fries	CIR
Dave Gossai	L'Oreal
Thomas Gremillion	CFA
Bart Heldreth	CIR
Carla Jackson	CIR
Wilbur Johnson, Jr.	CIR
Julia Linthicum	CIR
Linda Loretz	PCPC
Goran Periz	FDA
Laura Scott	CIR
David Steinberg	Steinberg and Associates

MINUTES FROM THE 143rd CIR EXPERT PANEL MEETING

CHAIRMAN'S OPENING REMARKS

Dr. Wilma Bergfeld welcomed all attendees to the 143rd meeting of the CIR Expert Panel, including the newly appointed Interim Director, Dr. Bart Heldreth, and Interim Deputy Director, Ms. Monice Fiume. She then recalled last night's celebration of Dr. Lillian Gill's retirement from CIR and well wishes that were extended. Dr. Bergfeld also thanked the CIR staff for their diligence and excellent work.

Dr. Bergfeld stated that the 13 ingredient reports included on the meeting agenda, 2 final reports, 4 tentative reports, 1 draft report, 5 re-review considerations, and 1 re-review summary, were discussed in Teams on the preceding day. Other discussion items included year 2018 ingredient priorities and the read-across document that was developed by Dr. Heldreth. Dr. Bergfeld noted that the content of the read-across document will change over time as comments from the Panel are incorporated. She added that future follow-up items include CIR boilerplates (aerosol boilerplate included) and endocrine activity and disruption, and that the Panel will hear presentations on these topics in the future. Another item that deserves that Panel's attention is the CIR hair dye document (posted at CIR's website). This document has been updated with new information on an annual basis, but has not been subjected to an in-depth review in a number of years. However, this level of document review by the Panel will be considered after an industry presentation on the topic, this December.

APPROVAL OF MINUTES

The minutes of the April 10-11, 2017 CIR Expert Panel meeting were unanimously approved.

DIRECTOR'S REPORT

Dr. Heldreth acknowledged the transition phase occurring at CIR. After Dr. Gill announced her retirement at the April meeting, Dr. Heldreth and Ms. Fiume were appointed to the roles of Interim Director and Interim Deputy Director of CIR, respectively.

Dr. Heldreth also welcomed the new liaison from the Consumer Federation of America (CFA), Mr. Thomas Gremillion. Additionally, he announced the retirement of CIR's industry liaison, Dr. Beth Jonas of PCPC, effective sometime later this year. She will be moving on to her new life in Park City, Utah, once a new head of PCPC Science is appointed.

An impending change of status was announced for 3 ingredients, set for later this year. Hydrolyzed Carrageenan, which received an insufficient data conclusion (needs: method of manufacture and impurities data) in September of 2015 (part of the Polysaccharide Gums report), has no uses according to 2017 VCRP data. Accordingly, Hydrolyzed Carrageenan will be moved to the "zero-use category." The other two ingredients, MEA-Hydrolyzed Silk and Silkworm Cocoon Extract, received insufficient data conclusions in December of 2015 (needs: method of manufacture and impurities; concentration of use; 28-day dermal toxicity, and if absorbed, genotoxicity and reproductive and developmental toxicity may be needed; skin irritation and sensitization; part of the Silk Proteins report). According to 2017 VCRP data, MEA-hydrolyzed silk is not listed as in use. Therefore, it will also be moved to the "zero-use category." Silkworm Cocoon Extract, on the other hand, has 2 reported uses in that data set. Accordingly, if data needs for Silkworm Cocoon Extract are not met by the end of this year, it will be moved to the "use not supported" category.

Input was received from stakeholders on the Information Sources Document, for which the Panel approved that report language at the April meeting. Once the CIR Staff have finished updating the document in light of that input, and uploaded the document to the CIR website, the language approved by the Panel will be added to new reports going forward.

With regard to visibility, Dr. Heldreth was invited to participate in a public discussion on ingredient safety and ingredient impurities. Speakers from NGOs, industry consultants, and he, participated in a podcast for Cosmetics

and Toiletries Magazine, which can be found on their website (www.cosmeticsandtoiletries.com). On the national level, the National Institute of Standards and Technology (NIST) published, last month, their Guide to United States Cosmetic Products Compliance Requirements. Therein, the purpose and independence of CIR is well portrayed.

Also, CIR's input is continuing to be requested globally. Later this month, Dr. Boyer will represent CIR at a cosmetic science conference in Shanghai, sharing the infrastructure of CIR and the safety assessment process performed herein, with members of the industry in Asia.

Final Safety Assessments

Hydroxyethyl-3,4-Methylenedioxyaniline HCl

The Expert Panel issued a final report with the conclusion that Hydroxyethyl-3,4-Methylenedioxyaniline HCl is safe for use as a hair dye ingredient in the present practices of use and concentration as specified in the report.

Data received in February 2017 from the Food and Drug Administration (FDA) Voluntary Cosmetic Reporting Program (VCRP) indicate 67 uses of this hair dye ingredient. A 2016 survey of the industry reports a maximum use concentration of 0.75% in hair dyes and colors. There is potential for *N*-nitrosation because Hydroxyethyl-3,4-Methylenedioxyaniline HCl contains a free, secondary aromatic substituted amine group (aniline derivative). The Panel advises that manufacturers may avoid these issues by formulating ingredients in a way that reduces the formation of nitrosamines, and by eliminating the presence of impurities that can be *N*-nitrosated (e.g., 3,4-methylenedioxyaniline) or contain nitrosating agents. Consequently, hair dye formulations containing Hydroxyethyl-3,4-Methylenedioxyaniline HCl, and formulations intended for admixture with this ingredient, should not contain nitrosating agents.

Ethers and Esters of Ascorbic Acid

The Expert Panel issued a final report with a conclusion that the following 7 ingredients are safe in the present practices of use and concentration:

Tetrahexyldecyl Ascorbate	Ascorbyl Palmitate
Ascorbyl Isostearate*	Ascorbyl Dipalmitate
Ascorbyl Linoleate	Ascorbyl Stearate
Ascorbyl Tetraisopalmitate	

*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 others in this group.

These ingredients are reported to function in cosmetic products as antioxidants, skin-conditioning agents, and skin protectants. Ascorbyl Palmitate is also reported to function as a fragrance ingredient, and Ascorbyl Linoleate as a skin bleaching agent. Skin bleaching is a drug function, not a cosmetic function. Therefore, the Panel did not evaluate the safety of Ascorbyl Linoleate for skin bleaching.

The Panel noted that the results of a computational method for predicting the reproductive toxicity potential of Ascorbyl Palmitate and Ascorbyl Stearate are the only information available to address this endpoint in the safety assessment. In the absence of experimental reproductive toxicity data on the ethers and esters of ascorbic acid, the Panel applied a weight-of-evidence (WoE) approach comprising, in part, a summary of safety data on analogous compounds (which contain fatty acyl chains, ascorbates, acyl glycerols, and fatty acyl saccharides) previously reviewed by CIR, in combination with the *in silico* results for Ascorbyl Palmitate and Ascorbyl Stearate.

Tentative Safety Assessments

Plant-Derived Proteins and Peptides

The Panel issued a tentative report for 19 plant-derived proteins and peptides for public comment. The Panel concluded that the following 18 ingredients are safe in cosmetics in the present practices of use and concentration:

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

However, the Panel concluded the data on Hydrolyzed Maple Sycamore Protein are insufficient to determine safety. The data needed to evaluate the safety of Hydrolyzed Maple Sycamore Protein 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. Human repeated insult patch tests (HRIPTs) and related tests do not detect Type I reactions. Thus, the Panel cautions people with known allergies to tree nut, seed, and avocado proteins about using personal care products that contain these ingredients.

Monoalkylglycol Dialkyl Acid Esters

The Panel issued a tentative report for 28 monoalkylglycol dialkyl acid esters. The Panel concluded that the following 25 ingredients are safe in cosmetics in the present practices of use and concentration.

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

*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.

However, the Panel concluded that the available data are insufficient to make a determination that the following 3 ingredients are safe under the intended conditions of use in cosmetic formulations:

Diethylpentanediol Dineopentanoate
 Dioctadecanyl Didecyltetradecanoate
 Dioctadecanyl Ditetradecyloctadecanoate

The additional data needed to determine the safe use of these ingredients, as outlined in the April 2017 Insufficient Data Announcement (IDA), are:

- Dermal penetration for Diethylpentanediol Dineopentanoate, Dioctadecanyl Didecyltetradecanoate, and Dioctadecanyl Ditetradecyloctadecanoate; if absorbed, then the following data may be needed: 28-day dermal toxicity, genotoxicity, and irritation and sensitization data at maximum concentration of use or greater ($\geq 57\%$).
- Because these three ingredients can potentially form ester hydrolysis products, toxicity data on the hydrolysis products of these three ingredients, including data on:

2,4-diethyl-1,5-pentanediol	decyltetradecanoic acid
neopentanoic acid	tetradecyloctadecanoic acid
9,10-dinonyl-1,18-octadecanediol	

Some data were received for one of these ingredients and two of these ester hydrolysis products. However, the data needs related to dermal absorption and 28-day dermal toxicity, are as of yet unmet for all three of these ingredients.

For those ingredients deemed safe, 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 component parts of the molecules of these ingredients were determined to be safe in previous CIR safety assessments.

Glycol Distearate was reported to be used in 1663 formulations, mostly in hair products (1041 formulations); this is an increase from 28 uses in 2001. Trimethyl Pentanyl Diisobutyrate and Neopentyl Glycol Diheptanoate are used in 399 (all nail products) and 415 (mostly in skin care products) formulations, 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%. Neopentyl Glycol Dicaprate had the next highest reported maximum concentration of use; it is used up to 50%.

Persulfates

The Panel issued a tentative amended report and confirmed their original conclusion (published in 2001) 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 ingredients in leave-on products and dentifrices.

In 2016 Panel, the Panel reopened the original report on Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate to evaluate the safety of these ingredients for the newly reported uses. At the December 2016 Panel meeting, the Panel issued an IDA for these 3 ingredients. The additional data needed to evaluate the safety of these ingredients in leave-on products and dentifrices are:

- No-Observed-Adverse Effect-Level (NOAEL) for sensitization and urticarial
- Concentrations of use in leave-on products and dentifrices.

Specific to dentifrices, an FDA public health notification was issued concerning the risk of allergic reactions in users of denture cleansers containing Sodium Persulfate, and the risks of misusing these products. To date, these data have not been received and the data needs remain unchanged.

Polysilsesquioxanes

The Panel issued a tentative report for public comment that the following 18 polysilsesquioxanes are safe in cosmetics in the present practices of use and concentration.

Acryloyloxypropyl Polysilsesquioxane*	Methacryloyloxypropyl Polysilsesquioxane*
C26-28 Alkyldimethylsilyl Polypropylsilsesquioxane*	Methoxy PEG-10 Polysilsesquioxane*
C30-45 Alkyldimethylsilyl Polypropylsilsesquioxane	Polycaprylsilsesquioxane
Dimethicone/Silsesquioxane Copolymer	Polymethylsilsesquioxane
Dimethiconol/Caprylsilsesquioxane/Silicate	Polydimethylsiloxo PEG/PPG-24/19 Butyl Ether
Crosspolymer*	Silsesquioxane
Ethyl Polysilsesquioxane*	Polydimethylsiloxo PPG-13 Butyl Ether
Hydrogen Dimethicone/Octyl Silsesquioxane	Silsesquioxane*
Copolymer	Polymethylsilsesquioxane/Trimethylsiloxysilicate*
Isobutyl/Methoxy PEG-10 Polysilsesquioxane*	Polypropylsilsesquioxane
Isobutyl Polysilsesquioxane*	Trimethylpentyl Polysilsesquioxane

*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 a lack of systemic toxicity data (i.e. reproductive and developmental toxicity and carcinogenicity data), but agreed that these ingredients are large, insoluble molecules that share dominant features/structures, and are not expected to penetrate the skin. The Panel also agreed that the weight of the evidence alleviated concerns about the potential for local effects, such as dermal irritation and sensitization. However, manufacturers should use current good manufacturing practices to ensure that the levels of monomers and source materials are minimized in the final products.

Polymethylsilsesquioxane was reported to be used in 397 formulations, i.e., 374 in leave-on formulations, 22 in rinse-off formulations, and 1 diluted for the bath formulation. All other ingredients reportedly in use were specified to be used in 14 formulations or fewer. Polymethylsilsesquioxane has the highest reported maximum concentration of use; it is used at up to 55.2% in the category of other makeup preparations. The rest of the ingredients reportedly in use were stated to be used at 4.9% (e.g., C30-45 Alkyldimethylsilyl Polypropylsilsesquioxane in foundations) or less.

Ectodermal-Derived Proteins and Peptides (previously Tissue-Derived Proteins and Peptides)

The Panel issued a tentative report for public comment with the conclusion that the following 19 ectodermal-derived proteins and peptides are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

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

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

These proteins and peptides, which are similar to the other proteins and peptides reviewed by the Panel in other reports, are found in foods 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 a lack of systemic toxicity data (i.e. reproductive and developmental toxicity, genotoxicity, and carcinogenicity data). However, they did not believe that these proteins and peptides would cause adverse systemic effects in the general population.

The Panel noted that fish proteins are known food allergens that can elicit Type I immediate hypersensitivity reactions when ingested by sensitized individuals. Case reports suggest that individuals with fish allergies may also react to topical exposures of fish-derived cosmetic ingredients. 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 names). The Panel strongly urged manufacturers to place a warning on the label of products that may contain fish-derived ingredients so that sensitive individuals may avoid exposure.

Re-Reviews

Quaternium-26

The Panel concluded in a final report (published in 2000) on the safety of Quaternium-26 (quaternary ammonium salt) that, based on the available data, this ingredient is safe in the present practices of use and concentrations. The conclusion also states that Quaternium-26 should not be used in products in which *N*-nitroso compounds may be formed.

In the absence of new safety test data, the Panel determined that the original published final safety assessment of Quaternium-26 should not be reopened, and reaffirmed their conclusion on Quaternium-26. The Panel determined that reopening the report to add 2 similar ingredients, Cetearamidopropyldimonium Chloride and Hydroxyethyl Erucamidopropyl Dimonium Chloride (both quaternary ammonium salts), is not warranted. The Panel noted the likelihood that additional data would be needed to assess the safety of these additional ingredients. Since the original report, the use of Quaternium-26 has narrowed to non-coloring hair products only, and the maximum use concentration has decreased from 5 % to 2%.

Biotin

The Panel reaffirmed their prior conclusion that Biotin is safe as used in cosmetics. The reported frequency of use of Biotin in cosmetics has increased since its safety was originally reviewed; according to VCRP data received from the FDA, 71 uses were reported in 1998, and 506 uses are reported in 2017. The reported maximum leave-on concentration of use of Biotin, however, has decreased, from 0.6% to 0.1%.

Some new data were identified in the published literature. The Panel discussed a study that reported a decrease in sperm count following dietary administration of Biotin, noting that the dose that produced this effect was much greater than what would be included in cosmetic formulations. In accord with the original review, the Panel recognized that data on the irritation and sensitization potential of Biotin are absent. However, the lack of case reports indicates that Biotin does not have a strong potential to cause skin irritation or sensitization.

Glyoxal

The Panel reaffirmed the conclusion that Glyoxal is safe for use in products intended to be applied to the nail at concentrations $\leq 1.25\%$. However, the available data are insufficient to support the safety of this ingredient for other uses.

According to VCRP survey data received in 2017, Glyoxal is reported to be used in 2 formulations (1 basecoats and undercoats product and 1 face and neck product). In 1998, there were no uses reported in the VCRP. The results of the concentration of use survey conducted by the Council in 2016 indicate that Glyoxal has no reported uses, and no concentrations of use were reported in 1998. The Panel urged suppliers to take steps to limit the concentration of the free formalin impurity to 0.2%, which is consistent with the 2013 CIR evaluation of Formaldehyde and Methylene Glycol.

Tabled

Parabens

Sodium Methylparaben (which had not been reviewed by the Panel) was included in the CIR 2017 Priority List due to the large number of reported uses in the FDA's VCRP database. The Expert Panel agreed that it would be appropriate to group this ingredient with 7 parabens reviewed in the CIR safety assessment published in 2008:

Methylparaben	Benzylparaben
Ethylparaben	Isopropylparaben
Propylparaben	Isobutylparaben
Butylparaben	

In addition, the Panel included 12 other parabens that had not yet been reviewed:

Calcium Paraben	Sodium Butylparaben
Potassium Butylparaben	Sodium Ethylparaben
Potassium Ethylparaben	Sodium Isobutylparaben
Potassium Methylparaben	Sodium Isopropylparaben
Potassium Paraben	Sodium Paraben
Potassium Propylparaben	Sodium Propylparaben

At the June 2017 meeting, the Panel also added 4-Hydroxybenzoic Acid to the group.

Methylparaben is reported to be used in 13,797 formulations; this is an increase from 8786 formulations in 2006. Propylparaben had the next highest number of reported uses at 10,642; this is an increase from 7118 formulations in 2006. All of the other previously reviewed parabens in this safety assessment increased in the number of reported uses since 2006, with the exception of Benzylparaben, which dropped from 1 reported use to none. Methylparaben had the highest reported maximum concentration of use; it is used at up to 0.9% in shampoos. The highest maximum concentration of use reported for products resulting in leave-on dermal exposure is Ethylparaben in eye shadows at 0.65%. In 2006, Methylparaben had the highest reported maximum concentration of use at 1% in lipsticks. The maximum concentrations of use of the previously reviewed parabens have remained under 1% and the patterns of use are similar to those reported in the previous safety assessment.

The Panel was concerned that new data from a developmental and reproductive toxicity (DART) study indicated reduced sperm counts and reduced expression of a specific enzyme, and a specific cell marker in the testes of offspring of female rats orally dosed with 10 mg/kg/day Butylparaben during the gestation and lactation periods. Reductions in anogenital distance and other effects were reported at 100 mg/kg/day in this study. In comparison, the previous CIR safety assessment of the parabens included the calculation of margin of safety (MOS) values for adults and infants, assuming a no observed adverse effect level (NOAEL) of 1000 mg/kg/day from an older DART study.

The Panel agreed that subject matter experts should be consulted to review the reproductive toxicity data available for the parabens, and identify additional relevant data that the Panel should consider. These experts should provide professional opinions on the relevance of the animal-model toxicity endpoints reported in the DART studies available for assessing the safety of the parabens as used in cosmetics. They should evaluate the quality and facilitate the interpretation of the data on which NOAELs, lowest-observed adverse effect levels (LOAELs), and MOS values may be derived to assess the safety of these cosmetic ingredients. The Panel agreed to table the review of the parabens pending the input of these experts.

Insufficient Data Announcements

Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

The Panel found that the data are insufficient to determine the safety of Polyaminopropyl Biguanide, and issued an IDA.

The data needs are:

- Calculation of a margin of safety for Polyaminopropyl Biguanide inhalation exposure, using exposure data from the short-term (28 days) rat inhalation toxicity study and current use concentration data on Polyaminopropyl Biguanide in hair sprays, both included in the CIR safety assessment.
- Further clarification of urticaria reactions reported in SCCS reports on Polyaminopropyl Biguanide.
- Raw data sheets (i.e., individual scores during induction and challenge phases) on subjects evaluated in the HRIPT on a product containing 0.2% Polyaminopropyl Biguanide, that was provided by the Council.
- A dermal sensitization quantitative risk assessment (QRA) for Polyaminopropyl Biguanide.

Additionally, industry was encouraged to provide any available HRIPT data that can yield a more refined no-expected-sensitization-induction-level (NESIL); the current NESIL, at 25 $\mu\text{g}/\text{cm}^2$, is likely to be overly conservative for use in the QRA.

The Panel spent considerable time discussing issues relating to Polyaminopropyl Biguanide-induced anaphylaxis, sensitization, contact urticaria (confirmed in skin prick tests and blood tests for IgE levels) and lung injuries induced by polyhexamethylene guanidine phosphate, a chemical that is structurally similar to Polyaminopropyl Biguanide, though not identical. The latter issue is the basis for the Panel's request for a MOS calculation for Polyaminopropyl Biguanide inhalation exposure.

The Council informed the Panel at the meeting that they will provide CIR with a corrected HRIPT summary and a corrected concentration of use table.

Malic Acid and Sodium Malate

The Panel issued an IDA for Malic Acid and Sodium Malate.

The data needs are:

- An HRIPT, or other suitable sensitization studies, at the maximum reported leave-on use concentration of 2.1%.

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

These ingredients were previously reviewed by the Panel in a safety assessment that was published in 2001. The Panel has reopened this safety assessment to revise the conclusion based on the receipt of new data that address insufficient data needs in the original report.

Other Items: Guidance, Priorities and Re-Review Summary

Guidance: Read-Across and Inference Description/Guidance

The Panel reviewed a draft document that was presented with the initial scope of providing guidance on the formalization of reporting uses of read-across and inference in CIR safety assessment reports. There was a lively discussion, and very much valuable input was provided about the tailoring and future of this document. The Panel agreed that this document would be a living document, constantly growing with the advancement of the related sciences (e.g., *in silico* predictive techniques) and regulatory acceptance. The Panel suggested broadening the scope

of the document to eventually encompass how read-across may be used to inform initial grouping strategies, or even expanding it to encompass broad topics such as aggregate and weight of evidence approaches that may use, in part, read-across or inference. Indeed, a suggestion was made that re-evaluation of this document should occur on a regular basis, possibly annually. The Panel also agreed that, after this initial draft document was updated to incorporate the provided input, it should be distributed for review by the CIR Science and Support Committee, and any interested stakeholder, before returning to the Panel meeting table.

2018 Final CIR Priorities List

Interested parties were invited to comment on the inclusion of the ingredients for 2018 Final CIR Priorities List. The selection of these ingredients was based on the list of ingredients that have not yet been reviewed by the CIR Expert Panel and have the greatest number of uses reported by the VCRP in 2017. While the number of proposed new ingredients below is fewer than usual, a number of previously prioritized report projects are being carried forward into 2018. Comments were also sought, and received, on the additional ingredients that might be included in each ingredient family. After responding to comments, the Panel finalized the 2018 Priorities list and groupings. Ingredient families may be found (for both newly proposed and previously prioritized report projects), in the document, which is available at the following url:

<http://www.cir-safety.org/sites/default/files/2018%20Final%20Priority%20List%20with%20Ingredient%20Groups.pdf>

All carryovers from previous prioritized report projects, are included and highlighted in blue in the document found at the url above. It is likely that not all of the ingredients listed below will be chosen for work in 2018. However, these ingredients will be tracked and carried forward, as appropriate.

Ingredient	Number of formulations containing ingredient
Sorbitol	1950
Tetrasodium Glutamate Diacetate	470
Isopropyl Titanium Triisostearate	457
Adenosine	447
Ascorbyl Glucoside	432
Polysilicone-11	358
VP/Eicosene Copolymer	356
Tris(Tetramethylhydroxypiperidinol) Citrate	320
Cocos Nucifera (Coconut) Fruit Extract	305
Glycereth-26	300
Sodium Stearoyl Lactylate	291
Hordeum Vulgare Extract	291
Punica Granatum Extract	273
Basic Red 76 (2018 Hair Dye)	45 (annual election)

Re-Review Summary: Lard and Lard-Derived Ingredients

The Panel approved the re-review summary of lard-derived ingredients with the conclusion that the following six ingredients are safe as used in cosmetic products, provided that established limitations imposed on heavy metal and pesticide concentrations are not exceeded.

Lard	Hydrogenated Lard Glyceride
Hydrogenated Lard*	Lard Glycerides*
Lard Glyceride	Hydrogenated Lard Glycerides*

*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 number of product formulations containing these ingredients did not increase significantly since the initial safety assessment, according to VCRP data received from the FDA in 2017. The maximum reported use concentration for Lard Glyceride decreased from 10% in 1984 to 1.6% in 2016, according to Council surveys. The established heavy metal and pesticide concentration limits for these ingredients are: lead ≤ 0.1 ppm; arsenic ≤ 3 ppm; mercury ≤ 1 ppm; and total PCB/pesticide contamination ≤ 40 ppm, with ≤ 10 ppm for any specific residue.

Glyoxal

CONCLUSION: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) first published a Final Report on the Safety Assessment of Glyoxal in 1995; in that report, the Panel stated that the data were insufficient to support the safety of Glyoxal.¹ The data needs were:

- (1) Types of cosmetic products Glyoxal is used in and the typical concentrations of use for each of these products
- (2) Impurities, especially with respect to selenium and chlorinated organic compounds and the Glyoxal monomer
- (3) Dermal carcinogenesis using the methods of the National Toxicology Program's skin-painting studies. It is recognized that there are no reproductive or developmental toxicity data available to analyze—depending on the results of the studies described, additional data may be requested.

In an amended safety assessment published in 2000, the Panel reviewed additional information, including dermal carcinogenicity in mice and impurity data, and concluded that Glyoxal is safe for use in products intended to be applied to the nail at concentrations $\leq 1.25\%$.² They also concluded 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.³⁻¹⁵ The Panel determined to not reopen this safety assessment and reaffirmed the conclusion published in 2000 that Glyoxal is safe for use in products intended to be applied to the nail at concentrations $\leq 1.25\%$ and that the available data are insufficient to support the safety for other uses.

DISCUSSION: In 1998, there were no uses reported for Glyoxal.² There were no reported concentrations of use in 1998 or 2016.^{2,7} However, in 2017, Glyoxal was reported to be used in 2 formulations (1 basecoats and undercoats and 1 face and neck product).⁵

The Panel 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.¹⁶

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Lillian C. Becker

N:\CIR\New N Drive\Production\Reference Manager Databases\Glyoxal

QUATERNIUM-26

CONCLUSION: In the year 2000 safety assessment of Quaternium-26, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) stated that this ingredient is safe as used in cosmetic products, provided that it is not being used in products in which *N*-nitroso compounds may be formed.¹ New safety test data, since the final report was issued on Quaternium-26, were neither found in the published literature nor provided by the Personal Care Products Council (Council); however, the Panel reviewed updated information regarding product types and ingredient use frequencies provided by the FDA and use concentrations provided by the Council.^{2,3} The Panel determined to not reopen this safety assessment and reaffirmed the original conclusion that Quaternium-26 is safe as used in cosmetic products as given in Table 1.

DISCUSSION: 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).³ 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 Quaternium-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).²

Table 1. Frequency and Concentration of Use of Quaternium-26 According to Duration and Exposure.^{2,3}

	# of Uses		Max Conc of Use (%)	
	Quaternium-26			
	2017	1997	2016	1984
Totals*	26	25	0.063-2	5
Duration of Use				
<i>Leave-On</i>	10	9	0.063-0.15	NR**
<i>Rinse-Off</i>	16	16	0.13-2	NR**
<i>Diluted for (Bath) Use</i>	NR	NR	NR	NR**
Exposure Type				
Eye Area	NR	NR	NR	NR**
Incidental Ingestion	NR	NR	NR	NR**
Incidental Inhalation-Spray	1;14*	NR;8*	NR;0.15*	NR**
Incidental Inhalation-Powder	NR	NR	NR	NR**
Dermal Contact	1	4	NR	NR**
Deodorant (underarm)	NR	NR	NR	NR**
Hair - Non-Coloring	25	21	0.063-2	NR**
Hair-Coloring	NR	NR	1.2	NR**
Nail	NR	NR	NR	NR**
Mucous Membrane	NR	1	NR	NR**
Baby Products	NR	NR	NR	NR**

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted (for Bath) Product Uses.

*It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

** Product formulation data submitted to the FDA in 1984, with no indication of use concentrations per product category, indicated that Quaternium-26 was used at concentrations up to 5.0%.

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BIOTIN

CONCLUSION: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published the Final Report on the Safety Assessment of Biotin in 2001.¹ Based on the available data, the Panel concluded that Biotin is safe as used in cosmetics. Some new data were identified in the published literature,²⁻¹¹ 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 FDA¹² and maximum use concentrations provided by the Personal Care Products Council.¹³ The Panel determined to not reopen this safety assessment and reaffirmed the original conclusion that Biotin is safe as used in cosmetic products as given in Table 1.

DISCUSSION: The reported frequency of use of Biotin in cosmetics has increased since safety was originally reviewed; 71 uses were reported 1998,¹ and 506 uses are reported in 2017.¹² The reported maximum leave-on concentration of use has decreased from 0.6% to 0.1%.^{1,13} 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 to spermatogenesis.¹¹ 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.

Finally, the Panel stated that manufacturers should be aware that naturally occurring Biotin comprises only the D-stereoisomer. When produced synthetically, however, a racemic mixture of D- and L-stereoisomers is possible. There are potentially some differences in the reactivity of the L-isomer, and the DL-Biotin, with biological systems. However, because of the very low concentrations of use, the Panel was not concerned about those differences regarding the safety of Biotin as used in cosmetics.

Table 1. Current and historical frequency and concentration of use of Biotin according to duration and exposure

	# of Uses		Max Conc of Use (%)	
	2017 ¹²	1998 ¹	2015-2016 ¹³	1999 ¹ #
Totals*	506	71	0.000002-0.1	0.001-0.6
<i>Leave-On</i>	365	34	0.000002-0.1	0.0001-0.6
<i>Rinse-Off</i>	140	36	0.000001-0.1	0.0001-0.01
<i>Diluted for (Bath) Use</i>	1	1	NR	NR
Eye Area	54	2	0.000002-0.1	0.001-0.01
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	141 ^a ; 106 ^b	20 ^a ; 2 ^b	0.001-0.1; 0.001-0.1 ^a	0.001-0.005 ^a ; 0.002-0.6 ^b
Incidental Inhalation-Powder	106 ^b	2 ^b	0.1; 0.000004-0.1 ^c	0.002-0.6 ^b
Dermal Contact	322	31	0.000002-0.1	0.0001-0.6
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	166	40	0.000002-0.1	0.0001-0.01
Hair-Coloring	5	NR	0.0003	NR
Nail	6	NR	0.0001-0.1	NR
Mucous Membrane	1	3	0.000006-0.001	NR
Baby Products	NR	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

at the time of the original safety assessment, concentration of use data were not reported by the FDA; however, some concentration of use data were received from industry

^a It is possible these products are sprays, but it is not specified whether the reported uses are sprays..

^b Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

^c It is possible these products are powders, but it is not specified whether the reported uses are powders

NR – no reported use

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Ivan J. Boyer, Ph.D., D.A.B.T.
Date: August 18, 2017
Subject: Draft Revised Aerosols Precedents and Framework Document

Enclosed is a draft of the CIR Precedents – Aerosols document (*aeroso092017rep.doc*), the transcripts of the discussion of the CIR Precedents – Aerosols document at the April 2017 CIR Expert Panel meeting (*aeroso092017min.doc*), and the comments of the Women’s Voices for the Earth (*aeroso092017wve.pdf*), which were received on April 3, 2017 and were presented to the Panel in wave 3 for the April meeting. In addition, enclosed is a paper titled “Principal Considerations for the Risk Assessment of Sprayed Consumer Products,” which is authored by Dr. Singal and her colleagues (*aeroso092017pub.pdf*). These documents are offered for your information in anticipation of the presentations by Dr. Nazarenko and Dr. Singal at the September 2017 meeting.

The enclosed CIR Precedents – Aerosols document has been updated (note highlighted text) to address some of the comments received to date, including those from the Women’s Voices for the Earth and from the Panel. At the April 2017 meeting, the Panel noted that a few sentences could be added to this document to address the topic of incidental inhalation exposures to nano-size ingredients that may be added to cosmetic formulations and may be present in the droplets/particulates released to the air in the breathing zone during the use of cosmetic sprays and powders. The document has not yet been revised to address this topic. The information presented by the speakers will be used to inform the revision after the September 2017 meeting.

No new comments were received from the CIR Science and Support Committee (CIR SSC).

The Panel should determine how, and to what extent, the attached draft of the CIR Precedents – Aerosols document should be revised further, based on the comments from the Women’s Voices for the Earth and the information presented by the speakers.

142d COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

Monday, April 10, 2017

Dr. Marks' team

DR. MARKS: So next one we're gonna discuss is the aerosol precedents and framework document. Ivan, you're up again, and there are several reference points here. It's an administrative document, page two in our flash drive. But we also got a wave 3, with a letter from The Women's Voices. And then Ivan's responses. And is there anybody here representing The Women's Voices, because I don't want to overlook an outside comment. Looking at the audience, even though it's predominantly male, that doesn't mean you can't speak for women. Okay. So we don't have any. And I assume in the other panel meeting there wasn't somebody from The Women's Voices present. And we'll see tomorrow. I'll ask that same question tomorrow, if there is anybody to represent them because I think it's important to allow them to speak if they're here. Okay. So Ivan, do you want to proceed?

DR. BOYER: Okay. Well this began as an effort to simply incorporate some verbiage that addressed powder, loose powder cosmetic products. Because we were kind of thin on that. We didn't have a lot of information. And about a year ago, the Council had submitted a sample calculation of the potential for inhalation of respirable particles from loose powder particles. And we did incorporate that information and that analysis at that time. And, in fact, we have been using the document as it's marked up since then.

This was meant, for this meeting, this was submitted to the panel so they could take one more look at it and maybe put a stamp of approval on it and so forth and make it official. But a few days ago, last week, we received an extensive list of comments from The Women's Voices for the Earth. And they were very thorough and they asked good questions and it gave us an opportunity to maybe elaborate the thinking and the rationale and so forth that is behind, that underlies this document and this particular approach.

So what I did was spend some time sort of synthesizing their comments, each one of their comments, getting to the essence of the comments, and then preparing draft responses to those comments. So a lot of it has to do with explaining that we're not just focused on inhalation of respirable particles, and that the particles of larger sizes that are inhaled may not be respirable but are inhalable may not produce any adverse effects.

We are concerned with the potential for adverse effects of particles that deposit higher up in the respiratory tract as well – we look at information that we have holistically, on a case by case basis, we look at the chemical reactivity of the ingredient, the potential for the ingredient to cause sensitization, maybe not from inhalation studies, but from patch tests and so forth. We look at the potential for these substances, these ingredients to irritate the skin and so on. That's gonna give us some sign that it has a potential to irritate the respiratory tract as well. So what we try to do is maybe repeat [in the Discussion section] some passages in [each of the current safety assessment reports] that address all of that, that address our overall approach to evaluating the potential for adverse effects from incidental inhalation of ingredients.

And then we address – she had some seven or eight specific comments and we address those, each one of those individually.

Some of the comments that she [Ms. Scranton] had include references to papers that examine nanoparticulates in cosmetic powders. And in fact, if you use the techniques that they used in these papers, you do find nano-sized particles. It's probably not very surprising. But, depending on how you look at that information, you could question some of the information that is presented in our document. But, in fact, these papers are looking at a very narrow range of particles sizes in cosmetic powders. These methods are not appropriate for looking at the full range of cosmetic particulates emanating from cosmetic powders. And so, I think to a great extent, addressing their comments is a matter of clarification, of maybe going into some additional detail to explain what it is that we're saying in the document.

But she does also ask questions such as, should the panel address, specifically address nanoparticles that might emanate from powders and might not emanate also from cosmetic sprays. So that's more or less a question for the panel. We haven't really directly evaluated that. Or we haven't specifically or explicitly addressed the potential for nanoparticles to be an important consideration in our safety assessments.

DR. MARKS: So I'm gonna have to start with Ron Shank. First in the boilerplate, which Ivan added the conservative estimates for the inhalation of once a day application of loose face powder or body dusting product. That's on page 27. Ron, did you have any comments about that? That as Ivan said, this was put in to clarify what we've already actually talked about previously. It's in the administrative book, 27.

DR. SHANK: Yes, I see it. No, that was fine.

DR. MARKS: Okay. And it gives us a chance also to look at the rest of the document again. Was there anything about the rest of the document, in re-reading, you would have any comments or changes?

DR. SHANK: No, not in the document.

DR. MARKS: No. Okay.

DR. SHANK: But in to the reply.

DR. MARKS: Yes. And that was a long letter. So, go ahead, Ron. What? So Ivan specifically regarding nanoparticles.

DR. SHANK: Ivan addressed everything quite specifically. But I felt it was a serious question raised in that letter about, it was a lack of confidence in our database on particle size and aerodynamic properties. That our technology was outdated and we were not seeing the total distribution. So what I would suggest is that we ask the manufacturers of the various sprays and aerosols and powders to look at that concern and see if indeed our current database for particle size distribution is correct.

And then our response to The Women's Voices for the Earth, we're looking into, asking the manufacturers to confirm the particle size distributions. To confirm that our database is correct. The nanoparticles situation is entirely different. If people are making aerosols, powders, specifically for a nanometer sizes, those would certainly be respirable. Whether they'll be deposited is a question. They may be, it's more than just particle size. Once you get down into the alveolar spaces, solubility is extremely important. And we have not considered these extremely small, aerodynamic properties, for inhalation. We were considering hair sprays, deodorant sprays, foot sprays, things like that. So the issue of nano-micrometer diameters brings a different aspect to inhalation toxicity. And that would require for our boilerplate another paragraph specifically on nanometer particle sizes. Does that? That's kinda convoluted.

DR. MARKS: No it isn't. I got the gist of it. So, if I interpret what you said, Ron, you would like an expert, whether it be from the manufacturers of these, or say an academic scientist who is an expert on particle science and its distribution to come in and talk about that relevant to inhalation.

DR. SHANK: Well I think the people who make, the manufacturers. They would know. Academically, okay, we can go into the laboratory and generate this stuff. But the important question is, what is the consumer getting?

DR. MARKS: Yep.

DR. SHANK: And I think the manufacturer will know the particle size distribution, including nanometer size particles.

DR. HILL: And it seems to me.

DR. SHANK: That's to whom I would go. Sorry.

DR. HILL: No. I interrupted. But I didn't realize you were. I was just going to say, it seems at least once, twice over the last five years, we've had a situation where we did solicit very detailed information from manufacturers related to things like agglomeration and what the effective particle sizes were in sprays of various kind.

DR. SHANK: Right

DR. HILL: And whether that happens every single time. I have to say, I'm not sure that it does. Then we're using sort of the generalities that we think we know. Which, loose powder. But nanoparticles, when you're trying to deliver something, like a therapeutic agent for inhalation delivery, then you're trying to make them so they don't agglomerate, so that the particles do stay small so that you do inhale them deeply into the lungs. And that's a different scenario then, I don't know how many personal care products, cosmetics to use the term, there's actually intent to get that. So maybe the starting place is to find out, in terms of cosmetic use, how much nano is actually happening.

DR. MARKS: We could ask that. So if I interpret Ron, which Ron Shank, what you said. We need to bring in an expert from industry who can review the inhalation toxicity specifically about particle size, solubility, etc. And also include nanometer particles in that, if that's relevant.

DR. SHANK: Well there's a lot already known.

DR. MARKS: Okay

DR. SHANK: In inhalation toxicology about all of this. The question is, in cosmetic products

DR. MARKS: Right

DR. SHANK: Are these very, very small particles a significant component of the aerosol.

DR. GILL: I would expect for the Science and Support Committee to talk about this at your upcoming meeting as well. I know that there's a nanoparticle effort going on in industry. But I think they contributed to our understanding of this before and I would look to them to give us some comment about particularly the nanoparticles.

DR. BERGFELD: I would like to also mention, I think it is prudent for us to respond in a relatively quick way to this women's group. Even if you have areas unknown, to say it's being investigated and you'll get back to them. Otherwise, they think you're a non-responder.

DR. SHANK: I agree.

DR. GILL: And I did promise her that I would personally get back to her right after this meeting. Did tell her that it may be at topic that we will have to discuss here and come back with additional questions or information. So that statement that says it's under investigation. But to the extent that you, that the panel likes some of the comments that Ivan has developed, we can certainly get back to her with those.

DR. MARKS: Well, and then with this one in particular, I think as you said, Lillian, we're going to investigate further. And it sounds like the first portion of that, as you point out, Ron, what we need to know would be addressed by the scientific committee. And if there's a feeling of a need somebody should come in and present to

us, we welcome that. We've had that done on multiple occasions. A la what you were talking about, Ron Hill. Okay. So I'll present it that way tomorrow. The boilerplate is fine with the changes you've made. As far as the letter from The Women's Voices, we feel that that is an excellent letter, with responses. But in terms of particle science and distribution, we're going to explore that further, in reference to particularly nanometer particles. Is that? Ron? And I might ask for you to comment tomorrow.

DR. SHANK: Okay

DR. MARKS: You can think about distilling your comments into something perhaps a little bit more pithy

DR. SHANK: A one-liner

DR. MARKS: but that's okay. No, it doesn't have to be a one-liner. I may or may not. Ron Shank. Obviously, feel comfortable saying this is what I feel, when Wilma asks for discussion points. Because I think that is very important since we have, not only for us, but the public in general, particularly since we have The Women's Voice of the Earth.

DR. SHANK: Right.

DR. MARKS: As you indicated, Ivan, there are many very good points in that. Okay. Does that sound reasonable, team?

DR. SHANK: Yes it does.

DR. MARKS: Okay. This is probably, well we'll see. Maybe generate the most discussion tomorrow. And as I said, I'll go through them in no particular order, other than starting out I think with the introduction...

Dr. Belsito's team

DR. BELSITO: ...So I mean, we have aerosol precedents, framework, hair dye findings we need to discuss. Those are in admin. So do you want to go there first to aerosol precedence and frameworks? Where are we going here? I mean we suppose to discuss that too, right?

DR. SNYDER: Yes.

DR. BELSITO: So let's go to aerosol precedents and frameworks and start with admin. And then we'll move to waves, is that fair? I guess we're on page...

DR. SNYDER: Well the most important part is the – Women's Voices and response coming from CIR I believe (inaudible).

DR. BELSITO: So you want to go to wave 3.

DR. SNYDER: I think -- I mean that's right I think. Unless...

DR. BELSITO: You know, actually when I read that and I read that first. And did without realizing the data that we had in our report. And so I was thinking that just reading it from her standpoint, particularly, I think the point that was made. If I'm following the argument that CIR is using or proposing to be used is that the studies that were done at Rutgers the upper limit of detection was 20 microns.

So everything seems to be 20 microns or less in those studies. And excuse the range of particle size to make it look like they're all very potentially (inaudible). So I think it's easier to go to our boilerplate first. Then to...

DR. LIEBLER: I agree, I actually did the same thing, I read the letter first. The wave 3 thing really to scan it to see what was it was about. So I had that in mind when read through the boilerplate. Then I read through the boilerplate and then I went back and looked at Ivan's draft response to that. And then I spent a lot more time just kind of looking at trying evaluate.

I think actually, she has some very reasonable points we need to consider carefully. And then other things I think that are left out of this (inaudible) not really.

DR. BELSITO: Okay. Well, since we've read everything then let's go to wave 3 and let's look at her points and the response. So we're on wave 3. So Ivan, why don't you take over the discussion?

DR. BOYER: What's the (inaudible).

DR. BELSITO: It's all wave 3. I just got it save as wave 3.

DR. ANSELL: Ivan's memorandum responded to the.

DR. BOYER: Right. So what I did for wave 3 -- actually, the comments from Women's Voices for the Earth came in last week toward the middle of the or so. And so we wanted to respond to them as quickly as possible. They're very extensive comments. There are eight specific comments in particular. So what I tried to do in wave 3 was to summarize, to sort of synthesize their comments. Then develop some post response to those comments.

DR. LIEBLER: Can I interrupt you just for a sec here and ask, are we planning to respond to her letter individually or specifically. With a document or we simply expected to take those comments into consideration during our discussion. In other words the CIR is going to generate a written response.

DR. BELSITO: I think we have to.

DR. BOYER: Well, we need to respond fairly quickly but we don't have to resolve every issue before we respond.

DR. BELSITO: We are going to respond.

DR. LIEBLER: This is a draft of a written response.

DR. BELSITO: Yes.

DR. BOYER: Exactly.

DR. LIEBLER: Okay. That's all I wanted to know. Thank you, you can go ahead.

DR. BOYER: So she did have some very good points. In particular, the fact that we really don't address nano particulates. We don't address those in our documents explicitly. And she refers to the Nazarenko reports of our (inaudible) so on. They used some, as she refers to them, very up-to-date techniques. And they are sophisticated techniques. They were interested in looking specifically at the nano-particle faction of whatever emanates from spray products and from loose powder products.

To some extent I think addressing some of those comments is just simply a matter of clarification. Maybe some elaboration that can go into the background document as revision and so on. I think a lot of it can be addressed simply by elaboration of that sort.

So as first cut, that wave 3 memo is what we produced, and whatever comes out of the discussion today and tomorrow is going to be incorporated. It's going to inform our response to Ms. Scranton. Even if it's, for instance, that we were taking her comments seriously and we're going to be investigating what we can do, further, by way of clarification – and by way of developing that document further.

DR. ANSELL: I think we're going to have to deal with nano particles separately. I think eventually we haven't gotten to that yet. Because they'll be other issues of (inaudible) related nano particles I assume.

DR. LIEBLER: I agree with you, I think that's actually one of the things that came out of Ms. Scranton's comments. they're very, very worthwhile for us to consider. I think we need to develop the nano particle part of our aerosol (inaudible). And it might not be ready to go with the version of the boilerplate that we're working on right now. And it sounds like data are beginning to appear that can be relevant but may not have all the data we need.

And the other question I have is, do we have any significant number of any nano-particle cosmetic ingredient materials that we're? I don't remember seeing any or much of any.

DR. ANSELL: The problem with nano as it (inaudible) is that nano is a regulatory term which is based on internal structure of particles. So a nano material is anything which has an internal structure in a nano range. But they aggregate and so from an aerodynamic standpoint, which is what we're interested in.

DR. LIEBLER: I'll grant you that. It's true that they aggregate but at the point when they're made or at least reduced and conceptually still nano. They haven't had chance to be sprayed out of a nozzle and aggregate or be mixed with some triglycerides. I mean, do we have ingredients that are actually nano materials yet.

DR. ANSELL: Carbon black.

DR. LIEBLER: Carbon black.

DR. ANSELL: Certain titanium and zinc.

DR. BELSITO: Yeah.

DR. ANSELL: Sunscreens.

DR. BELSITO: There are sunscreens.

DR. LIEBLER: Okay. So there are a few.

DR. ANSELL: But pigmentary grade because...

DR. LIEBLER: Is this something that's going to expand do you think?

DR. ANSELL: No. And these have undergone review by SCCS in accordance with European regulations. But there's very few actually facilities.

DR. BELSITO: But they're not labeled as nano particles.

DR. ANSELL: No. FDA has --

DR. BELSITO: There's no -- like if you had titanium dioxide, whether it's a nano particle or not. It's on the label of the sunscreen as titanium dioxide.

DR. SNYDER: There's no aerosol usage.

DR. LIEBLER: What I'm wondering is nano stuff a wave of the future for cosmetic ingredients that we need to prepare a boilerplate for? Or is sort of the exception to the rule and always will be?

DR. ANSELL: I believe more the latter. I think what came out of a lot of the inventories, is that these are old materials. Which have now been redefined as nano because of the attention. Carbon black's been used forever.

DR. LIEBLER: Right.

DR. ANSELL: But all of sudden now it's nano and had to be resubmitted. The titanium and zinc nano size materials in sunscreen date to the '80s. One of the complaints we hear about a number of these nano inventories. Is that, this is all old stuff where's all this new dangerous stuff that we've been told about. Some silicas a couple of polymers.

DR. ANSELL: I think we need to separate the safety assessment from the nano regulatory discussion and that's what FDA has done in their assessment. They conducted a very comprehensive review and concluded that there's nothing in size which suggests that nano size materials are more toxic, less toxic, or any different than the non nano size materials. And as such labelling per se would tell the consumer nothing.

DR. LIEBLER: So we do a boilerplate to have a consistent approach to a problem that recurs frequently. And it seems to me that given what I've just heard there's no point in making a nano particle material boilerplate, because we would encounter true nano materials infrequently enough, and their circumstances might be individualized different enough that we should simply address those as the particulars, no pun intended, as they come to us.

Because I was thinking operationally do we slow this down to bring in a nano anything component? It doesn't sound like we need to.

DR. BOYER: Well one thing to consider about that is that, in fact, the claims for cosmetic products, including spray products, that they contain nano particles, nano particulates, as a marketing strategy is on the increase. We're seeing more and more of these kinds of products advertised this way. And the Nazarenko papers in fact looked at some spray products and some loose powder products that had those claims associated with them versus -- they paired those up against equivalent products that didn't make those claims. And they did find nano-sized particulates, based on their particular method or set of methods, in those formulations.

So if we were to develop something general, it probably would be a matter of trying to address the claims, because we're certainly going to be getting questions about that.

DR. ANSELL: I'm not sure I agree that there's increase in claims in the cosmetic area. I think antibacterials, nano silver perhaps we're seeing more in swimming pools, but not in cosmetics. In fact I think --

DR. LIEBLER: But from what you've said just now, even though there may be more marketing claims of nano materials as the Nazarenko papers purport to detect these, they were using a detection methodology that is highly capable of detecting small diameter particles. And, in fact, was even biased towards assessing distributions as we'll come to in a moment. But I'm just trying to determine if we need to spend the time to develop a nano boilerplate within the aerosols boilerplate.

I guess I'm hearing, my two cents worth would be to not do that right now.

DR. ANSELL: I don't know what you would say.

DR. LIEBLER: Yeah, right.

DR. ANSELL: You know if it's nano size it still has all of the obligations to demonstrate safety.

DR. BOYER: Well some of the things we could say, for instance, is that even though there are nano particles, within the defined size range, may appear in some products, that, even based on those Nazarenko papers they do not represent a whole lot of material. You could say something about the studies that have been done to examine the inhalation and deposition of nano particles in the respiratory track and shown that, even though you have very fine particles, it doesn't represent very large mass in total, and so you get very little deposition.

In particular in the pulmonary region because they are so light for the most part that they're simply going to be exhaled. So it's unlikely, given of course consideration of the chemical properties of those materials, it's unlikely that there's going to be any significant deposition in the lungs of particles of those sizes.

I mean there's some research out there that we can incorporate into maybe a short paragraph or so that could be helpful.

DR. LIEBLER: So one thing is, the analytical technique that they point to that picks up these small particle sizes, it seems to me that it might be picking up the low end tail of distribution with a measurement capability that wasn't previously available. So you're seeing something that was presumably always there, but now you're actually seeing it.

DR. BOYER: Correct.

DR. LIEBLER: Which again isn't really a nano phenomenon. It's not like the ingredients are nano manufactured to be nano entities and then there are brand-new new chemical entities that are coming into our radar. So I think we can deal with that issue without doing any new boilerplate.

DR. SYNDER: So why not invite him to come give us the talk?

DR. BELSITO: Who?

DR. SYNDER: Dr. Nazarenko. He's the expert in measuring particle sizes in cosmetics and his data suggests that there are nano particles in cosmetics that aren't --

DR. ANSELL: I'm not sure what he used. Was it -- I mean part of the problem is that, the materials requires such extensive work up, is that the materials they end up assaying with the analytical methods have very little to do with what they looked like in the formulated products.

DR. BELSITO: Right.

DR. ANSELL: But I honestly think putting the nano term in here would be inflammatory. Particularly since we would then just have to dismiss it and on the whole when we've come up with these cases where there's a cancer report, which we don't believe is unreliable, we don't report it as being a terrible study and then try to dismiss it. We say we're just not going to include it.

DR. LIEBLER: I think we're probably going to circle back to this issue again. I want to come back to the general comment that Ms. Scranton made, which was the first bold font thing you had, which was really

the Epidemiology association of respiratory disease in hairdressers and beauticians. To what extent do we need to deal with that?

DR. SYNDER: That's a workplace issue. Same thing with the formaldehyde we dealt with, right. It's a workplace issue.

DR. LIEBLER: I'm not really familiar with the epidemiology on this honestly.

DR. BELSITO: Well it's the same as the hair dyes where there's some evidence of bladder cancer in hairdressers and barbers. And we say that it's not our purview, that they're exposed to multiple other chemicals, that it's not our purview to regulate workplace exposures. That would be OSHA. But from the data that we have in consumers, there is no strong data. The data is not strong. It's not conclusive. It's not pointing in any one direction that can tell us that this is or is not a concern. That the data seems to indicate that for beauticians there may be for bladder cancer, but of course one of my questions when we're looking at, and we're going to go to hair dye again with some new studies and I didn't have time to actually read through the studies, but how well are these controlled for confounding factors. Because we know that beauticians smoke more than the average population. And smoking is a bladder cancer risk. So how well do they control the beautician smoking habits, how well do they control the breast cancer? We know that breast cancer is linked to diet. We know that from the Japanese studies when the Japanese moved from Japan to Hawaii their incidents of breast and colon cancer goes up astronomically and it's thought to be related to the fat in their diet.

DR. LIEBLER: So this grant raises asthmas and respiratory disease. So I think we need to respond and we need to just think about the responses here.

DR. BELSITO: Well these people are also getting exposed to formaldehyde. They're getting exposed to acrylates in nails that are being done at salons. They're being exposed to a million things.

DR. LIEBLER: I don't really know how strong the epidemiology was, but I thought if it would be really strong it would have been something we had already discussed in great depth. So let me just cut to my comment on this, Ivan, you have a couple of pagers where you're taking quotes from various sections of the boilerplate. But it's not until the end of the second page of the draft letter that says, "as noted the epidemiologic studies." I think the only part that we can respond to begins right there. All the stuff that comes before it about particle sizes and factors that dictate toxicity, that's not relative to her general comment. Her general comment was on the epi. So I think the response should be on the epi and why and whether to what extent we deal with that.

And this other stuff it just gets in the way. It's not relevant to her question.

DR. BOYER: Basically her general comment I think was meant to summarize all of her specific comments and boil it down to just two sentences. So all those quotes really were an attempt to address the first sentence in her general comment and then move on to her second sentence which addresses the epidemiology.

DR. LIEBLER: Instead of laying out all of this stuff, you could simply say, you know, the boilerplate document is an attempt to describe the features, the chemical properties or physical features of particles in cosmetic products that dictate that. We will deal with those in the following responses to side comments. Rather than putting all this stuff up front, because it just.

DR. BOYER: I don't want to belabor it, but the stuff up front was really an attempt to make the case that in fact the particles sizes aren't the only thing the panel considers. And that, in fact, when it's evaluating the potential for an incidental inhalation to produce adverse effects, it considers the chemistry of the particles, their reactivity, their potential to cause sensitization and so forth. Which I think was a point that it wasn't clear from her comments that she grasped.

DR. ANSELL: I think a paragraph to that end is --

DR. LIEBLER: I think it's correct but not succinct. It needs to be succinct.

DR. ANSELL: Like two paragraphs.

DR. LIEBLER: You could deal with this in a paragraph or two and then cut to the end. Because I think the response that you have on the epi is probably the best we can do.

DR. SYNDER: It's not a question, Jay, so that part of her critique was that the spray and powder sample calculations were not appropriate. And those that were referenced in the document in our boilerplate were given to us by the Science and Support Committee. So have they gone back to consider her argument that they're not? We can't make an argument for something that we didn't generate. We just utilized that data that was given to us. We didn't generate that data.

DR. BOYER: What Carol made clear in the other meeting with the other team is that the Science and Support Committee is going to have a chance to review this along with all of the boilerplates. They're meeting in May.

DR. LIEBLER: The other thing, Ivan, I would suggest that when you're summarizing, particularly the general comment, rather than you paraphrasing her comment, quote her comment word for word in quotes. So that you don't create the impression of misrepresenting if she feels that you haven't considered her actual words, which we actually have, but you don't want to give the impression that you haven't. So I would just take that paragraph from her letter and put quotes on it to put that right there in place of the new paraphrased version.

So do you want to go on to specific comments?

I think her specific comment Number 1 was basically saying that deodorants have a greater fraction of small potentially-respirable particle sizes. And that the language that we provide doesn't take that into consideration enough and that the sample calculations we use for different types of sprays, including the deodorant spray used was dependent on an assumption of a 5% respirable particle, and she said that deodorant spray aerosols have a median aerodynamic diameter of 10 microns with a coefficient of variation of 3, suggesting that half of these particles are within the range considered to be respirable; i.e., below 10 microns.

And she suggested 5% might be a typo, that it might be 50%. And then you basically follow that this calculation is based on the assumption that 5% of the particle distribution consisted of respirable particles. This 5% comes out of the PCPC memo which wasn't available to her, or at least she didn't know that it was available to her. And so she's working not from that assumption. And I thought that she's basically saying that your assumption of 5% respirable is at odds with the median 10 microns and 3 coefficient, which would give you 7 to 13 basically. Your pointing to the estimate of 5% respirable from deodorant spray seems like circular reasoning. So you're saying this is our assumption was started with, but the assumption isn't necessarily justified. And in fact she's actually pointed out that you've already said ten plus or minus 3, plus or minus 30%, which is it? It can't be both. And that's one of the points that I thought was a reasonable point. That's unresolved as it stands.

DR. BOYER: Well it is based on data that was presented in the European guidance or evaluating cosmetics including aerosols. And it is based on a statistical kind of analysis. It was more or less an informal analysis and sort of mentioned off-hand. And it is based on only three samples. So you expect a coefficient of variation of whatever is going to be huge just because you have very few samples and it's not clear either to what extent that those samples are representative for deodorant sprays in general. So that was the argument.

And then the other part of the argument is that, even if you assumed 50%, the results that you get are really not that different from when you assume 5%. I mean it is circular. We've taken a 5% value from PCPC's analysis and I would imagine that if they were to attempt to respond to that particular comment they might do something like what I did as first draft. But one option might be simply to redo the calculation and assume 50% and then explain how that is extremely conservative.

DR. LIEBLER: I think that's more reasonable. It sounds like, from what you've just described, that the chain of evidence for supporting data, modeling and calculation is relatively weak.

DR. BOYER: Correct.

DR. LIEBLER: By any reasonable standard in this area. And so when we have pretty weak evidence, I think you need pretty conservative assumptions. And I think it would be reasonable to revise our boilerplate by using the more conservative assumption in the calculation. I don't know what you all think about this.

DR. KLAASSEN: I don't have any solid statements either, other than this 10 microns has been around in the scientific community for at least 35 years. Maybe much longer than that, but that's kind of what it takes to get it down. And I don't know how good the data was, but everybody's kind of used that. And it's probably not that great. So I think you could kind of reply, this time be a little soft and say that traditionally toxicologists have used this but if there are these later papers with deodorants showing a smaller median mass diameter, maybe we need to reconsider this and make it a little smaller. Although we'd sure like to see more data on this area. You know, kind of half-way answer it. And then we can think about what we want to put in our new boilerplate, want to be more general. I guess I would like to know what goes on back in the toxicology data 35 years ago that everybody said 10 microns. I know I summarized that data 35 years ago and it was 10 microns. What I reviewed and what I remember from then it does not exist here anymore. But I think there are more than just a couple three studies that have kind of concluded this 10 microns. And it would be nice to see all of the papers that have done this before we change our boilerplate.

But I think for her I would just kind of generalize it like that. The committee is looking into this, are you aware of any more papers. It'd be nice to have a larger n to have some confidence. Just because this one paper recently said that it's a little smaller than that with deodorants, but what's specific about deodorant? Is it something in the deodorant that makes it a smaller particle than hairspray? I mean what's going on here. What's the chemistry here?

DR. BOYER: Right. And some of those questions are probably best answered by industry if we could get some additional information from industry. Our document specifically addresses the fact that we really could benefit from this kind of information. Is it something about the spray nozzles that's different on deodorant versus a hairspray for instance? We don't know. There are just a lot of questions.

DR. KLAASSEN: And there also could be a big difference in all the stuff between dry particles and wet particles, let's say. Most of the things that we use are what I would call wet particles.

DR. BOYER: Although there is some information that even sprays that come out of the nozzle wet, within less than a second or so the volatiles, including water, pretty much evaporate from most particles, so you'll end up with something that looks like a solid particle.

DR. KLAASSEN: No kidding?

DR. BOYER: Yeah.

DR. BELSITO: I guess since we're on deodorant sprays you made a comment, Ivan, about how they wouldn't be expected to be in the breathing zone or something to that effect. And I had an issue with that because I don't use spray underarm deodorants, but I think most people who do probably go like this and it is right into your breathing zone. Because they're looking at where they're spraying it and their head's here and their axilla's there. So I disagree with that comment. And the other comment that she made that really resonated with me is I thought that when we were looking at aerodynamic size of powders are references are 1979, that's the most recent reference. There's got to be more recent data in the literature than that.

DR. BOYER: There's not a lot. In fact the Nazarenko papers that she found were really the only

substantial papers that have come out since then that speak specifically to this issue.

DR. BELSITO: But we didn't reference those.

DR. LIEBLER: The Nazarenko papers, we didn't reference those.

DR. BOYER: We didn't reference those.

DR. BELSITO: For powders.

DR. BOYER: That's right. We didn't reference them for powders.

DR. BELSITO: I mean I think we need to. We need to update. I mean that's pretty bad that 40 years is our last reference on particle size for powders.

DR. LIEBLER: I actually was struck in reading this by the analytical challenge of characterizing the particle sizes. Because we're trying to know about particles that are floating through the air, and slowly settling and then going down our airways maybe or maybe not. So we're trying to do that, but there's no like magic camera. Well they're trying to do that, but that's not ready for primetime. Literally take a microscopic scale photo image of what we want to observe. So then we're left with two options. One is to let them settle on a surface and image them on the surface, or to capture them in a solution and to image them in solution. And you pointed out those are the two things. And you kind of hinted I think at some of the potential errors associated. Now you're looking at particles that are interacting with the surface and maybe with each other. And in the solution approach you're looking at particles that are now being re-solvenated and maybe having their size changing because the solvent that was part of the particle is now exchanging with the solvent you dissolved them in to try and get the measurement, and it may be one of these things where the nature of the measurement process makes it impossible to actually measure the true value of what you're trying to measure.

DR. KLAASSEN: All of this air pollution, but the 2.5 is that this unit?

DR. ANSELL: Yeah. I mean the major exposure to the small particles in the household come from vacuum cleaning and using gas-fired appliances.

DR. KLAASSEN: What I'm getting at, there's tremendous science that 2.5 micron, I think it's the same units as your 10 here, that make us live a lot less time. And they're killers. And that's all come about in the last 20 years. So I'll bet you the technology in this whole area must have changed tremendously. So how does Beijing determine how much 2.5 --

DR. LIEBLER: PM 2.5.

DR. KLAASSEN: -- PM 2.5 that's in the air every day? Or how do they do it in Washington D.C. So I'm sure the technology today to do that is very different than 1970. I don't know how they did it in '70 either.

DR. LIEBLER: I think you've got a really good point. Sorry, I was rambling. Basically to cut to the key point I think for us is that whatever boilerplate we end up with, should also describe where these numbers come from. And these numbers come from measurements. And the measurement technology is certainly (inaudible). And I think it should consider the great example Curt just mentioned. Even though those aren't measurements of cosmetic products or deodorant sprays, they are particle measurements. What is sort of the standard in the field for measuring particles, particularly in a context of tox, I think it's quite relevant. And I would like to see in a boilerplate a little bit of background. Maybe a paragraph or two on the analytical methods and the sources of uncertainty in the measurements. Because if we had three references we could point to, to respond to Ms. Scranton's comments with a definitive yes, you're right here are the references; no, you're dead wrong, here are the references, we could do that. But we can't. And so our hands are waving.

And I think it's up to us to identify what are the limitations of our knowledge right now? What do we really know? What do we really don't know. Even if we've been relying on numbers with some weaknesses inherent in them, now's the time to identify our weaknesses and see if we can minimize them as much as possible. But these were really good questions that I think identified for me what a gap in this boilerplate is. And one of them is what is the analytical technology used to get the numbers that we're relying on.

DR. KLAASSEN: I would say to her basically thank you for bringing this up. We're going into this in great detail and blah, blah, blah. Rather than trying to defend what we have been doing, because we don't know. It's a good time to look at this.

DR. BOYER: I agree. But just to elaborate a little more, the PM 2.5, and that is microns, PM 2.5, PM 5, these are particulate fractions that have been measured in air by regulatory agencies since the 1970s and it was established that those particles represent a special threat because they're respirable. So I don't know whether or not the analytical methodology that was used back in the 70s is the same as they used now. But those are the particles that the regulatory agencies are concerned about.

The other thing is that it doesn't necessarily reflect what comes out of cosmetic products. So you've got this whole other issue as to whether or not that methodology that they used to enforce compliance with regulations, air pollution regulations, are applicable to cosmetics that come out of a spray can. That's actually a big gap in our knowledge.

We did have someone come in and give us a presentation on this, a Dr. Rothe some years ago. And she was able to answer some of these questions, but only in a very general way. We weren't able to get any specifics that would help us really nail this down. That's why there is some ambiguity even in our write up, simply because we don't have that information that's specific for cosmetic products. And I think it may be the case that it's really industry that needs to give us some insight, some additional detail.

DR. LIEBLER: I think that might happen if we get into a situation where we say there's insufficient data to support safety. Because industry's not naturally curious. They don't want to generate data they don't have to for good reason. But I think the idea of characterizing the analytical methodologies and their limitations and shortcomings that were used for the numbers we've always relied on, and that are used in this much larger field of environmental health, inhaled particles, it's worth at least investigating and comparing those. If it turns out they're basically the same methodologies give or take that we use on these particles, then we'll know at least we're using something that's considered acceptable standard in the field with its caveat.

And, in fact, there probably is literature by somebody on the potential errors in measurements of air particles, air particulates, and what are those sources of error that might inform our interpretation of the data that we've always used. So I think that this draft, this boilerplate is a good start. These questions are really helpful in addressing some weaknesses. And I think invalidated assumptions or at least not well enough documented assumptions that it allows us to do a nice sharpening up. I don't think we're going to approve a final boilerplate tomorrow.

DR. KLAASSEN: I think there's another thing in our boilerplate that we've kind of not looked at seriously enough, is that we need to get smaller than supposedly 10 microns to get down into the alveoli so it's absorbed into the general circulation. And larger particles deposit in various parts of the respiratory tract, and we never kind of say anything about that.

DR. BOYER: The document actually does go into some detailed discussion of that.

DR. KLAASSEN: But it's not in the short boilerplate, I don't believe is it that we put in the paper?

DR. BOYER: No.

DR. KLAASSEN: Maybe it should be something.

DR. BOYER: Actually, when it's applicable the framework does provide the panel with some suggested language for incorporation.

DR. LIEBLER: And I think the boilerplate's actually really pretty good as it is. But the weakness I think we've identified here is we have a tendency to simply say well, here's our so few particles will be less than 10 microns, and therefore be respirable, that it's not a significant hazard consideration for us. And she's saying now wait a minute. Depending on the types of spray and your own numbers, that can't be true. So you can't just blow that off. So it might turn out that we might end up making the same conclusion, but we'll need better numbers to do that. And that's the thing.

So I think it's the strength of the numbers that we're using and that's what it all hinges on.

DR. BELSITO: She also says that the numbers that we're using were generated only off of two of three specific products.

DR. LIEBLER: Which would bother me.

DR. BELSITO: Right.

DR. BOYER: Well the other thing too is that 5% respirable from the spray, hairsprays and so forth, that comes right out of Dr. Rothe's presentation in answer to a question. And we don't have the specifics about the methodology that was used to come up with that 5% figure.

DR. ANSELL: It wasn't just particle size, it was particle size, it was duration, it an overall exposure calculation.

DR. BELSITO: Right, which is in the document.

DR. ANSELL: I think all these are good points and worth polishing. But I would hate to go back and start challenging cornerstone foundations and look to redevelop deposition data on the basis of an assumption --

DR. LIEBLER: I'm not going there. I simply want to make sure that one key number isn't bullshit.

DR. BELSITO: Well I think we are re-challenging the foundations. We're saying that there's some new science that hasn't been brought in and we need to look at it. I mean I would like to see the more recent data on powder formation. I think she has a good point that we're basing our assumptions only on a couple different products that were tested and not on a range of products. I think she has a good point that the size of underarm deodorants, which of all the sprays are probably more in your breathing zone than a hairspray, because when women use a hairspray they're using looking in a mirror going like this. And when you're using an underarm spray, you're usually going like that. So I think she raised a lot of very valid points. And it may be that we continue to use our foundations as our foundations, but I mean these are very valid points. In the end we're responsible. I'm responsible. Every voting member or the panel is responsible for saying that we thought that it was safe despite lack of significant inhalation data, because we didn't think it was going to be respirable. And this woman has raised a lot of questions in my mind as to whether that data is in fact totally correct, or that assumption that we've made is totally correct. And it may be. But I do think we need to relook at it.

And relook at it more than just in terms of yes. We need a response to her now, and I agree with what Curt said. It should be thanks for bringing this to our attention. We are looking into it. We don't have all the answers. And I think we need to begin to look into some of those. Perhaps grab 10, since the weakest link seems to be underarm deodorants, grab ten off the shelf and look at the range of --

DR. SYNDER: Worst case scenario.

DR. BELSITO: -- particle size. Rather --

DR. SYNDER: There are two issues here. One is the particle size within the final formulation, but then there's also the exposure ratio. And then how much of the product is actually getting in the respirable zone. Because it's always about exposure.

MR. 8: In the long run we're probably saved by the fact that you don't spray your underarm for two hours a day. I mean as far as total exposure. I mean they only do it for ten seconds, so you don't get that much. But we still got to have solid numbers I think.

DR. SYNDER: And I think I remember seeing in that original document exposure data calculating on breathing zones.

DR. ANSELL: It dropped to zero in minutes.

MR. 8: One of the best inhalation tox groups in the country is down in New Mexico. I wonder --

DR. SYNDER: Not anymore.

MR. 8: Oh yeah?

DR. SYNDER: The Global Inhalation Institute is now a CRO basically. It no longer really does much inhalation.

MR. 8: Who is doing inhalation?

DR. SYNDER: I don't know.

DR. LIEBLER: That used to be EPA, at Lovelace, there were like three or four groups that were.

MR. 8: In Rochester.

DR. LIEBLER: The end of an era.

DR. BELSITO: I mean who's doing our respiratory stuff for -- that guy's moved up to Rutgers too?

DR. LIEBLER: Greg [inaudible]

DR. BELSITO: Yeah, he's up at Rutgers.

DR. LIEBLER: He's doing basically biochemistry, molecular biology, cell biology of the respiratory system area responses to chemicals in slices.

DR. BELSITO: No, but I'm just saying that these people here were at Rutgers. He's at Rutgers. So I'm wondering if, Rutgers if just up the road, what kind of respiratory program have they put together at Robert Wood Johnson?

DR. LIEBLER: And I don't know. This is not so much respiratory per se, the issues we're talking

about are actually particle behavior and particle measurements.

DR. BELSITO: Okay.

DR. SYNDER: How many are in those papers? I didn't really those clinical papers.

DR. ANSELL: It's classic analytical methodology.

DR. BELSITO: They looked at a bunch of different grouping like silver, and I think they only did a couple in each, or maybe one in each category essentially.

DR. SYNDER: It was nano focused. That doesn't have very much relevance to us.

DR. BELSITO: Well but they did nano and regular. So they did a nano product and a regular product. And what they found was there really wasn't a lot of difference between the two.

DR. LIEBLER: So if we think ahead to how we would use this, we most typically use this type of information, our particle size information, some of the features we think that attribute to having particle sizes mostly above 10 let's say, as being this is not a significant concern for respiratory toxicity with this ingredient. But if we actually have a model that says a certain fraction of the ingredient that's applied that's used by the consumer is actually accessible to the consumer, then that becomes part of our framework for some sort of a risk calculation or a risk assessment that allows us to make a decision other than don't worry about it.

And I think in a way that's our big point of (inaudible) is you need to do better than just don't worry about it it's more than 10.

DR. ANSELL: I honestly think our boilerplate is better than that. That it does look at exposure. It also looks at duration. It compares that against workplace standards and concludes that there are substantial safety margins.

Now I absolutely agree that we could do a better job, but I think it's better than that. We're not relying on ancient science. We just finished a paper in 2015 on analytical methods or assessing size and there's nothing there that was earth shattering. It's flow methods. It's photographic methods. It was sedimentation methods. So I think we can precise this and be helpful, but I think the data we have is reasonable and reliable.]

DR. LIEBLER: She says it's not.

DR. ANSELL: She does. But she starts with the basis, I think --

DR. LIEBLER: She uses some of our numbers.

DR. ANSELL: That please are sick and therefore they must be exposed. So she starts with a conclusion.

DR. LIEBLER: That's the epi. That's the epi issues, which I think is a separate issue. And I think we do have a model. We do have exposure data to some extent. And we do have particle measurements. We have all the things that you mentioned. But any of those numbers, if they're wrong, could lead to erroneous conclusions from the model. Garbage in, garbage out even with a good model. And I think it's just up to us to make sure that it's not garbage in.

MR. 8: That's what we're saying, we want to net zero more convinced that this 10 micron that we've always believed in is what we should still kind of believe in.

DR. BELSITO: I think the 10 microns is probably to be believed in from at least my reading.

DR. LIEBLER: That's correct.

DR. BELSITO: The thing that we need to know is particle size.

DR. LIEBLER: What's the distribution like.

DR. BELSITO: That's the distribution. And I think that probably the first step would be to ask industry, or someone to pull off the shelf 10 different underarm sprays, which seem to be the weakest link, and measure them using modern technology and show us the range of particle size that comes out of those.

Because if we're looking at chemicals that don't penetrate the skin but penetrate mucosa, which we often times do, and we find them safe because of lack of penetration and they're used in an underarm deo spray, and I can't think of what a chemical would be, but they are and there are particle sizes that are getting down to potentially respirable, then we would want inhalation tox studies for those. Or we go insufficient for deo use.

So I think that we do need a little more data here.

DR. LIEBLER: Methyl silicon, they're there. I mean propylene glycol, and methyl silicones, and whatever else is a cocktail that's your deodorant. I mean that's all stuff other than the silicates. Now those are all things that are being sprayed out on people. So if we can generate, I don't know who would generate this data, somebody's got to get paid to do it. I'm just trying to think how we could have some leverage because industry's not just going to do this. It's not like RIFM where there's some budget to do some research. I don't know how this gets done. But let's look at --

DR. BELSITO: Is there some kind of consortium, like there is the (inaudible) consortium of --

DR. ANSELL: I'm not sure that we don't have the data. I mean we're just speculating that it's.

DR. LIEBLER: Maybe we do. It's not that the 10 micron limit of what goes down respirable is the issue. It's what is the distribution of particles within these products that is below that and at what point do we go wait a minute this is a potential problem and then how do we quantify our response to that.

DR. LIEBLER: That's the exercise we did a couple years ago. Let's pull it back out and take a look at it and not assume that the data's old and unreliable.

DR. BELSITO: But I don't, I think we are assuming the data's old and unreliable. I think that the issue is that she's right. We only looked at a couple of products and I don't even know that we looked at underarm deodorants and these sprays as opposed to pumps.

So my point is I think we should get a little bit more representative sample from the weakest link. Make sure that we have sampled underarm deodorants have a sense of what the particle size range is in those products and then go from there. I mean at this point I don't know what else we need.

DR. LIEBLER: Could we have a session in an upcoming meeting, have a couple presentations on this, on the powders?

DR. BELSITO: Yeah. I mean I would like to invite the lady who gave us the first go around and the gentleman from Rutgers.

DR. LIEBLER: Nazarenko?

DR. BELSITO: Yeah.

DR. LIEBLER: I don't know if it was a gentleman or a guy or --

DR. BELSITO: I don't know, but Nazarenko from Rutgers. Let them both present their viewpoints and see where they differ, and see if we can get them to clarify their differences.

DR. LIEBLER: Right. I think that could be really useful. Let's talk about that tomorrow.

DR. BELSITO: That's what I would like to do and see.

DR. LIEBLER: Who's presenting on this?

DR. BELSITO: Ivan.

DR. LIEBLER: Oh, it's not you [or Jim 14:05]

DR. BELSITO: No, I think it was said to be me but I mean it's silly for me to lead this discussion reports advancing priorities. No, Marks, boilerplates.

DR. LIEBLER: Marks, okay so we can respond to whatever they say...

142d COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

Tuesday, April 11, 2017

PROCEEDINGS

DR. MARKS: The last draft revised boilerplate we had is on aerosols. And Ivan sent us a memo with this on March the 17th. That's in the Administrative tab. Page 22. But subsequent to that, we received a wave 3 with a letter from The Women's Voice, expressing a number of points about the boilerplate. Our team felt the boilerplate was fine. We felt though, that a letter raised the issue of particle sizes and distribution. And nanometer-size particles. Are they (inaudible), etcetera? So, we suggested that the manufacturing industry respond to us. Perhaps at presentation by an expert on these issues and aerosols. And, likewise, the PCPC Science and Support Committee address it too. Did I paraphrase that correctly Ron Shank?

DR. SHANK: Yes.

DR. BERGFELD: Comments?

DR. BELSITO: Yeah. So we thought this was a very thoughtful letter that should be thoughtfully responded to. And, essentially, thanking her for bringing these issues to our attention. We also thought that she had some very valid points that we had only looked at a couple different-sized distributions from pumps and sprays that may not necessarily be representative. That the deodorant seemed to have the smaller-size materials. That, particularly, in terms of the size of powdered materials, our references were quite old. 1979. And that we should look at updated references. We actually thought that it would be nice to invite Dr. Nazarenko, who was the individual from Rutgers whose paper she quoted. As well as, I just blanked on the name of the woman who gave us the original presentation on aerosol diameter. If you can help me out?

DR. BOYER: That was Dr. Rothe. R-O-T-H-E.

DR. BELSITO: Okay. Dr. Rothe, both to come here and present their information on their --

DR. BERGFELD: Science.

DR. BELSITO: -- feeling, so to speak, as to what the particle-range size was in these pumps and sprays. Specifically deodorant sprays. We also thought it would be nice if someone, and we didn't know who, would go out there and just purchase off the shelf, the worst case, or what appears to be the worst-case scenario, which would be underarm deodorant sprays. And do some analysis on more than just two products, to get an idea of what the range and size of respirable products are.

I did have one comment in the proposed draft response in wave 3 at this point, that had to do with the fact that use of underarm deodorant sprays would not necessarily result in, I forget how it was phrased, in the respirable zone. But my impression is that when people do an underarm deodorant, they go like this. And it actually, I think, could be quite respirable. And probably even more so than, you know, hair sprays. Because, when I watch the women in my life do that, they usually go like this and spray on top.

So, but I would like a little more information on molecular or size of deodorant sprays. And I'd like to hear more from Dr. Nazarenko and Dr. Rothe on this. I think that the current information we have is as good as we have. But we should look for some updated stuff on powders as well.

DR. MARKS: Ivan, in your review, did you see anything from the EU specifically? Because, what I notice is underarm deodorants in Europe are much more heavily weighted towards sprays, than the solids that we have here in the U.S. It's very interesting. When I go and look at the grocery market shelves in the Netherlands, they're dominated by sprays, not by the gels or sticks or whatever.

DR. BOYER: In fact, the limited data that we do have is from the Netherlands. And the data on which we based the observation that deodorant sprays, in particular, have particle-size distributions that extend fairly lower-down the scale than hair dyes, hair sprays for instance, that actually comes from a guidance document that was prepared in the Netherlands.

DR. MARKS: Interesting.

DR. HILL: I also had made the comment that I didn't -- I don't have a grasp of in terms of across the cosmetic industry, how many cases we have for people are actually formulating purposefully nano sized particles. And I also wanted to make mention that there's a group from FDA looking carefully at nano particle areas. And that one of the representatives has been here at more than one meeting. So, possibly, if we had a session, to talk about this, if we can find out whether they're actually looking at anything cosmetic in that context.

DR. BERGFELD: Nakissa, do you want to comment on that?

DR. SADRIEH: Yes. Actually, I was doing some -- in CDER, I was doing research on nano particles. And mostly drug products.

DR. HILL: Mm-hmm.

DR. SADRIEH: And then, we were looking at dermal absorption sunscreens. For the most part, those were other types of formulations. Nano crystals that are used as well in other types of drugs. I also did one study looking at spray-sunscreen products. That was, I sort of started it when I was in CDER, and I've finished it now. I haven't written it up yet. But, I also was going to do a study on cosmetic inhaled particles and powders. So, I haven't really gotten to that study yet. But, we do have an interest in looking at sort of effects of nano particles in, you know, in inhaled products that are regulated by the FDA.

DR. HILL: I mean, in the drug industry, there are people intentionally creating nano particle formulations for, and it's, I mean, it has exploded in the pharmaceuticals industry in terms of the work that's being done. And that will end up having numerous consequences. But I didn't really have a sense of, in terms of other than putting something flashy on the label, nano delivery or something, how much activity in the cosmetic and personal care product.

DR. SADRIEH: Right. We don't know, I mean, obviously we don't know what products people are making --

DR. HILL: Yeah.

DR. SADRIEH: -- and since we don't have any idea about that.

DR. HILL: We're just looking at ingredients, but --.

DR. SADRIEH: Right. We're looking at, well, I think the first thing that we'd like to know is actually, are there measurable nano particles?

DR. HILL: Mm-hmm.

DR. SADRIEH: -- in cosmetics.

DR. HILL: Yeah.

DR. SADRIEH: That's what I don't know right now. And so whether they're making it intentionally or not, that's beside the point.

DR. HILL: Yeah.

DR. SADRIEH: Because if you're getting exposed to it, you're getting exposed to it. So, you know, if it's there and it can be measured, then the question is, measuring them is also a difficulty, because you have to figure out the methodology that you use. And oftentimes, you have to use probably more than five, six different types of methods, in order to be able to actually determine what the particle size distribution is.

So, I think, you know, knowing whether there are products that are formulated that contain nano particles is the first step. Then step number two is, are these actually, you know, where would these be deposited? And then, what would be some functional effects that they might have in the, you know, respiratory system? So, there are a number of sort of questions that we have to ask.

And then, sort of kind of move forward. The first thing is really characterization. Because if we don't really know what it is that we're evaluating, then I think it's worth us trying to figure out what the biological effects, you know, are going to be. So, we're kind of at the stage where we're trying to sort of do --. Now, for the sunscreens, we've done a little bit more. But, you know, we're still working on that. And we do

have an interest.

But again, as I said, I mean, having worked a little bit on the nano particle issue in CDER, you know, the fact that it's nano doesn't, by itself, make it all of a sudden, you know, different. It's, you know, it's chemistry at the end of the day. So, you know, the particle size happens to be smaller. It doesn't really change the chemical identity of something. But it does increase, or change some of its physical chemical characteristics, because now you have more surface area to be able to have, you know, chemical reactions happening. And so, that may be the novel aspect.

But again, they are also doing formulation, because so many things can happen during the formulation. So, the particle, what happens with the particle, may or not be relevant, because in the formulation, it might be completely different based on whether it's aggregated or agglomerated and/or agglomerated. You know, so I think that there are a number of factors.

I don't think that it's going to be -- there's going to be a way to kind of like answer the question about nano particles in a generic way. Because, depending on what type of nano particle it is, whether it's a soluble one or whether it's an insoluble one, it's a metal or organic. Or, you know, it's going to have a lot of different characteristics and properties. So, that's what has to be evaluated. So, the bottom line is it's not simple.

DR. HILL: No. I know. That was also my contention.

DR. BERGFELD: Thank you very much.

DR. MARKS: I want to ask if there's anybody (inaudible).

DR. BERGFELD: Why don't you do that?

DR. MARKS: Yesterday, I asked if there was anybody from the Women's Voice for the Earth within the audience, who wanted to comment. There was nobody. I just wanted to repeat that today to, so give the public the ability to come up if you were shy. Apparently not.

DR. BERGFELD: Mm-hmm.

DR. MARKS: Okay.

DR. BERGFELD: So, there's a bit of work to do on this boilerplate obviously. And, I want the clarification to occur. And I think the idea of inviting guests who have knowledge in this area, is very good for us. And obviously, to have the FDA participate would be excellent. So, more to come, so to speak. But, in response to the women's environmental group, Voices, I guess. I forgot how they go exactly.

DR. MARKS: Women's Voice for the Earth.

DR. BERGFELD: Voice of -- Women's Voices for the Earth. We will be responding. And we will be stating in those areas that need clarification that we were getting back to them regarding that specific question. So, thank you very much Jim. And thank you Ivan. Thank you very much. Excellent response...

COSMETIC INGREDIENT REVIEW

CIR Precedents

Aerosols

8/2017

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

Sprays/Powders

Update 8/2017

BACKGROUND

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

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

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

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

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

There is broad scientific consensus that the probability of penetration of droplets/particles with $d_{ae} > 10 \text{ }\mu\text{m}$ into the pulmonary region is essentially zero.^{1,5,11-15} Thus, only droplets/particles with $d_{ae} < 10 \text{ }\mu\text{m}$ are considered to be respirable. This is a conservative assumption because a d_{ae} of $5 \text{ }\mu\text{m}$ or less is often reported in the scientific literature as the threshold below which droplets/particles can reach the alveoli.^{1,16} In addition, there is consensus that droplets/particles with $d_{ae} > 15 \text{ }\mu\text{m}$ are deposited almost exclusively in the nasopharyngeal and bronchial regions of the respiratory tract, and that healthy people will clear particles with $d_{ae} > 7 \text{ }\mu\text{m}$ from these regions within 24 hours through mucociliary action.¹

Particle size distributions are product specific. Numerous factors determine the initial size distribution of droplets or particles released from a spray product, including the product formulation (e.g., volatile or nonvolatile solvent), propellant, can size, and differential pressure through the nozzle for

propellant sprays, and formulation and nozzle characteristics for pump sprays.^{1,17} After release to the air, the particle size distribution can change rapidly through aggregation, agglomeration, sedimentation, evaporation of volatile components, or hygroscopic absorption of water.^{1,8,9,12,18,19} For example, all of the water and other volatile solvents and propellants in droplets with $d_{ae} < 40 \mu\text{m}$ will evaporate within 1 second of release from a spray can, so that the remaining particles will contain non- or low-volatile constituents (e.g., polymers with little or no biological activity in hair sprays).^{1,18,20,21} Accordingly, a wide spectrum of particle size distributions can be released from cosmetic sprays.

Both pump sprays and propellant sprays (also called "aerosol sprays") produce aerosols, but the aerosols from propellant sprays have larger fractions of respirable droplets/particles than aerosols from pump sprays.¹ For example, the median d_{ae} of the airborne droplets/particles of pump hair sprays range from $60 \mu\text{m}$ to $80 \mu\text{m}$.^{1,17,18} Typically, $< 1\%$ of the airborne droplets/particles released from pump sprays are in the range considered to be respirable (i.e., $d_{ae} < 10 \mu\text{m}$).¹⁷ In comparison, the median d_{ae} of the airborne droplets/particles of propellant hair sprays range from $25 \mu\text{m}$ to $50 \mu\text{m}$.^{1,17,18} Usually, 1% to 2.5% but no more than 5% of the droplets/particles emitted from propellant hair sprays are within the respirable range.¹⁷

Furthermore, different types of propellant-spray products may yield substantially different particle size distributions. For example, conservative estimates indicate that propellant hair-spray aerosols have a median d_{ae} of $35 \mu\text{m}$ with a coefficient of variation of 0.3 .^{12,18} Thus, the insoluble aerosol particles inhaled during hair-spray use will be deposited primarily in the nasopharyngeal and bronchial regions, where they can be trapped and cleared from the respiratory tract through mucociliary action. In contrast, analogous estimates indicate that the tested deodorant-spray aerosols have a median d_{ae} of $10 \mu\text{m}$ with a coefficient of variation of 0.3 , suggesting that half of these particles are within the range considered to be respirable.^{12,18}

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

The droplets/particles released from a propellant hair spray are distributed within a 1 to 2 m^3 space in the breathing zone during the first 2 minutes after spraying, which expands to form an homogenous 10 m^3 cloud (about the size of a bathroom) over the subsequent 18 minutes.^{1,17} Simulation studies revealed that all of the droplets/particles released from both pump sprays and propellant sprays settle quickly after spraying, including the respirable and inhalable fractions, which substantially reduces the overall potential for inhalation exposure.^{5,8,17-19} Specifically, about 35% of the airborne droplets/particles drop away from the breathing zone in the first minute, 60% in the second minute, 90% in six minutes, and 95% in eight minutes after spraying.¹⁷ The droplets/particles are likely to be undetectable in the breathing zone within 10 minutes after spraying.

Pulmonary overload is a condition in which the accumulation of any inert, poorly soluble particulate material in the lungs overwhelms the capacity of the alveolar macrophages to clear the material from the lungs. Chronic pulmonary overload can cause persistent inflammatory responses, fibrosis and tumors,²² although the mechanism(s) of overload-induced tumor formation is not completely understood.²²⁻²⁵ The European Union's current threshold for protecting workers from pulmonary overload during occupational exposure to respirable dust particles is 1.5 mg/m^3 8 hour time-weighted average. In comparison, inhalation exposures to aerosols from cosmetic sprays will be much lower than this

threshold, primarily because of the much shorter exposure duration associated with cosmetic spray use (i.e., only a few minutes).^{1,17}

Industry can ensure that inhalation exposures to cosmetic sprays and powders are minimized.¹⁷ For example, particle size distributions can be characterized and exposures estimated each time a significant change is made in the formulation or spray mechanisms of spray products to ensure that potential inhalation exposures are very low.

Similarly, industry can minimize airborne particles from cosmetic powder products by controlling the milling of the ingredients and adding binding materials, such as oils, waxes or hygroscopic ingredients to the formulations.²⁶ The binding materials foster the agglomeration of the ingredients and substantially increase their cohesivity. These measures increase the size of the particles in the product.

However, characterizing the particle size distributions released from finished powder products under use conditions is difficult. This is because the methods used to measure the particle sizes of powder products involve dispersing the powder in a solvent or applying a pressure differential to break up the agglomerated particles.²⁶ Thus, these measurements may not correlate well with the size distributions of the particles released from the product under use conditions. Some photographic methods are being developed to characterize the actual sizes and shapes of the particles released from powder products during use. However, it is not clear whether these methods are amenable to characterizing the aerodynamic equivalent diameters of such particles, **because factors such as density are important considerations.**

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

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

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

The Panel will continue to review all of the relevant inhalation toxicity, use, and other data to determine the safety of cosmetic ingredients. The Panel will evaluate the importance of the inhalation route for assessing the safety of an ingredient or group of ingredients, and evaluate data that may be available to estimate potential respiratory doses from aerosolized products. Factors to consider include whether or how much of the spray products enter the breathing zone, the likely droplet/particle size distributions in the breathing zone, and the exposure durations that can be expected during product use. The Panel agreed that, generally, inhalation exposure to ingredients in aerosolized cosmetic products is

unlikely to be significant compared to the dermal or other exposure routes associated with the use of cosmetic products.

For example, conservative estimates indicate that inhalation exposures for once-a-day application of a propellant deodorant spray, pump hair spray, or propellant hair spray containing 10% of an ingredient would be no more than 3, 7, and 20 $\mu\text{g}/\text{kg}/\text{day}$, respectively.²⁷ These estimates were based on the following conservative assumptions:

- All of the spray enters the breathing zone (i.e., 100% is available for inhalation)
- Exposure duration: 20 minutes
- The droplets/particles:
 - Form a 1 m^3 cloud in the first 2 minutes after spraying
 - Dissipate to fill 10 m^3 space around the user in the next 18 minutes
- 25% of the inhaled droplets/particles are exhaled
- Breathing rate: 0.01 m^3/minute
- Body weight: 60 kg
- Amount of product used: 1.43, 15.6 and 9.89 g/day deodorant, pump-hair, and propellant-hair spray, respectively²⁸
- Respirable fraction: 5%, 1%, 5% for deodorant, pump-hair, and propellant-hair spray, respectively

The greatest respirable fraction reported for the particle distributions measured for 3 deodorant spray products was 33%.¹⁸ Repeating the calculation assuming 33% as the respirable fraction, rather than 5%, results in an inhalation exposure of no more than 20 $\mu\text{g}/\text{kg}/\text{day}$ of an ingredient present at a concentration of 10% in a deodorant spray product. Assuming 50% as the respirable fraction yields an estimated exposure no more than 30 $\mu\text{g}/\text{kg}/\text{day}$.

Similarly, conservative estimates indicate that inhalation exposures for once-a-day application of a loose face powder or body dusting product range from 0.1 to 1.05 $\mu\text{g}/\text{kg}/\text{day}$ for infants or adults, based on the following assumptions:²⁹⁻³¹

- Concentration of respirable particles: 0.19 to 2.03 mg/m^3 in the breathing zone
- Breathing rate: 0.01 m^3/minute
- Body weight: 10 kg (infant) or 60 kg (adult)
- Exposure duration: 0.3 to 5 minutes

The calculations for a loose-powder cosmetic product, above, were modeled after the calculation of exposure factors in a published paper cited by the Personal Care Products Council's CIR Science and Support Committee.^{29,31} In that paper, exposure factors were defined as the ratio of the American Conference of Governmental Industrial Hygienists (ACGIH) workplace Time-Weighted Average (TWA) Threshold Limit Value (TLV) for respirable particles (3 mg/m^3) and the corresponding TWA concentrations of respirable particles to which infants and adults are estimated to be exposed during the use of cosmetic powders. Adults were assumed to powder once a day and infants to be powdered 3 times a day, 7 days/week, to calculate exposure factors of 600 and 2,182 for adults and infants, respectively. Assuming, more conservatively, that that adults powder an average of 1.5 times a day and infants are powdered an average of 6 times a day, 7 days/week, yields exposure factors of 400 and 1,091 for adults and infants, respectively.

Workplace exposure limits, such as the ACGIH TWA-TLV, are likely to be protective for occupational exposures at the workplace. However, the use of such values as benchmarks against which to gauge exposures to the general public can be informative. In this case, the TWA concentrations derived from a workplace exposure limit (i.e., the ACGIH TWA-TLV for the respirable fraction of nuisance dusts) are 2 and 3 orders of magnitude greater than conservative estimates of TWAs for cosmetic powder use at home.

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

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

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

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

Precedent language for specific report sections:**Cosmetic Use Section**

[INGREDIENT(S)] was/were reported to be used in [LIST TYPE(S) OF SPRAY PRODUCT(S), e.g., [cosmetic sprays, including hair, deodorant, foot, and other propellant and pump spray products](#)], and could possibly be inhaled. [NOTE THE HIGHEST MAXIMUM USE CONCENTRATION OF THE INGREDIENT IN A SPRAY PRODUCT IF THIS INFORMATION IS AVAILABLE, e.g., [These ingredients are reportedly used at concentrations up to 4% in spray products](#)] In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm [IF PRODUCT(S) MAY INCLUDE BOTH PROPELLANT AND PUMP SPRAYS, ADD: [, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump sprays](#)]. (Rothe et al 2011, Bremmer et al 2006, Rothe 2011, Johnsen 2004).^{1,12,17,32} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount. Rothe et al 2011, Bremmer et al 2006).^{1,12} [IF PRODUCT(S) INCLUDE DEODORANT SPRAY(S), ADD: [There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable \(Bremmer et al 2006\).](#)¹² However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. [IF PRODUCTS INCLUDE POWDER(S), ADD: INGREDIENT(S)] was/were reported to be used in [LIST TYPE(S) OF POWDER PRODUCT(S), e.g., [baby powders, dusting powders, talc powders, face powders, foot powders](#)], and could possibly be inhaled. [NOTE THE HIGHEST MAXIMUM USE CONCENTRATION OF THE INGREDIENT IN A POWDER PRODUCT IF THIS INFORMATION IS AVAILABLE, e.g., [These ingredients are reportedly used in loose powder products at concentrations up to 4%](#)]. Conservative estimates of inhalation exposures to respirable particles during the use of loose-powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace. [Aylott et al 1979, Russell et al 1979, CIR SSC 2015](#)).²⁹⁻³¹]

Discussion Section**For Tentative Reports**

The Panel discussed the issue of incidental inhalation exposure from [LIST PERTINENT PRODUCT TYPES FOR THE INGREDIENT(S); [EXAMPLE: body and hand sprays, hair color sprays, fragrance preparations and foot powders.](#)] [IF APPROPRIATE, ADD: [There were no inhalation toxicity data available.](#)] The Panel considered pertinent data indicating that incidental inhalation exposures to [[this ingredient OR these ingredients OR some of these ingredients](#)] in such cosmetic products would not cause adverse health effects, including [BRIEFLY LIST WHATEVER DATA THE PANEL DEEMED TO SUPPORT THE CONCLUSION; THIS WILL VARY FROM INGREDIENT (GROUP) TO INGREDIENT (GROUP); [EXAMPLE: data characterizing the potential for \[INGREDIENT\(S\)\] to cause systemic toxicity, ocular or dermal irritation or sensitization, and other effects](#)]. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs; in principle, Inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local

respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <http://www.cir-safety.org/cir-findings>.

Field Code Changed

For Final Reports and Re-Review Summaries

The Panel discussed the issue of incidental inhalation exposure from [LIST PERTINENT PRODUCT TYPES FOR THE INGREDIENT(S); Example: ...body and hand sprays, hair color sprays, fragrance preparations and foot powders.]

[NOTE INHALATION TOXICITY DATA, **IF APPLICABLE**: Examples: (1) The limited data available from inhalation studies, including acute and chronic exposure data, suggest little potential for respiratory effects at relevant doses OR (2) The data available from multiple inhalation studies, including acute and chronic exposure data, indicate little potential for respiratory effects at relevant doses.]

[ADDRESS PARTICLE SIZES TESTED, **IF APPLICABLE**; EXAMPLE: Although particles appear to have reached the lungs in these animal studies, the sizes of the particles used were either clearly within the respirable range (i.e., $\leq 10 \mu\text{m}$) or were not reported.]

[ALTERNATIVELY, ADD THE FOLLOWING, **IF APPROPRIATE**: There were no inhalation toxicity data available.]

[ADDRESS PARTICLE SIZES IN COSMETICS, **IF POSSIBLE**; EXAMPLES: (1) The Expert Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. Thus, the adverse effects reported using high doses of respirable particles in the inhalation studies do not indicate risks posed by use in cosmetics OR (2) The particle sizes of these ingredients was reported to range from 50 nm – 1000 μm with the largest portion being in the 50 – 300 μm range. The Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation OR (3) Several of these ingredients are used to increase viscosity, indicating that they tend to swell and aggregate in water and other solvents and would, thus, be too large to be inhaled or respired.]

[NOTE MAXIMUM USE CONCENTRATIONS IN SPRAYS AND/OR LOOSE POWDERS; EXAMPLES: (1) These ingredients are reportedly used at concentrations up to 4% in cosmetic products that may be sprayed and up to 97% in loose powder products that may become airborne OR (2) These ingredients are reportedly used at concentrations up to 0.01% in cosmetic products that may be aerosolized.]

The Panel noted that droplets/particles from cosmetic products would not be respirable to any appreciable amount.

[ADDRESS POTENTIAL EXPOSURES TO UPPER AND MID RESPIRATORY TRACT, **AS APPROPRIATE**; EXAMPLES: (1) Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of this ingredient OR (2) Furthermore, these ingredients are not likely to cause any direct toxic effects in the upper respiratory tract, based on the properties of the [INGREDIENT(S)] and on data that shows that these ingredients are not

irritants OR (3) The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs; In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties.]

Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects.

The Panel considered other data available to characterize the potential for [INGREDIENT(S)] to cause [LIST PERTINENT TOXICITIES EVALUATED; EXAMPLES: (1) irritation and sensitization OR (2) systemic toxicity, irritation, sensitization, reproductive and developmental toxicity, and genotoxicity.]

[SUM UP PERTINENT TOXICOLOGY RESULTS; EXAMPLES: (1) They noted the lack of systemic toxicity at high doses in several acute and subchronic oral exposure studies and one chronic oral exposure study, little or no irritation or sensitization in multiple tests of dermal and ocular exposure, the absence of genotoxicity in multiple Ames tests and a Chinese hamster ovary test, and lack of carcinogenicity in a lifetime oral exposure study OR (2) They noted the lack of irritation or sensitization in tests of dermal exposure, no systemic toxicity at 5000 mg/kg, and the absence of genotoxicity in an Ames test of a related chemical.]

[SUM UP PERTINANT PHYSICOCHEMICAL PROPERTIES, IF APPLICABLE; EXAMPLES: (1) [INGREDIENT(S)] is/are chemically inert and thus not systemically toxic OR (2) In addition, these ingredients are large macromolecules, insoluble in water, and chemically inert under physiological conditions or conditions of use, which supports the view that they are unlikely to be absorbed or cause local effects in the respiratory tract.]

A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <http://www.cir-safety.org/cir-findings>.

Field Code Changed

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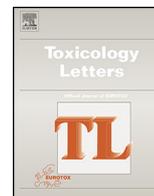
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Mini review

Principle considerations for the risk assessment of sprayed consumer products



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ABSTRACT

In recent years, the official regulation of chemicals and chemical products has been intensified. Explicitly for spray products enhanced requirements to assess the consumers'/professionals' exposure to such product type have been introduced.

In this regard the Aerosol-Dispensers-Directive (75/324/EEC) with obligation for marketing aerosol dispensers, and the Cosmetic-Products-Regulation (1223/2009/EC) which obliges the insurance of a safety assessment, have to be mentioned. Both enactments, similar to the REACH regulation (1907/2006/EC), require a robust chemical safety assessment. From such assessment, appropriate risk management measures may be identified to adequately control the risk of these chemicals/products to human health and the environment when used.

Currently, the above-mentioned regulations lack the guidance on which data are needed for preparing a proper hazard analysis and safety assessment of spray products.

Mandatory in the process of inhalation risk and safety assessment is the determination and quantification of the actual exposure to the spray product and more specifically, its ingredients. In this respect the current article, prepared by the European Aerosol Federation (FEA, Brussels) task force "Inhalation Toxicology", intends to introduce toxicological principles and the state of the art in currently available exposure models adapted for typical application scenarios. This review on current methodologies is intended to guide safety assessors to better estimate inhalation exposure by using the most relevant data.

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Contents

1. Introduction	42
2. Aims	42
3. Principles of the inhalation safety assessment	42
3.1. Data collection	42
3.2. Hazard assessment	42

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3.3.	Exposure assessment	42
3.4.	Risk characterization	43
4.	Inhalation safety assessment in detail	43
4.1.	Data collection	43
4.2.	Hazard assessment	44
4.2.1.	Hazard identification	44
4.2.2.	Hazard characterization	44
4.3.	Exposure assessment	44
4.3.1.	Screening approach	44
4.3.2.	Exposure Modelling	44
4.3.3.	Exposure measurement	47
4.4.	Risk characterization	47
4.4.1.	Risk-characterization-ratio (RCR)	47
4.4.2.	Margin of safety (MoS)	47
5.	Discussion	48
6.	Conclusion	48
	Conflict of interest	48
	Transparency document	48
	References	48

1. Introduction

The human respiratory tract is a dynamic system responsible for the gas exchange and the filtering of airborne pathogens and foreign material (Salem and Katz, 2006).

To understand the specific defence mechanisms and filter function of the respiratory tract, some anatomical basics are introduced. The vestibular hairs in the nose, mucociliary clearance, and high-velocity clearance/reflex mechanisms (sneezing and coughing) are first mechanisms of such defence. Additional, non-ciliated airway secretions, blood/lymph clearance, immunological responses, contribute to this protective function.

As illustrated in Fig. 1, particle/droplet deposition throughout the respiratory tract is determined by the inhalation characteristics (duration, frequency, and strength), the size (aerodynamic diameter) of sprayed particles/droplets and their physicochemical properties and specific clearance mechanisms.

Particles/droplets exceeding a diameter of 30 μm are normally filtered in the nasopharyngeal passage and would not reach the lung. In contrast, smaller ones may reach the lower airways. The mucosal lining of the upper respiratory tract can serve as a protective barrier and a trap for such smaller particles/droplets. The mucociliary escalator, which promotes the movement of mucosal fluid up the extrathoracic region (nose, mouth and throat) plays a major role in the clearance process of inhaled material.

The German MAK Commission stated that the particles/droplets with an aerodynamic diameter of $>15 \mu\text{m}$ are deposited almost exclusively in the extrathoracic region, and healthy humans will clear particles $>7 \mu\text{m}$ within 24 h from the tracheobronchial compartment. The threshold of particle/droplet diameters small enough to reach the alveoli is often set to be 5 μm (MAK, 2012). However, in this document particles/droplets with an aerodynamic diameter $<10 \mu\text{m}$ are conservatively considered to be respirable and suspected to reach the deeper lung.

Beside the mentioned deposition of particles/droplets propellants (gases) and solvents (vapours), often used in spray products, could have an additional health impact which has to be taken into account for the overall hazard assessment of inhalable chemicals and products.

2. Aims

This article is intended to introduce important elements for the inhalation safety assessment, to enable safe use of spray products in both occupational and consumer settings, and help improve the

understanding of relevant inhalation exposure scenarios in typical application environments. Product-type specific approaches for modelling the inhalation exposure of spray products will be reviewed.

A tiered (step-wise) approach for preparing a robust safety assessment is recommended, why detailed information on the ingredients hazard, the spray characteristics and data on the explicit exposure is needed. Both, local effects in the respiratory tract and the systemic inhalation toxicity have to be taken into account for the acute and repeated exposure.

It is essential to understand the realistic occupational or consumer exposure and application habits, in order to estimate the impact of other possible routes (such as dermal, oral and/or environmental background exposure) on the total systemic exposure and body burden.

3. Principles of the inhalation safety assessment

Four key elements have to be addressed:

3.1. Data collection

Available safety data for all ingredients and their specific regulation have to be evaluated.

3.2. Hazard assessment

The hazard assessment is processed in hazard identification and hazard characterization. Within hazard identification, ingredients are identified which are suspected to cause health concern when inhaled. For hazard characterization, the level of exposure due to the specific content of certain chemicals in the spray product is considered.

With this information, a decision should be made on the need of an explicit exposure assessment. If no hazardous chemicals are used in the spray product, or if they are only present at negligible, low concentrations, a risk characterization without an explicit exposure assessment could be sufficient.

3.3. Exposure assessment

To get knowledge on the realistic inhalation exposure to identified hazardous ingredients data on the room size in which the individual is present during spraying, and details on the spray application, e.g. frequency, duration and direction is needed. With one

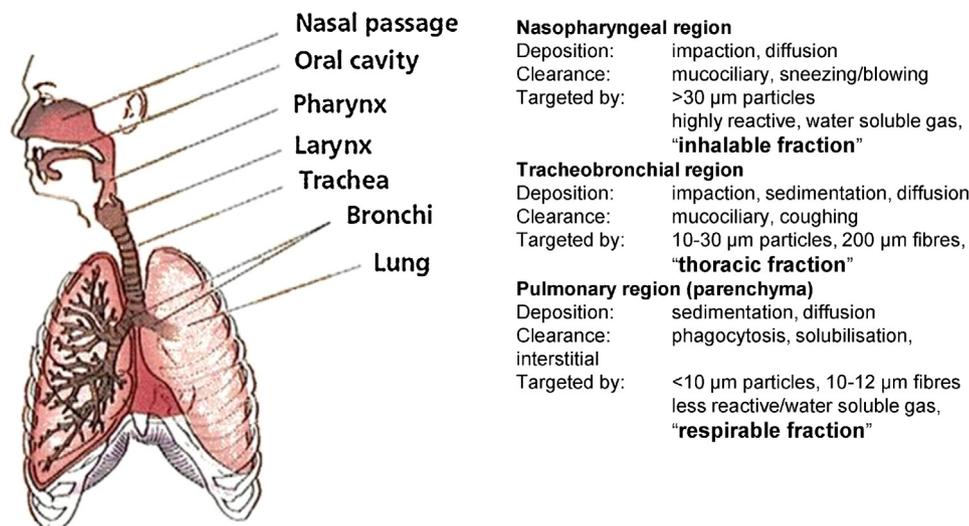


Fig. 1. Leading terms within the human respiratory tract.

of the following options a more sufficient exposure estimate could be reached:

- Screening assessment as worst-case exposure.
- Progressively more complex exposure modelling.
- Measuring the actual amount of spray inhaled, or potentially inhaled by simulating the realistic exposure scenario.

It is important to note that the final exposure is determined by the particle size and the distribution of particles/droplets in the exposure room under use conditions. The composition of the formulation and the technical details of the spray can (e.g. nozzle, size, propellant type) are of significant impact.

3.4. Risk characterization

Modelled or measured human inhalation exposure data has to be compared with suitable derived threshold values of no concern.

In case of an unfavourable risk characterization, there is a need to further refine the exposure assessment (e.g. using a more realistic approach), technically modify the spray characteristics, or to reformulate the product.

Fig. 2 illustrates the basic principles of this tiered safety assessment of spray products.

It is important to keep in mind that techniques and terminology used in the safety assessment should be checked for their compliance with relevant legislation and official guidance.

4. Inhalation safety assessment in detail

4.1. Data collection

It is recommended to start a safety assessment of spray products with the acquisition of available hazard data of individual ingredients and the understanding of their specific content in the spray product.

The hazard identification of individual ingredients typically starts with the information given in related material safety data sheets (MSDS). Especially the toxicological classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS)/EU Classification, Labelling and Packaging Regulation (1272/2008/EC, CLP) could be a starting point to get

knowledge on basic toxicological hazards. Additional data sources for the safety assessment could be found in related toxicological reports, official data files, safety studies, peer-reviewed articles, and opinions by regulatory bodies.

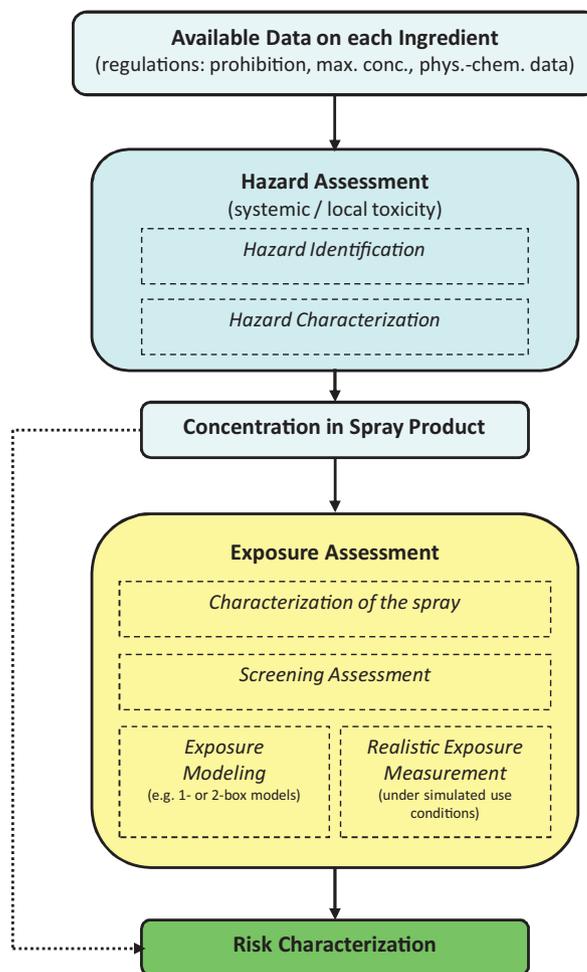


Fig. 2. Tiered approach for the Inhalation Safety Assessment (SCCS, 2012). Colour code in boxes: Blue related to ingredients. Yellow related to product exposure. (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

4.2. Hazard assessment

4.2.1. Hazard identification

With the mentioned data collection a useful understanding of the principle toxicological properties of the related chemicals could be reached, but for a scientifically robust safety assessment, detailed information on the following toxicological endpoints may be needed:

- Acute systemic toxicity after oral, dermal or inhalation exposure.
- Irritation/corrosion (local effects) after mucosal, dermal and/or inhalation exposure.
- Dermal and respiratory sensitization.
- Mutagenic/genotoxic potential.
- Repeated dose toxicity (e.g. 28-day/90-day studies) when orally, or topically exposed, or when inhaled, with the corresponding thresholds identified: No-Observed-Adverse-Effect-Level (NOAEL)/No-Observed-Effect-Level (NOEL), or No-Observed-Adverse-Effect-Concentration (NOAEC)/No-Observed-Effect-Concentration (NOEC).
- Reproductive/developmental toxicity (maternal/foetal).

The reliability and robustness of the final hazard identification is related to the quality of individual information used (Schneider et al., 2009), why the most robust studies should be preferred, ideally those directly related to inhalation (e.g. OECD testing guideline #412 or #413).

In case inhalation data are lacking, this data gap might be bridged by other appropriate toxicological information in a Weight of Evidence approach (WoE). In this approach e.g. robust oral toxicity data, may function as an adequate surrogate with a route-to-route extrapolation as described in the European Chemicals Agency (ECHA) guidance (ECHA, 2012a).

4.2.2. Hazard characterization

For the hazard characterization all compiled toxicity data, systemic as well as local ones, have to be considered and determined by adequate dose descriptors like [mg/kg bw/day] for systemic and [mg/cm² lung surface area] or [mg/g lung weight] for local effects. Usually these descriptors are expressed as a NOAEC (for local and systemic effects) or LC₅₀ (acute lethal concentration), respectively.

Once the overall hazard has been determined for the individual ingredients, its health impact during product inhalation can be estimated related to their individual content. The likelihood of reactivity between individual ingredients should be considered.

In cases where the content of certain ingredients is very low an Exposure-Based-Waiving (EBW) approach could be applied (Carthew et al., 2009) as a justification for concluding that there is no risk. The application of such approach requires expert knowledge and a detailed understanding about its restrictions and limitations.

4.3. Exposure assessment

Spray products have a wide variety of applications and the actual health related risk to humans (workers, professionals, consumers) depends on the hazard and exposure to the sprayed chemicals at specified use conditions. Therefore, a proper exposure assessment is crucial and should be based on detailed knowledge of the use conditions established from data on habits and practices.

Generally, the exposure to inhalable substances is determined by:

Spray can	Size Pressurizing system (propellant driven spray, pump spray) Geometry of the spray container (volume) and the nozzle Content delivery
Spray formulation	Qualitative/quantitative composition Propellant and solvents used Application format e.g. foam, mousse, jet, fine spray, coarse spray
Spray usage	Frequency Duration Product release per application/time Spraying jet Spray direction (e.g. towards or away from the body)
Exposure situation	Application type (consumer, industrial/professional) Particle/droplet size distribution at spraying and its maturation Duration of stay in spray environment Room volume and temperature Ventilation rate (air exchange) Activity level of the exposed individual (e.g. moving, resting)

For practical reasons only those data, which are expected to have a relevant impact on the specific exposure have to be taken into account.

4.3.1. Screening approach

ECHA has published some guidance for the exposure estimation to spray products (ECHA, 2012b). For screening purposes, a rough estimate of the exposure to a certain sprayed product/chemical could be sufficient or even appropriate. In such first screening assessment, it is assumed that exposure is to a certain ingredient quantity which released the dispenser instantaneously. An immediate homogenous distribution in a fixed exposure room is assumed.

Concentration (exposure)

$$= \frac{\text{weight of ingredient in the released spray formulation [mg]}}{\text{room volume [m}^3\text{]}} \quad (1)$$

This conservative approach will provide overestimated exposure for volatile substances (fixed room volume without air exchange), but will underestimate short-term local exposure for particles/droplets (inhomogeneous distribution shortly after spraying) as the sprayed formulation needs a while to become homogeneously distributed in the room.

The distribution/exposure scenario has to be representative for the specific product type. For cosmetic and personal care products, which are sprayed towards the body, it is assumed that the total amount of the sprayed product enters immediately and homogeneously the “personal zone”/“breathing zone”, of about 2 m³.

For many hazardous ingredients in spray products such simple exposure assessment may be appropriate to prepare a reliable risk characterization.

4.3.2. Exposure Modelling

Based on the diversity of spray products and their variability in applications, a number of models for a more realistic exposure assessment, varying in complexity, have been developed and are in use. An understanding of certain individual strengths and weaknesses of these models is needed for a proper choice.

For a robust exposure assessment the amount of sprayed product/chemical in a given time and realistic room conditions should be taken into account. The initial air concentration, dilution by

ventilation and sedimentation are additional important parameters to describe the 'real use' conditions. In this regard, the Time-Weighted-Average concentration (TWA) expresses the time-dependent change of product concentration in the exposure room after spraying.

Typical spraying values of some common consumer products are given in the following tables (Tables 1–3), however, some of these parameters are triggered by individual habits and any two people may use the same product type differently (Steiling et al., 2012). To build realistic exposure scenarios it is therefore important to understand how spray products are realistically used (Table 1).

Table 1

Discharge rates (including propellants and solvents) and typical spray times for some consumer products.

Consumer product	Discharge rate (g/s)	Spray time (s)
Hairspray ^a	0.7	3–4
Antiperspirant/deodorant spray (90th percentile)	0.8 ^c	1.4 ^d
Air freshener ^a	1.5–1.8	4–5
Furniture polish ^a	1.8	2–3
All-purpose cleaning spray	1.2 ^e	24 ^e
Starch ^a	2.0	2–3
Carpet cleaner ^a	2.0	20–30
Oven cleaner ^a	2.0	10–15
Flying insect killer ^b	1.5	10
Crawling insect killer ^b	1.5	60–90
De-icer ^a	2.5	15–20
Paints ^a	0.8	30–40

^a BAMA (2008).

^b Bremmer (2006).

^c Bremmer et al. (2006).

^d Steiling et al. (2012).

^e Weerdesteijn et al. (1999).

Values for the daily applied amounts and the application frequency of some cosmetic products are given in Table 2. The amount per application represents the total amount of product including the related propellant and solvent content (can weight loss), but not the quantity of product landing on the skin or hair, which is much lower (Steiling et al., 2012).

Table 2

Cosmetic spray products: amounts (including propellants and solvents) applied and frequency of use.

Product application	Amount/day (g)	Frequency of application/day	Reference
Deodorant (aerosol)	6.1 (90th percentile)	2	McNamara et al. (2007) and Hall et al. (2007)
Hairspray (aerosol)	6.8 (75th percentile)	1	Bremmer (2006)
Hairspray (pump spray)	3.6	1	Loretz et al. (2006)

Typical exposure data of some household aerosol products are given in Table 3.

Table 3

Exposure time of some sprayed household products (US-EPA, 2011).

Products	Mean spraying duration per use (min)	90th percentile
Spray shoe polish	7.49	18
Aerosol spray paint	39.54	60
Aerosol rust remover	18.57	60
Aerosol spray paints for cars	42.77	120
Spray lubricant for cars	9.90	15

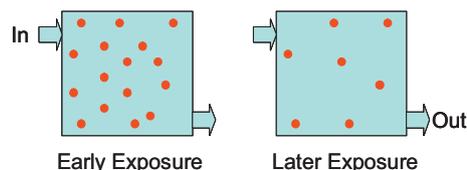
Beside the aforementioned conservative exposure calculation, using standard values of well designed surveys and specific studies on typical application/use habits, several computational exposure models have been developed in parallel.

Such computer programmes, developed to calculate the expected inhalation exposure varies from simple ones to sophisticated models. Later takes into account various factors to determine most realistically how much of a spray/chemical is actually inhaled, exhaled, is reaching deeper lung are or is deposited. Currently, the following models have been established with preferred application to certain exposure scenarios:

- BAMA/FEA Indoor Air model (one-box).
- RIVM ConsExpo 4.1 models (one-box).
- BAuA SprayExpo 2.0 model (one-box).
- RIFM 2-Box Indoor Air Dispersion model (two-box).
- RIFM Computational Fluid Dynamics (CFD) and Multiple Path Particle Deposition (MPPD) model.

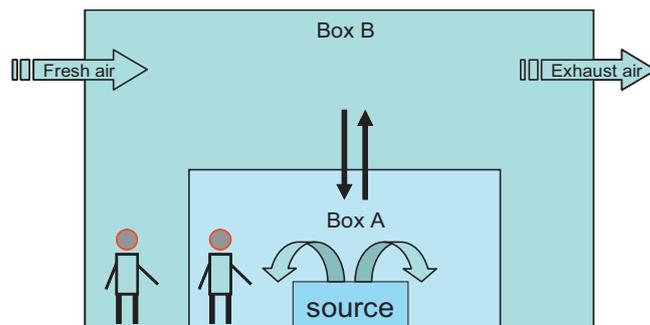
The most obvious differences between these models are the number of assumed exposure rooms (boxes). Some are utilizing a single exposure room, others use two or more zones/rooms.

4.3.2.1. One-box models. The one-box model (Fig. 3) is based on the assumption that particles/droplets are homogeneously distributed in an exposure room of known volume. Concentrations are calculated as a function of the sprayed amount, the room volume and the ventilation rate as well as the time elapsed from the start of the emission and staying in this room.

**Fig. 3.** Theoretical behaviour of a sprayed product in a room.

4.3.2.2. Two-box models. A more sophisticated approach is the two-box model, which assumes 2 different zones/rooms (Box A and Box B) in which the emitted material is homogeneously dispersed as illustrated in Fig. 4. This scenario automatically results in two separate exposure environments which have to be taken into account when calculating the overall exposure.

Although the air concentration will be higher in Box A, total exposure will depend on the residency time in each box. The amount of material which could be inhaled is determined by its concentration in individual boxes, the specific residency times and the

**Fig. 4.** Principles of a two-box model (far field; spray directed away from the body).

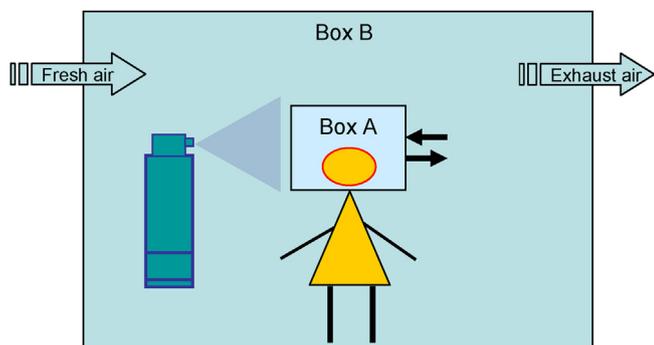


Fig. 5. Near field/far field exposure with products sprayed towards the body.

physiological minute ventilation (breathing frequency multiplied with the depth of ventilation) of the exposed individual.

For products directed towards the body, e.g. hairspray, the two-box model can be divided in a short term “near field” exposure (e.g. 2 min in 2 m^3) and a longer “far field” scenario (e.g. 18 min in 10 m^3) (Rothe et al., 2011). In this case, Box A stands for the breathing zone and Box B for the rest of the room (e.g. a smaller bathroom) (Fig. 5).

4.3.2.3. Multiple path particle deposition model. The Multiple Path Particle Deposition (MPPD) model is a higher tier exposure assessment model utilizing a computational model of human and rat specific anatomical differences in the respiratory tract (the nasal cavity and lung airways). The MPPD allows the direct extrapolation of laboratory animal data to human exposure and is capable to estimate dose-related kinetics of inhaled material (Schroeter and Kimbell, 2006a,b; Martonen and Schroeter, 2003; Garcia and Kimbell, 2009; Schroeter, 2009). The MPPD model allows the specific determination of the dose deposited at various sites of the respiratory tract, and to calculate the dose which can be systemically up taken across the tissue surface in the lung. The correct quantification of the deposited/penetrated amount of material requires the use of respiratory or at least dermal penetration coefficients and sufficient knowledge on physicochemical characteristics of the individual chemical.

During the last couple of years, some of these models became publicly available such as the BAMA/FEA Indoor Air Model, RIVM ConsExpo 4.1, SprayExpo (Koch et al., 2012) and BG-Spray (Eickmann, 2007) and found to be useful for determining systemic exposure. Model-specific advantages and drawbacks are described in the literature (Eickmann et al., 2007).

The product-specific application of these models is summarized in Table 4.

4.3.2.4. Example for using the one-box model. To better understand the various exposure modelling methods discussed, an example is given for calculating the user's exposure to a hypothetical spray air freshener (AF) with ingredient “A” (chemical of interest) formulated at a content of 0.5%. Following the content of Table. 4, the BAMA/FEA Indoor Air model, a one-box model, should suffice to calculate exposure for such a scenario.

The typical spraying time for an AF is 5 s with a product release of 1.5 g/s (BAMA, 2008). The room in which an AF is more commonly sprayed is the bathroom. A small bathroom has a volume of 10 m^3 (RIVM, 2006). For this scenario we also assume an adult with a respiration rate of 13 L/min for light activity (Salem and Katz, 2006) and a body weight (bw) of 65 kg. If the person stays in this bathroom for 30 min, the amount this person will be exposed to ingredient “A” is calculated as follows:

Table 4
Consumer exposure models for spray products.

Exposure model	Products for which the model is useful
BAMA/FEA Indoor Air model (one-box)	Products sprayed into the air (e.g. air freshener) Products sprayed onto a horizontal surface (e.g. carpet cleaner)
RIVM ConsExpo 4.1 model (one-box) (RIVM, 2007)	Products sprayed into the air (e.g. air freshener) Products sprayed at the body (e.g. cosmetic products) Products sprayed at a vertical surface (e.g. paints) Products sprayed on to a horizontal surface (e.g. carpet cleaner)
BAuA SprayExpo 2.0 model (one-box)	Products sprayed into the air (e.g. air freshener) Products sprayed towards a surface (e.g. paints)
RIFM 2-Boxes Indoor Air Dispersion model (two-boxes)	Products sprayed into the air (e.g. air freshener) Products sprayed at the body (e.g. cosmetic products) Products that are combustible (candles) Products that are passive or heated diffusers
RIFM Computational-Fluid-Dynamics (CFD) and MPPD model	Products sprayed into the air (e.g. air freshener) Products sprayed at the body (e.g. cosmetic products) Products sprayed at a vertical surface (e.g. paints) Products sprayed on to a horizontal surface (e.g. carpet cleaner)

- 1.5 g/s product release for 5 s spraying ($1.5 \text{ g/s} \times 5 \text{ s}$) ends up in 7.5 g product released.
- 0.5% of ingredient “A” in the air freshener ($7.5 \text{ g} \times 0.005 = 0.037 \text{ g}$) results in 37.5 mg.
- Assuming this amount is homogenously distributed in 10 m^3 bathroom, this gives an initial concentration of 0.00375 mg/L [$(37.5 \text{ mg}/10 \text{ m}^3)/\text{m}^3/1000 \text{ L}$].
- Assuming no ventilation (i.e. “sealed room”), and a respiration rate of 13 L/min ($0.00375 \text{ mg/L} \times 13 \text{ L/min}$), comes to 0.04875 mg/min of inhaled substance “A”.
- For the duration of 30 min spent in the bathroom the person will be exposed to ($0.04875 \text{ mg/min} \times 30 \text{ min}$) 1.4625 mg of substance “A” or $22.5 \mu\text{g/kg}$ for a 65 kg person ($1.4625 \text{ mg}/65 \text{ kg} = 0.0225 \text{ mg/kg bw}$ or $22.5 \mu\text{g/kg bw}$).

However when running the mentioned BAMA/FEA Indoor Air model this worst-case exposure scenario will become more realistic by incorporating an air exchange of 2 times per hour, the ventilation rate associated with a bathroom (RIVM, 2006). Taking this air exchange into consideration, a 30 min time weighted average bathroom concentration (30 min TWA) for chemical “A” is calculated to be 2.4 mg/m^3 . With this TWA value, the modelling calculates the 30 min exposure to ingredient “A” to be 0.936 mg or $14.4 \mu\text{g/kg bw}$ (vs. $22.5 \mu\text{g/kg bw}$ as calculated above). This refinement is more realistic than the previously calculated value, but remains conservative, as other relevant information (such as particle size distribution) are not considered. Following the scheme given in Fig. 1, for a robust risk assessment, the more details one considers the more realistic will be the estimate of the respirable fraction and ultimate local or systemic exposure to the substance of interest.

4.3.3. Exposure measurement

For some applications and/or products computational modelling data may not give a sufficient level of confidence necessary to be taken in the risk characterization. For exposure scenarios where the spray is directed to men (e.g. a hair spray) experimental measurements of the respirable fraction of the spray into the 'breathing zone' of this individual may be needed.

For such measurement it should be understood that particle/droplet size could be dynamic due to the evaporation of e.g. the solvent after releasing the spray container. During such maturation of particle size larger particles/droplets become smaller and under specific conditions particles/droplets could become bigger by aggregation (EAF, 2009). In either case, droplet size and density directly affect their settling velocity and elimination from the "breathing zone." Product spray clouds are complex and their description is time-related and determined by e.g. the product composition and geometry of the spraying dispenser. Currently, no computational modelling is available to conduct a sufficiently reliable simulation of this particle/droplet maturation; this is why it is necessary to resort to measurement.

4.3.3.1. Measurement of spray exposure under simulated use conditions. Mannequins with simulated anatomical features, equipped with an aerosol sampler in the modelled upper respiratory tract are properly connected to a particle size spectrometer (Fig. 6), to measure the respirable dose, small enough to reach the deeper lung. Individual use conditions (adult, child) and habits and practices of spraying (frequency and duration) could be simulated with such model. The aerodynamic diameter and the number of individual particles/droplets in a defined volume per minute can be measured, even specifically in the 'breathing zone' over a certain time period. The resulted particle size distribution data allows the extrapolation of the respirable dose for that given formulation under that application conditions (Carthew et al., 2002).

In cases where spray products are not intentionally directed towards men, a slightly different measurement procedure could be useful. For such application the product has to be sprayed into a cabinet of defined volume and an installed impactor will



Fig. 6. Mannequin with particle sizer spectrometer.

collect specifically defined airborne fraction on integrated filters with defined mesh-sizes. The respirable fraction deposited on the corresponding impactor inlet is typically gravimetrically measured or chemically analyzed.

4.4. Risk characterization

Once the exposure to the relevant spray fraction is reliably understood, by estimation, modelling or measurements, the risk to human health at that level of exposure can be reliably assessed. For the final risk characterization regulators often require their specific safety factors and calculations for getting their acceptance. In this regard the most commonly used values for the risk assessments of chemicals are the Margin-of-Safety (MoS) and the Risk-Characterization-Ratio (RCR).

In a quantitative risk assessment it has to be decided if the identified hazards are linked to a certain threshold or not. A threshold in this regard is defined as a dose below which no statistically significant increase in adverse effects on the exposed organism can be identified. Adverse effects without a threshold are for example genotoxic carcinogens. A method developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for assessing non-threshold effects of genotoxic carcinogens (Barlow et al., 2006) could be applied to characterize the risk of possibly unavoidable non-threshold contaminants in sprays.

4.4.1. Risk-characterization-ratio (RCR)

Under REACH a risk assessment is part of a challenging process which is known as a Chemical Safety Assessment (CSA). Details how this has to be achieved and in particular, how to estimate e.g. inhalation exposure is given in the ECHA IR/CSA guidance (ECHA, 2012b).

Important in such CSA risk assessment is the calculated RCR, the ratio between the actual exposure and the estimated derived no effect level (DNEL) for certain adverse effects. Thus, for a given exposure to an individual ingredient the RCR is defined by:

$$\text{RCR} = \frac{\text{Exposure}}{\text{DNEL}} \quad (2)$$

RCR values < 1 are interpreted as of no concern and risk reduction measures are not necessary. In cases of RCR > 1, a refinement of exposure is required or risk reduction measures are necessary (e.g. modification of the spray characteristics or reformulation of the product) (ECHA, 2012a).

4.4.2. Margin of safety (MoS)

The MoS is commonly defined as a dimensionless number that establishes the relationship between the dose of a certain chemical necessary for a desired effect and the dose of the same chemical resulting in an undesired effect. Such calculation is regularly used in the safety assessment for e.g. drugs where a clear beneficial or effective dose can be distinguished from those which are toxic or ineffective.

For other areas like cosmetics, the term MoS is used quite differently to represent the relationship between the estimated or measured Systemic-Exposure-Dose (SED) for the exposed person and the NOAEL/NOAEC determined in appropriate animal tests. Usually, the NOAEC represents the highest systemic concentration for which a test chemical does not induce an adverse effect in the test animal when exposed repeatedly (e.g. for 90 days) to that concentration.

In this form the MoS, sometimes known as a Margin of Exposure (MoE), is regularly used in risk-assessment procedures. The EU Scientific Committee on Consumer Safety (SCCS, 2012) applies this MoS approach regularly to define the expected level of safety in the assessment of cosmetic products.

Besides the estimated or measured exposure dose, the NOAEL/NOAEC has to be measured in animal tests using the most relevant exposure route (oral, dermal, inhalation). In case of dermal or oral exposure both the SED and the NOAEL are given as [mg/kgbw/d]. For inhalation, the NOAEC are typically given as [mg/m³] or [ppm].

$$\text{MoS} = \frac{\text{NOAEL (or NOAEC)}}{\text{SED}} \quad (3)$$

The general assumption is that a MoS value of at least 100 ensures an appropriate level of safety for systemic exposure from consumer products like cosmetics. The same factor is currently requested by the US EPA for demonstrating chemical safety.

For the safety assessment of spray products, the MoS calculation is more complex compared to other applications, in addition to the dose the physical nature of the particles (e.g. size) will have a significant impact on the exposure as explained before. Finally, technical details determine where exposure occurs in the respiratory tract (see Fig. 1; different cell types in the different regions of the respiratory tract may be affected uniquely). As both, the site of exposure and the particle/droplet size influence the local exposure [mg/cm² lung tissue], a risk assessment based on a “simple” MoS calculation may not be appropriate.

Specific exposure data for certain areas in the respiratory tract and appropriate information (dose–response–relationship) on both systemic and local effects from standard toxicity tests are useful in a proper risk assessment of sprayed products.

5. Discussion

Products and in particular, consumer products have to be safe under conditions of foreseeable use as required by numerous regulations. Consequently, it is important to agree on the key data needed for an informed and representative risk assessment. During the last few decades, both industry partners and regulators have built expertise in the risk assessment of consumer products which come into contact with the skin or could be occasionally ingested. For spray products, a risk assessment is essentially more complex, due to the number of variables influencing the exposure as well as the nature of the particles/droplets released during a spraying event.

For uptake via the inhalation route, the particle/droplet sizes and velocity dictate if exposure will be mainly local sedimentation in the upper respiratory tract or diffusion in the alveolar region. The size of particle/droplets and velocity of a spray is influenced by technical details such as the pressure in the spray can, the can size and even the geometry of the spray nozzle. In addition, product composition such as propellant and solvent use may trigger an exposure episode in particular areas of the respiratory tract. As the final exposure scenario is sensitive to all the above parameters, and is often not comparable to the exposure scenario used in standard inhalation toxicity studies (e.g. OECD #413), a more appropriate exposure characterization is necessary for a robust and reliable risk assessment.

6. Conclusion

This review summarizes current best practices on how to evaluate the risk of inhaled ingredients from spray products. Using a tiered approach, based on consideration of exposure, the discussed evaluation strategy is useful and appropriate in providing a robust risk assessment for both the consumer and the occupational use of spray products. The particular requirements of the various regulatory bodies involved in the safety evaluations of spray products have been described. This should enable companies and authorities to prepare risk assessments for spray products with an

approach relevant to the level of concern. This could be based on modelling exposure for the particular formulation and application scenario, or at a higher tier, to measure real exposure under simulated use conditions for a more accurate exposure characterization. The introduced ranked hierarchy of approaches will be useful to better ensure safety of spray products.

Conflict of interest

The Authors report no conflicts of interest. The Authors are employees of the organizations and companies: Henkel AG & Co KGaA, Montana Air SL, Unilever UK, Ardagh Group, SC Johnson, European Aerosol Federation (FEA), British Aerosol Manufacturers Association (BAMA), L’Oreal, Procter & Gamble Service GmbH, Research Institute for Fragrance Materials Inc. (RIFM)

Transparency document

The [Transparency document](#) associated with this article can be found in the online version.

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WOMEN'S VOICES FOR THE EARTH

OUR HEALTH. OUR FUTURE. TOXIC FREE.

By email: cirinfo@cir-safety.org

April 3, 2017

To: Cosmetic Ingredient Review Expert Panel Members and Liaisons,

I am writing on behalf of Women's Voices for the Earth to provide comments on the Aerosols boilerplate revisions.

The Aerosols boilerplate language has concerned me for some time as it appears to imply, based on the relatively little data that is available, that respiratory harm from any cosmetic spray or powder is likely to be negligible due to large particle sizes. Given the epidemiological data on hairdressers and beauticians which notes a significantly increased risk of asthma, and other respiratory disease, it appears that real respiratory harm due to inhalation of cosmetic products is possible and should be a concern for the CIR. I am writing to provide comments and additional scientific information to further improve the Aerosols boilerplate document.

Comments:

1) On page 3 of the Aerosols document, it states:

"Usually, 1% to 2.5% but no more than 5% of the droplets/particles emitted from propellant hair sprays are within the respirable range."

Further on this page it states:

"In contrast, analogous estimates indicate that the tested deodorant-spray aerosols have a median d_{ae} of 10 μm with a coefficient of variation of 0.3, suggesting that half of these particles are within the range considered to be respirable."

The CIR's citations for this statement are quite clear – showing that indeed up to 50% of particles from deodorant sprays are less than 10 μm in diameter and would be respirable. (See Page 19 and 20 of <http://www.rivm.nl/bibliotheek/rapporten/320104005.pdf>)

The document language is then inconsistent with this data on page 4, (and in the resulting sample boilerplate language) which states that :

"The CIR Expert Panel noted that, in practice, 95% to 99 % of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters greater than 10 μm ."

This statement is accurate for the data cited here for hair sprays and pump sprays but is inaccurate for deodorant sprays – which are also “cosmetic sprays”. There is a big difference between 95%-100% and 50%. This overgeneralization of the data to all “cosmetic sprays” is troubling and could lead to significant underestimates of the inhalation safety of ingredients.

I understand that the boilerplate language does include the caveat language:

“[IF PRODUCT(S) INCLUDE DEODORANT SPRAY(S), ADD: There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable (Bremmer et al 2006).¹² However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.”

This statement is confusing. It is not clear why the data indicating that hair sprays and pumps sprays largely have particles > 10 microns in diameter is considered sufficient to determine that there would be no appreciable lung exposures (and thus no inhalation hazard) from these products. Whereas the very same data source for deodorant sprays which indicates that half of the particles are respirable (<10 microns in diameter) would be insufficient to determine that there would likely be greater lung exposures from these products. An explanation of the logic for these disparate conclusions which are based on the same data source would be appreciated.

- 2) On page 5 of the Aerosols document, there is another instance in which the potential inhalation hazards of deodorant sprays is significantly underestimated. Here, conservative estimates of inhalation exposures to propellant deodorant spray, pump hair spray, or propellant hair sprays are given. Listed below the estimated exposures are the conservative assumptions which were used to develop those inhalation exposure estimates. Confusingly, the assumptions for respirable fraction of the sprays are given as:

“Respirable fraction: 5%, 1%, 5% for deodorant, pump-hair, and propellant-hair spray, respectively”

Clearly, given the data cited in this document, a conservative estimate for respirable fraction of particles from deodorant spray is 50%, not 5%. It is unclear if this is merely a typo, or if the inhalation exposure estimate for deodorant sprays also needs to be recalculated with the appropriate conservative estimate of 50%.

- 3) Furthermore, the Aerosols document states:

“The Panel will continue to review all of the relevant inhalation toxicity, use, and other data to determine the safety of cosmetic ingredients.”

However, there is considerable additional relevant published data available on the particle size distribution and inhalation hazard from cosmetic products that has not been referenced in this document.

Specifically, a 2011 paper discusses measurement of particles from consumer spray products:

YEVGEN NAZARENKO, TAE WON HAN, PAUL J. LIOY, and GEDIMINAS MAINELIS. Potential for exposure to engineered nanoparticles from nanotechnology-based consumer spray products. *J Expo Sci Environ Epidemiol*. 2011 Sep-Oct; 21(5): 515–528.

Available in full text at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4027967/>

While the focus of this paper is to investigate potential exposures to nanoparticles, the paper provides data on both sprays marketed as containing nanoparticles as well as “regular” (non-nano) sprays including hair sprays, and facial mist sprays. More than one technology is used to measure particle sizes of these sprays which range from 13nm to 20 µm. Analysis of exposure during simulated use of the products was also conducted using mannequins, drawing air through the mannequin’s nostrils towards sampling equipment. This research seems highly relevant to the CIR’s discussion of Aerosols. Especially as the results of this analysis find that even for hair sprays a much more significant percentage of spray particles would be respirable, than shown in the data previously cited by the CIR.

The paper concludes:

“During the use of most nanotechnology-based and regular sprays, particles ranging from 13 nm to 20 µm were released, indicating that they could be inhaled and consequently deposited in all regions of the respiratory system. The results indicate that exposures to nanoparticles as well as micrometer-sized particles can be encountered owing to the use of nanotechnology-based sprays as well as regular spray products.” (emphasis added)

A followup paper by the same authors, quantifying inhalation exposure and estimated deposition doses from consumer spray products found that up to 10% of the aerosol dose from cosmetic sprays would be deposited in the lungs (alveolar region).

(Paper available at: <https://www.ncbi.nlm.nih.gov/pubmed/25621175>)

These conclusions are contrary to the current conclusion of the CIR’s Aerosols boilerplate language. This research should be assessed by the CIR and the discrepancy in the data should be reconciled in the Aerosols document.

4) On page 5 of the Aerosols document, new estimates on exposures to cosmetic powders were added. I was surprised to see that the citations given to backup this new data were just two papers on talc particles from 1979, and an unpublished memo from the Personal Care Products Council (which is publicly unavailable as far as I can tell.) Clearly there have been major advances in technology of particle size measurement since 1979, and newer data should also be referenced.

Specifically, there are a number of papers published recently on particle size and inhalation exposures to cosmetic powders that are relevant to the CIR's document on Aerosols. These papers are open access and available here;

[Nazarenko Y](#), [Zhen H](#), [Han T](#), [Lioy PJ](#), [Mainelis G](#). Potential for inhalation exposure to engineered nanoparticles from nanotechnology-based cosmetic powders. [Environ Health Perspect](#). 2012 Jun;120(6):885-92. doi: 10.1289/ehp.1104350. <https://ehp.niehs.nih.gov/1104350/>

[Nazarenko Y](#)¹, [Zhen H](#), [Han T](#), [Lioy PJ](#), [Mainelis G](#). Nanomaterial inhalation exposure from nanotechnology-based cosmetic powders: a quantitative assessment. [J Nanopart Res](#). 2012 Nov 1;14(11). pii: 1229. <https://www.ncbi.nlm.nih.gov/pubmed/23175627>

These papers both indicate that the vast majority of particle sizes from cosmetic powders (both nano and non-nano powders) are in the respirable range.

5) On page 4 of the Aerosols document it states:

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

This section seems quite outdated given recent technology, particularly in the sophisticated advances of nanotechnology research. Particle size measurement using aerodynamic and scanning mobility particle sizers (APS, SMPS) as well as particle characterization using transmission electron microscopy (TEM) is fairly common in current research on fine, ultrafine and nanoparticle research currently. The problem of addressing particle size distributions "under use conditions" has also been solved through new techniques. In the research noted above, particle size distribution of cosmetic powders was measured in real time in simulated use conditions on a mannequin, using the brushes and/or applicators that came with the product and following the directions for use. The conclusion that *"it is not clear whether these methods are amenable to characterizing the aerodynamic equivalent diameters of such particles"* appears to be outdated and no longer correct.

6) On page 7 of the Aerosols document it states:

" Conservative estimates of inhalation exposures to respirable particles during the use of loose-powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace. Aylott et al 1979, Russell et al 1979, CIR SSC 2015)."

I assume that the comparison of inhalation exposure estimates with guidance limits for airborne respirable particles comes from the "CIR SSC 2015" citation. It would be useful to either append or link that document to the Aerosols document to better explain this claim. It is unclear which regulatory and guidance limits are being referred to, and for which substances. There is also considerable controversy over whether current regulatory limits (such as OSHA PELs) are even in fact protective of health. For such a broad claim to be included in a safety assessment, providing additional details on these calculations is important for credibility.

7) Nowhere in the Aerosols document is there a mention of the potential hazards of inhalation of nanoparticles despite their increasingly common use in cosmetics in recent years. While certainly the research on nanotechnology is still evolving, it seems an oversight to omit any mention of the potential for exposure, even a statement to acknowledge the uncertainties. The data in both the cosmetic powder research and the consumer spray research noted above indicate that even products that are not marketed as containing nanoparticles all emitted some amount of nanoparticles in their aerosols which were respirable.

8) Finally, I would recommend that the CIR discuss whether the concluding statement in the Aerosols boilerplate language which states:

"The Panel noted that droplets/particles from cosmetic products would not be respirable to any appreciable amount."

is still a statement the panel believes is accurate and protective of health.

Thank you for your consideration of these comments, and hope they are helpful to your discussion.

Sincerely,

A handwritten signature in black ink, appearing to read "Alexandra Scranton". The signature is written in a cursive, flowing style.

Alexandra Scranton
Director of Science and Research
Women's Voices for the Earth



Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Ivan J. Boyer, Ph.D., D.A.B.T.
Date: August 18, 2017
Subject: Revised Draft Endocrine Activity and Endocrine Disruption Background and Framework Document

Enclosed is the second draft of the CIR Expert Panel Endocrine Activity and Endocrine Disruption Background and Framework document (Document). The enclosed draft is identified as *endist092017rep*. The first draft was reviewed by the Panel at the April 2017 meeting. Comments on the first draft received from the Personal Care Products Council (PCPC) CIR Science and Support Committee (CIR SSC) and from Dr. Mihaich have been addressed in the second draft. Changes to the first draft are highlighted in the second draft.

Also enclosed please find the pertinent Panel meeting transcripts (*endist092017min.doc*), comments from the PCPC (*endist092017PCPC.pdf*) and the CIR SSC (*endist092017ssc.pdf*), and the first draft of the Document with Dr. Mihaich's review comments in MS Word "show markup" mode (*endist092017emm.doc*).

The Panel should review the second draft of the Document for the adequacy of the content, scope, and detail of this draft, including the draft Framework for Discussion Sections that appears at the end of the Document, and the adequacy of the revisions implemented in response to the comments received.

141th COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

Monday, December 5, 2016 (MAIN SESSION)

DR. GILL: ...We are happy to have with us today our speaker, Dr. Ellen Mihaich, got that correct, who is the owner and principal scientist of Environmental and Regulatory Resources. That's the company that's focused on environmental toxicology and risk assessment. She's also an adjunct professor at the Nicholas School of the Environment at Duke University where she received her Ph.D. in environmental toxicology.

Dr. Mihaich has been engaged for quite a long time in the area of endocrine disruptor screening and testing. She is active in the US and international efforts and in the OECD programs for validating assays. She told me to keep it short so with that, I'll turn it over to Dr. Mihaich.

DR. MIHAICH: Well, good morning, and thank you for having me here. This is a topic that's fairly near and dear to my heart so I really appreciate the opportunity to talk to you this morning. I wanted to start with one group that I am the scientific coordinator for, and that's the Endocrine Policy Forum.

The policy forum is a consortium of List I test-order recipients. So everybody that got test orders from the first endocrine disruptor screening program, and if you're not familiar with it you will be in a minute. We get -- we sort of banded together to try to figure out how best to do all of the screening that we had to do, and how to interpret, and so we had quite a large group and we also had some additional stakeholders like CropLife America and the American Chemistry Council and others.

And so in doing this, because we knew this was a very new program, we had very new studies. We wanted to be able to try to understand it. And so a lot of the things that I'm going to talk about today as far as weight of evidence goes are things that we actually developed through this consortium.

So what is an endocrine disruptor? That is a huge thing if there's anything that you can walk away from is understand what an endocrine disruptor is because it is a legal term. And it's based on the WHO IPCS 2002 definition. And so the key here is that it's a -- let me just put the pretty little picture there. It's the mechanism that is linked to an adverse effect. It's not just a change. It's not just a binding.

It is the mechanism and primary adverse effect that gets the moniker of endocrine disruptor. Unfortunately, we have gotten very, very sloppy in the language and everything is an endocrine disruptor, okay? And if there's anything that you can do is as you go forward make sure you keep in mind this because it has significant regulatory consequences. Not so much in the US because we're a risk-based legislation but in Europe currently it's a hazard-based. So any activity can get that -- they will put that name on it and it will end up in bans.

So, I mean, chemicals will be banned just because they have activity not because they actually caused an adverse effect. So it's a really important thing to keep in mind. Okay.

So in the US and we actually got pretty much started in '96 we had the passing of the Food Quality Protection Act and the Safe Drinking Water Act amendments. And what these required was, for the Food Quality Protection Act, it required pesticides to be screened. Originally, the legislation said endo -- or estrogenic activity. It was broadened to estrogen, androgen, thyroid and steroidogenesis.

And it was also only human health at the beginning. It's now human health and the environment. So it has expanded. And, but, the admini -- EPA administrator was allowed to throw in other endocrine effects as we knew more.

The Safe Drinking Water Act amendments were that you had to screen drinking water contaminants to which substantial numbers of people are exposed. The problem with that is they never define "substantial numbers" and

so that's still a little bit hazy and "may be found in sources of drinking water" is also not specifically defined. So those are a little bit -- it's a little unclear.

However, that is what got all of this started was these two acts. So, getting a little history here, it started after the passage of the acts. We had the Endocrine Disruptor Screening and Testing Advisory Committee. It was a FACA (Federal Advisory Committee Act) and it had multiple stakeholders. I actually was a groupie. I followed it around the country. They met all around the country so for two years and then, they came up with a report.

And it was a pretty good report actually in the end. And what was required, they came up with a two-tiered testing scheme and then, the next 10 years were spent trying to validate because one of the parts of the legislation was that they had to be validated test systems. So that's what took so long and you get a lot of people that complain about, you know, industry's trying to slow things down. No, it's just that they weren't validated and they had to go through that process.

In 2009 we got the first test order, so we had a List I, and List I got -- had 67 pesticides and pesticide inerts on it. And so those registrants got test orders requiring them to do all 11 of the screens that there are in the endocrine, the Tier I of the EDSP (Endocrine Disruptor Screening Program). People went off and started working on those.

That's when the Endocrine Policy Forum started, around that time. In 2013 a second list came -- was published. However, I would venture to guess that that list is not going to necessarily be the list that'll ever do anything in the future, and we'll get into why that's going to be in a minute. So well, actually, the next one kind of gets on that.

So work is ongoing to prioritize the 10,000 chemicals universe, and so that, because what ended up happening was, when the first list was tested there were really very few effects. And you could have predicted that because these were pesticides. Pesticides are highly tested, and so we already knew what they did and what they didn't do, but you had -- they were essentially going backwards and doing the screening even though we already had the definitive tests.

So, but it was essentially a cost of doing business. It was really just to validate the -- to continue to validate the screens, but that's fine. So I think that in the end we're going to be looking at any additional screening much differently than we do today.

All right, so the EDSTAC (Endocrine Disruptor Screening and Testing Advisory Committee) conceptual framework, this is what came out of that FACA that went around the country. It's 11 in vitro and in vivo assays, estrogen, androgen, and thyroid -- maximizes sensitivity to minimize false negatives. You can just about get an effect in any of these at any time for anything. You can look at them and they'll probably give you an effect.

That's why EPA was very, very careful, and we really appreciate this. They said it has to be a battery. You have to look at all of them. And that way you do weight-of-evidence and you say does it all make sense? And that was a really important point, and unfortunately other places around the globe are not necessarily taking that type of a stand.

Tier II, if you have a potential, and that's actually, that's the other key word there, potentially interact. So it's the potential to interact. It's not the chief ca -- you've defined anything. It's the potential to interact. Tier II testing or multi-gen studies that are in a range of species, that's supposed to confirm the endocrine activity and give you a no effect level for risk assessment.

So that's what these two things are and I'll show you the -- it's probably a little hard to see, so there are five in vitro studies in the endocrine disruptor screening program, ER binding, ER transcriptional activation, AR binding, steroidogenesis, and aromatase. And then, there are four mammalian in vivo studies, the uterotrophic and the

Hershberger and the male and female pubertals. And there are two in vivo eco tox, which are the fish short-term reproduction assay and the amphibian metamorphosis assay.

DR. BELSITO: What's the Hershberger? I'm not familiar with (inaudible).

DR. MIHAICH: It's essentially it's for androgen, looking at an androgenic mode of action. It's in male rats.

And then, Tier II there's only rodent study. The two-gen rat is actually now kind of moved to the extended one-gen. And the -- but there are three -- originally there were four but now there's three eco tox and that's the medaka extended one generation, the larval amphibian growth and development test, and the avian two-gen. There originally was a mysid two-gen but because mysid and most invertebrates don't have estrogen, androgen, or thyroid it kind of didn't quite fit when you were trying to do this.

Ultimately it does get used, but for other kinds of things, but it's not part of the EDSP. When EDSTAC came up with this, they were told that the screens would be very inexpensive and very fast. Part of that was because a researcher out of Boston said that she could do the, oh, what was that, oh, the breast cancer estrogen study for like-- huh?

No, I can't -- it'll come to me but anyway, for like \$50 in her lab. Well, if you do all 11 of these Tier I screens it's about a million, 750 to a million dollars for one chemical and it definitely took more than two years to get them done. Yeah?

DR. MARKS: Is there problems in the EU with using in vivo testing?

DR. MIHAICH: If it's done for another regulation, no. So if it has to be done here, then no. You can use that information. I'm not totally familiar with the cosmetics directive, but I thought that that was the case is that, if it had to be done for another regulation, then you could work on vertebrates. Interestingly, they asked for a lot of these kinds of things over there, too.

So yeah. Okay, so what happened in this one? Remembering that that was 67 pesticides, in the end, it was actually only 52. They gave us -- they gave an option to opt out, essentially, for inerts to say I'm not going to sell to the pesticide industry any more. And so then, they didn't have to go through it. So in the end, it was 52 chemicals. There were 52 -- 50 pesticides, 2 chemicals. They had isophorone and acetone, were the two that did go forward.

And all of their weight-of-evidence evaluations are on the web. You can get them. All you have to do is Google "EPA endocrine" and they're right there. And what they found was no evidence for potential interaction for 20 of the chemicals. 14 showed potential interaction but they already felt like they had enough information to be able to do an adequate risk assessment. And then, the remaining 18 did have some potential uncertainties associated with them, and so they are now in the queue to possibly go forward into a Tier II.

What they said of those things, the ones that needed things, they've asked for a comparative thyroid assay for four chemicals. The problem with that is the comparative thyroid is not part of the Tier II, and so the information collection request that they submitted to the Office of Management and Budget has not moved forward partly because of that. And so they have to actually amend that information collection request, have the Office of Management and Budget approve it, before they can ask for that information.

Those are crazy ridiculous studies that compared to thyroid; it's just an amazing number of animals. I can't off the top of my head; it's just a phenomenal number of animals. It's -- there's got to be a better way.

The medaka extended one-generation is going to be asked for 13 chemicals, many of it actually because they just didn't have a long-term fish study, I think. Didn't really see the endocrine but that's okay. And larval amphibian growth and development is for five.

However, we have a problem with Tier II don't we? Because what do we do? We test for effects, right? We -- when we do our testing. And so how -- it's going to be -- it's very difficult to decide that it was an endocrine, a primary endocrine mode of action that caused the adverse effect or not.

And again, it's not so much of a problem here in the US, but in Europe I don't think they're going to move off of this hazard-based regulation. And so that's going to be a huge issue if you can't exactly tell that it was an endocrine mode of action that was the primary cause of the adverse effect.

So what do you have to do? You have to do weight-of-evidence. And this fits in with how EPA wanted to do it, and, because you have to bring all of the information together. And this is one of the issues, is the dilemma of many endpoints. So in the Tier I with the 11 screens, there are approximately 89 endpoints. So the chance that you would actually get a clean chemical, I mean a clean chemical with screen clean, with no potential adverse effects is about one percent if they were all independent endpoints.

Of course, they're not independent endpoints. If you said every fourth was, maybe it's about 32 percent. So you can see, it's very heavily weighted to find an effect, which is why weight of evidence is really critical.

So, I didn't get a chance to send you all these papers. You guys will have the slides, so you can look them up. This is the two Borgert et al. publications, are where we came up with the weight-of-evidence for how to do the weight-of-evidence for endocrine effects. The last one was -- is a paper that I wrote with Ann de Peyster, and, on methyl tert-butyl ether, and so we actually put it into practice, so we took all of the methyl tert-butyl ether data and went through the whole weight-of-evidence process.

So obviously you need to make sure you have reliable information, relevant information. It's got to be fit for purpose, and you want to look for that consistent pattern of responses for a particular hypothesis. One of the problems that keeps coming up, especially when you go to scientific meetings, is there's a lot of accusations of bias, especially on the part of the agency, for not picking certain data to use. And a lot of that's because it's not fit for the purpose that we need to have it for in the regulation. You know, bench level studies are great, but if they don't work towards that risk assessment, then it's not going to be as useful.

So this is now -- the process that I'm talking about is what the Endocrine Policy Forum did with a large number of experts. We came up with eight total hypotheses. So is the chemical an estrogen? It is an anti-estrogen? Is it an androgen, anti-androgen? Does it inhibit thyroid? Does it -- so all the way through, okay? So you have all of those.

And when you do this then you do a systematic literature review. You evaluate the data quality. You weight the endpoints quantitatively, or at least rank-order them based on explicit criteria and data, and I'll show you why we do that in a minute. Then we can -- it would be great if you could weight results with the context of no positives and negatives to get sort -- add a potency component to this. Unfortunately, it's very difficult, and you can do it pretty well with the in vitros, but it's very rare that you're going to put in extra animals to do a positive control on a pubertal male or female study.

So you don't -- that's a little harder to assess. And then, you get -- you develop a narrative interpretation of it. All right, when we get into the endpoints, what we did was we looked at every single endpoint that are in those screens and we decided which ones were the most relevant for each hypothesis that we were testing, because they're not all going to be the same weight for each hypothesis, right? So we said, you can't decide on a hypothesis on a single assay. It's got to be the battery approach.

We ranked the relevance of each of these endpoints based on the hypothesis. And so, rank-one endpoints are sensitive and specific. They -- for that particular hypothesis, you can generally interpret them without other

endpoints and they're in vivo. And we said that they needed to be in vivo so that you had the -- you had ADME taken care of, and you rarely get them confounded by other types of toxicity.

Rank-two are sensitive and specific for hypothesis. You can interpret them alone, but they're less informative than rank-one because they can be confounded. So for example, and unfortunately, I'm going to pull most of my examples from the eco world, so you're just going to have, bear with me on this -- so vitellogenin is an egg yolk protein in fish that females have. Males can produce it if they're exposed to an estrogenic compound. And so, what -- if you're looking at, say, an anti-estrogen or an androgen, you would expect that the female vitellogenin would go down, because it's going to be up-regulated by estrogen, down-regulated by the opposite. But hepatotoxicants can also down-regulate vitellogenin, because that's where it's produced. It's produced in the liver.

And so you can -- that's where this issue of potentially confounding, so you have to look a little further. One of the things, just as an aside, when we started to do these tests that weren't part of it, was, we realized early on, we needed to keep the livers of the fish. That wasn't part of it, and, but if you had a down-regulation of female vitellogenin, you wanted to be able to go and look at the livers to see if it was hepatotoxicity or not.

Rank-three, irrelevant, but only when they're corroborative of rank-one and rank-two, and these are apical endpoints, and we have a lot more of the apical endpoints in the eco tox studies than we do in the mammalian studies. But still, it's that things -- fecundity, fertility, those things -- can be impacted by lots of different types of toxicity or no response.

I do want to say, though, so I don't forget it is that, we see this as somewhat of an evergreen process. As we learn more, things, you know, places where these endpoints are ranked may change. So I know this is really hard to read, but this is just sort of how this is laid out.

So for an estrogen agonist hypothesis, okay, and all of the 11 screens, we have those two right there, the first two rank-one endpoints in the FSTRA study, the Fish Short-Term Reproduction Study, an increase in male vitellogenin. If you're looking at an estrogen agonist, and you increase male vitellogenin, you probably have some type of an estrogen agonist in some form.

Also, on the uterotrophic study, an increase in uterine weight in the uterotrophic study would be considered rank-one. So we felt that they were pretty clear. Interestingly, you might notice that ER binding is a rank-three endpoint, and you'd say, well, heck, it's an estrogen agonist hypothesis. Why would that not be there? Well, it's because you can't tell whether it's an agonist or an antagonist. There's not an antagonist arm to that study.

They're working on it, but currently it's not. So that's one, for example, that might move once we had that. Let me see if there are any other good ones here.

Again, I've got a lot to talk about, so we'll keep moving on, but this is how we did that. And so then, what you can do is you take all your studies and you say, okay, do I have this one, and which way is it going? And do I have this one, and which way is it going? And then, you can kind of lay it out to see if it looks like you have something. If all you ever have is rank-three endpoints, then you really can't tell if it's an estrogen agonist or not, because those are things that can be impacted by a lot of different types of toxicity.

Here it's just to throw it up here. It's the androgen agonists. So in the Hershberger, to your question, there are weights of five different endpoints, so the Cowper's gland, seminal vesicle, the LAB glans penis, ventral prostate, and to have it a rank-one you have to have the concordance of all five. But you can see rank-two might be a few of them, and rank three might be maybe just one. So that you can see that, you know, that's pretty telling of an androgen agonist, if you have changes in those.

On the FSTRA secondary sex characteristics in the fathead minnow – fathead minnow have tubercles on their head, and so, if you have an androgen agonist, you probably are going to have a lot more. So let's see. I think that's pretty much all I wanted to say there.

This is just really quickly, again, to show you that endpoints don't weigh the same for every hypothesis. So let's just take -- it's the easiest one, sorry, for me is the vitellogenin on the top. So I have all eight of the hypotheses across the top, and so you can see that vitellogenin is a rank one for an estrogen agonist because an increase in male is pretty good. However, for thyroid, it's not going to be meaningful.

So the key -- the reason then that you have to do this by hypothesis is that you may have a rank-three endpoint impacted in the estrogen agonist hypothesis and you may have a rank-three on another hypothesis. And if you start to really put them together, somebody, if you didn't try to do them out by hypothesis testing, might say oh, it looks like an endocrine-active chemical, probably an endocrine disruptor. But if you really look at it, you can probably see that it may not be because of where the different things are impacted.

So we have these kinds of tables for all of them in the paper that I showed you earlier. Directionality is important in this, too.

And so, I threw up here a -- one of the tables from a paper that is now in press with critical reviews. Passed -- got my comments back yesterday and they accepted it yesterday. So it is in press, critical reviews in toxicology. I was really hoping to be able to share that one because I figure triclosan might be a little bit more interesting than methyl tert-butyl ether for you guys. But, so, what you see here is, and again, unfortunately, the best example was an eco-example.

But in the -- I have stars next to on the amphibian ones there for the snout-vent length and the wet weight. And that's because, with the thyroid agonist, you would have expected the snout-vent length and the wet weight to go down because, with the thyroid, you're going to speed along metamorphosis. And so, as the frog enters metamorphosis and changes into a -- a tadpole changes into a frog, he loses weight, snout-vent length shortens. So, but in this case, the study went the other way.

So there was an increase in wet weight. It was an increase in snout-vent length. So, for a thyroid-agonist hypothesis, it's not relevant. And so I listed it as no effect. So that's, again, another thing that you need to think about. It's not just whether or not you have an effect. Is the directionality of it appropriate? And I have a number of those kinds of things in both this paper and that MTBE (methyl-tert-butyl ether) paper.

DR. BELSITO: But then, would that suggest that it's a thyroid antagonist?

DR. MIHAICH: Well, but then you have to go into the thyroid antagonist hypothesis and look to see where it fits. And no, it actually doesn't. It doesn't, so it's really, I mean, it's -- that's why it's really interesting to be able to -- you really need to be able to take it apart this way because, yeah, that would be a very logical thing to say was, oh, well, one that's a rank-three here. It's actually; I think it's at least a rank-two in a thyroid antagonist. So it's a little bit more meaningful, but you have to look at the rest of the endpoints to be able to understand.

Yeah, the bottom line is, no, triclosan is not an endocrine disruptor. But, anyway, so evaluating the response here. So if you have positive or negative responses in rank-ones, then you have some preliminary indication for or against that hypothesis. If you corroborate that with rank-twos, then you're starting to feel a lot more comfortable about that hypothesis.

However, if you have positive responses in rank-twos but not rank-ones, then you know you're going to have to look to the rank-threes, I think I have, no, I thought I had one more, but the thing is, with rank-three, you don't look at the rank-three. If you have no response in rank-one, no response in rank-two, you don't need to look at rank-three,

because they're not going to be useful, all right? It's only if you have responses that you really care about the rank-threes.

So, just to sort of tie the weight-of-evidence thing up, there are -- the key is hypothesis testing. Unfortunately, we see an awful lot of hypothesis generating in the literature. Oh, gosh, I have all these endpoints. I think it must be, rather than going and saying, okay, this is what I would expect and then looking at it that way.

And again, it's an evergreen process. Things can change as we learn more, as studies change. It can be applied to Tier II. I did that with the MTBE work especially. I did it -- I also had to do some of that with the triclosan work to get some more endpoints. And it's just a good way to resolve inconsistencies.

Okay, so that was their first shot at screening. However, EPA is moving towards faster screening methodologies now. They took a lot of heat and they've been taking a lot of heat for how slow the process is. Let's think about it. It started in '96 and we've done 52 chemicals. So I can understand.

So they're moving into a program called ToxCast. I don't know if anybody's familiar with it, but it's a battery currently of more than 700 in vitro high-throughput screens, and approximately 15 percent of them are directly relevant to the endocrine program. And so today I think the number's higher than 1,800 now but, as of a couple of months ago, it was about 1,800 that have been screened, and that data is in the public domain.

It's a really cool program. You can -- you just, you go right in. You put in your CAS number and if it's there, the information pops out. One caveat to this is if you've got a volatile chemical, it's probably not accurate, because these are done in 96 well plates. It's probably not there.

I know that -- I do a lot of work on silicones, and one of ours is in there, and I even had asked them, I said, do you think you even found, you know, had it in there, and they said probably not. So they are going back right now, though, on all of the volatile chemicals and trying to do essentially a QA/QC on it to try to figure out what might have had -- where you might have actually had the material in the wells during the test.

There's also an ExpoCast part to this, and that is to look at potential exposure. Right now it's only human health and does a lot with PBPK models and things like that. So that -- to get at a little bit of, again, trying to decide who's -- what's the low-hanging fruit? What are the things we need to look at first? So, where do you have a lot of activity and potential exposure?

And you'll see this a little bit better later. That's actually ethinyl estradiol down there, but we'll be coming back to this in a little bit. The other thing that they're using this for is to try to get at adverse outcome pathways.

And so, the key here is that, if you start with some sort of a molecular-initiating event or initial-molecular event, which is what I prefer, it goes through some set of key events that would lead to an adverse outcome. So again, we're trying to get to that adverse outcome to know that there is a link between the endocrine, potential endocrine mode of action, the endocrine-molecular event, and that adverse effect.

These look wonderfully linear in this picture. They're not linear, and one of the key -- other things that you have to understand, or be sure you understand, is the essentiality of these key events. If you block it, you block a key event, do you still see the adverse effect or don't you? And, because if you do, then that may not be the prime pathway that's going on.

Okay, so I thought I'd done something. So here's just another way of looking at these adverse outcomes and you see you start with, you know, toxicant exposure, some sort of molecular interaction, moving down to individual responses, and population responses, which we care more about on the eco side. This is an example of fadrozole, or they're using an example of an aromatase inhibition with fadrozole.

And so you get aromatase inhibition, and by doing that you have less estradiol because aromatase is, you know, involved with testosterone to estradiol at the end of steroidogenesis. And so, if you have less estradiol, then you're going to impair vitellogenesis, because vitellogenesis is, again, that egg-yolk protein that is produced, and it's produced because of estrogen. And if you have less of the egg-yolk protein that goes into the eggs, the eggs are not as healthy and, so, you would have reduced fecundity in your fish.

So that's an example of this adverse-outcome pathway. However, as I said, they're rarely the only pathway and they're rarely linear. And this is an example for propiconazole, a triazole fungicide, and there's really good information down the aromatase inhibition pathway for it. But it also -- you can have other impacts on different pathways, both mitochondrial dysfunction or the, yeah, CAR/PXR constitutive androgen -- androstane receptor and don't ask me again on PXR. It's not coming and you guys probably know it.

Anyway, it's a non-endocrine specific pathway. However, they all can lead down to reduction in fecundity and an issue with population. So, and thinking back, and I got this a lot. So, this paper that has this in it was just accepted by IEAM (Integrated Environmental Assessment and Management), one of the SETAC (Society for Environmental Toxicology and Chemistry) journals, and it's a paper on how do you find -- what do you have to look at if you're trying to identify an endocrine active chemical? And it was mostly focused on eco; however, most of the things that we talked about are -- would work for both human health and eco assessment.

And the -- one of my reviewers continually said, well, why do we care if exactly it's the primary pathway? Well, in the US we don't. In Europe, and whatever other regulatory authority might be working on a hazard-basis, we do very much because, if you call it an endocrine disruptor, it's probably going to get banned. So it's very important to try to identify what that primary pathway is, and this one comes back around in a second, and it's really kind of interesting.

So the other thing that we did in this last paper that I was talking about is, we were looking for different lines of empirical evidence to help us try to decide whether or not something is -- that it is a primary endocrine pathway. So one of the nice things that we've got a lot of times, and I'm assuming you can do it on the human health side, but we do it fairly frequently on the endo -- on the eco side is, acute-to-chronic ratios (ACRs). So you have an acute LC_{50} and you compare that to your chronic no effect level.

And so we actually have done -- used it for years -- in studying what are quality criteria when you don't have chronic and a chronic endpoint. But in this case, if you've got data from both acute and chronic, you can use it to help you try to decide if you may have an endocrine pathway going on.

So, the more potent an endocrine-disrupting agent is, the higher the acute-to-chronic ratio. If you look at ethinyl estradiol, the acute-to-chronic ratio is over five million. Most industrial chemicals, 10 to 100, and you can't really tell the difference.

So when we were looking at this as possibly some way of helping to tease apart data, we looked at, you know, did our systematic literature search to get the data, and we looked at the LC_{50} for the mortality endpoint, and then, chronic no effects for survival, growth and development, reproduction. We didn't limit it to -- it was whatever that NOEC (No Observed Effect Concentration) was. And then, what I did was, I put all the species together and did an ACR. And then, I took out survival from the chronic.

So if you had a chron -- the chronic endpoint was survival, took that out, and looked at only reproduction endpoints. And then, I also did all of that by separating fish from invertebrates from plants and algae. Because again, you wouldn't expect that, if it's an endocrine pathway, you're going to see impacts on invertebrates or aquatic plants and algae, because they're -- especially if we're looking at estrogen, androgen, thyroid, invertebrates don't have it.

So what ended up happening is, this is in that paper, although, I don't think I have BPA (Bisphenol A) in it. So I have two estrogens, I have an androgen, I have an anti-androgen, anti-estrogen, and then, my two chemicals, propiconazole and Bisphenol A. Everybody's poster child.

And what you can see here, if you look at the fact that we have fish invertebrates and algae there, huge, huge difference in the ACR between fish, invertebrates, and algae. And so that fits that pattern that the pieces fit together for an endocrine mechanism. Propiconazole and Bisphenol A, uh-uh. Straight across all less than 100, it's really about less than 40, all 3 of them, and you really can't see a difference between that.

So it suggests that endocrine is not the primary pathway that's impacting these organisms. You can see tamoxifen, there, so that's kind of an interesting one. It's less than 100, and obviously, tamoxifen's an anti-estrogen, right? But it's a pro-drug, and so it needs to be metabolized. So interestingly, with fish in particular, because they take it in through their gills mostly, it needs to be metabolized or it misses first-pass metabolism. So, and that's actually why you see impacts on fish with Bisphenol A, because it misses first-pass metabolism in fish.

So that's why you'll generally see an increase in vitellogenin, but you do not see changes in fecundity and fertility. So it doesn't -- you have to consider metabolism in some of these systems, too.

Anyway, it's just a piece of the puzzle. It's not a major one, but it's a piece of the puzzle that you can use. But does it make sense? So here we go looking at, these are ToxCast printouts for ethinyl estradiol there, and you can see here, if you squint really hard, that's the estrogen receptor. And the activity is very much lower than everything else.

On these graphs you can see this is the limit of cytotoxicity, and what you have to be very cautious of looking -- be sure to look at the limit of cytotoxicity for these because, if your activity is in that area where you also have cytotoxicity, it's probably not very meaningful to look at the results, because you've impacted your system, you know? So, but anything lower than the cytotoxic element is fine, so ethinyl estradiol hits the estrogen receptor pretty actively, makes sense for why you would see that difference.

Propiconazole not so much. So we have the androgen receptor right there, sorry. Estrogen receptor right there, and aromatase right there, remembering that propiconazole is considered to be an aromatase inhibitor. But you can see here that, actually what's happening is that, there's a lot of other kinds of activity that are much lower, so the activity is much higher than the EC_{50} is than the endocrine pathways. And again, that makes sense when you go back and you start to look at the weight-of-evidence and you look at that acute-to-chronic ratio.

And for Bisphenol A very similar. Here you have quite a lot of activity less than the cytotoxic limit. But a lot of it is also around other forms of toxicity. So again, makes sense that it may not -- the endocrine may not be the primary pathway.

Okay. Wanted to talk just briefly about lists, because they're very -- everybody sees them. We have a lot of problems with lists, because they're always lists of endocrine disruptors, not lists of potentially endocrine-active chemicals, but lists of endocrine disruptors. So in 2002, a contractor named BKH under contract to DG Environment in Europe, developed a list of substances for further evaluation, and that's what it was supposed to be -- for further evaluation, just potential, you know, wanted to look further at them.

Unfortunately, that list has taken on a life of its own, and other regulatory authorities are using them. I was just out in Washington State recently because of a particular chemical and it was not actually on the 2002 list. It didn't come in until 2007, put there by a stakeholder who decided they wanted it on that list because of one study, one screening study -- nothing else, one screening study.

The problem is, unfortunately, that list says a list of endocrine disruptors. And so it's now become the European list of endocrine disruptors, and it's not. It's a list, if you read down what it actually is, it's a list that has, you know, they didn't do a lot of -- they didn't do any weight-of-evidence. They didn't really do any systemic or systematic literature searching. It just -- one study got it on the list. So be very careful with that.

Recently, UNEP (United Nations Environment Programme) did it again, and so they were told by CYCO not to make a list, and they did it anyway and, so, and what they did was they compiled lists of lists. And so there was no -- chemicals were on lists for different purposes with different, you know, robustness. It was just a whole long laundry list of chemicals. And there was no requirement for data quality or weight-of-evidence in any of that.

Not sure where that's going to go. They got a lot of complaints, but hopefully, they'll at least qualify it a little bit. And now we have an endocrine-active substance information system in Europe. And so this was also released by DG Environment, and it is a searchable database of more than 500 substances. It is horrible to try to get through. It is not user friendly in any way, but, and it has a disclaimer that it has both positive and negative substances on there. However, every last one of them is probably there because either somebody put it there or it has one study.

So it's, again, a very, very poor list, but these things get a life of their own, so be very cautious and careful, because everybody's calling them endocrine disruptors and the only program, to date, that's been starting to look at that is the US, even though, if you talk to the Europeans, they'll tell you that they're way ahead of everybody else. But they actually don't require testing that.

One more thing, state-of-the-science of endocrine disrupting chemicals. So there was a 2002 report from the World Health Organization that was really quite well done, looked at things from a weight-of-evidence perspective, did systematic literature searches. It was then updated in 2012. That was not so well done.

So there is a critical review of the 2012 report that describes process and methods that went on in developing that 2012 report, compared it to the 2002 report, and evaluated all the different chapters for their strengths and weaknesses. This paper by Lamb et al. did look at some of the key issues. There was quite a number of unsupported claims, and it was not a comprehensive reassessment in any way, shape, or form. In case you're interested, that manuscript's in Reg Tox and Pharm, really quite well done, really trying to compare the two.

Some of the concerns. So the 2012 report was not an objective state-of-the-science review. It was not an update of the 2002 report. There were very, very little additional new studies in there, and it was very much cherry-picked what was in there. Causation was often inferred, it wasn't established. There are very -- there were a number of controversial topics that really weren't very well addressed.

And then, they also published a summary for decision-makers, interestingly enough, that was not a summary of the report. They brought in new concerns and, but, put it in decision-maker speak. So it was very interesting that that happened. And this is just a really quick example of some of just the difference.

So in the 2002 report, and I know it's very hard to read, this was talking about semen/sperm quality. Evidence is judged to be weak, lack of exposure data; however, it's biologically plausible. Okay. Something can be biologically plausible but not have empirical evidence to support it in -- for a simple -- for a particular chemical.

In 2012, that same discussion was evidence of suboptimal or poor semen quality in large proportion of men in countries in which they had been studied, evidence for a declining semen quality in these countries. So very different tone, not taking it in a very scientifically robust --

DR. GILL: Question the -- back to your last slide --

DR. MIHAICH: Uh-huh.

DR. GILL: -- the 2012 statement was that based on just reviewing the studies from 2002 or was there any new information?

DR. MIHAICH: There is not very much new information so that's -- and that was part of the problem -- is that it really wasn't much new information. It was just essentially a different turn on how somebody looked at it. Authors were somewhat different. There is definitely a push from essentially, I don't want to step on anybody's toes, there's sort of an activist side of this that is really wanting to continue the controversy and not look at things as quite as robustly as others.

And if you go to that Lamb et al. report you can get some of it. I'm sure some of it was. I mean, there were some very good people on that 2012 report. So that I know that they would have brought in good information, but it really was not what it was supposed to be, which was an update, of bringing in new data. It really was not, and a lot of the data was, again, what became really interesting is, that there is a lot of data that's been published through -- because of -- the US program, and most of that didn't get in.

So it was things that the authors had done, yeah. Okay, there's also another activity going on right now, and that's the cost of endocrine disruptors. I don't know if you've seen some of these papers. There's one, cost of endocrine disruptors in Europe. Recently there's the cost of endocrine disruptors in the US. We're worse, by the way, than Europe, because Europe has the precautionary principle.

So it's claiming that it's costing, you know, hundreds of billions of euros and dollars and, but if you look at some of the response on the papers, you can see that it's very poorly done. It's really -- if you -- I mean, there's economists that are looking at this going these are not appropriate methods to look at what costs, you know, things are costing.

But it lacks transparency in the methodology, incompletely assessment, but there is a big push right now, in fact, there's a -- unfortunately, the same authors published something in (inaudible) just recently, and it's making the way all around Europe now about how much endocrine disruptors cost and it's just not, if you look at the data, it's just not here.

However, flashy headlines are news. So just, again, just a little -- be very cautious when you look at things. Just to kind of finish up I wanted to go around the world.

I've already talked a little bit about Europe, and it's very hazard-based. Japan is currently developing assays. They've been working very closely with the US and through the OECD to develop these assays. And they've actually done quite a bit of work, are risk-based in their approach, have a two-tiered system similar to the US, and they also are working on in vitro assays to prioritize, so that they can enhance efficiency in choosing tests to do.

China also has a two-tiered program. They just recently -- it came out in late 2014, but the final version was implemented in April of this year. They're only focusing on mammalian tests, but they do have a two-tiered system similar to ours, and do plan to look at it from a risk-based perspective.

Elsewhere in the Asia-Pacific region, most APAC countries are just waiting, seeing how things shake out, this whole issue in Europe, which now is going to be pushed off a little bit more to get the criteria, is what's sort of keeping everybody on pins and needles. Australia has publicly come out and said that they will -- they don't see the endocrine disruption as any different than any other mode of action, and just to think about it, you know, when we regulate like on cancer. Yes, carcinogenesis is a mode, I guess, but there's a cancer endpoint, but with endocrine disruption, you're actually regulating on a mechanism of action, not an impact, an adverse impact. So you're -- it's not that there is something that's really that you can put, you know, a pin on right there. So it's a little -- it's just different, the way this is all coming about.

But anyway, Australia says they'll do a risk-based approach and, but some of them are starting to ask for data, and again, we can use some of this, but we're really trying very hard to make sure everybody's looking at it from a battery approach. Latin America, Brazil, and Chile are really the only ones that are thinking about endocrine issues, although there is some interest that's being gained on the part of NGOs, particularly in Argentina with pesticides.

Brazil appeared originally to be inclined to a hazard-based approach, but they are now open to other possibilities. I had a chat with their environment minister recently, and she said that they really can't -- they probably can't regulate based on hazard, and so she knows that they'll have to be, consider a risk-based approach. And Chile appears to be considering the risk-based approach also.

All right. I hope you guys can see this. I've gone through all of this, and this is your quiz, okay? So here you have this chemical, and I'm asking you if you think it should be banned, all right? And this is what happens. They'll look at these sorts of things.

So we have an in vitro ER transactivation that was negative. We have a steroidogenesis study, where there was an increase in estrogen production at 500 and 1,000 micromols. You have a male rat pubertal, where you have a decrease in body weight, decrease in prostate weight, decrease in seminal-vesicle weight, increase in testes weight, decrease in plasma progesterone, and a female pubertal, where you have a decrease in ovarian weight, decrease in adrenal gland weight, an increase in mRNA levels for FSH, decrease in mRNA levels for prolactin, increased mean length of estrous cycle, delay in vaginal opening, and an increase in age at the first estrous.

Are you worried?

DR. MARKS: A bit.

DR. MIHAICH: Unfortunately, in some countries you'd look at this and, because -- and see this is where, again, you need to look at every single hypothesis separately, because you get all of this data together and some might say, oh my gosh, it looks like an awful lot of stuff is going on in the endocrine system. But if you start to tease this apart, you actually may find that most of these are not relevant, you know, are not very telling for each of the hypotheses by themselves, and it's a good thing, because most of you all have it in front of you, right not, and that's caffeine.

So that's why, when you start to get into the data, it's really important to tease this stuff apart, and then remember what the definition is for an endocrine disruptor, which is that mech -- you know, you have to have that mechanistic link between that mode of action and the adverse effect. And that's it.

Have questions? Yeah.

DR. MARKS: Have you looked at this with parabens?

DR. MIHAICH: Oh, use your mic. He asked you to use your mic. Sorry.

DR. MARKS: Have you -- can you comment on parabens?

DR. MIHAICH: No. And I knew you guys were working at it this year. I can't. Again, I was really trying to get triclosan out for you, because I figured you might have a bit more of a, you know, knowledge base there possibly. I don't know about parabens.

I would just say that when you start looking at them, I would be sure that you think about this when you do. I did just find -- I was telling right before we started that I found out yesterday or last week, I guess, since yesterday was Sunday, that right now (inaudible) in France is refusing to register anything with methyl paraben in it because they're calling it an endocrine disruptor.

And interestingly, the person I was talking to has it in an organically-certified pesticide. So here we go. I just think it has to -- I think we have to look at all the data and I don't know it -- maybe if I have the right client I will. Yeah?

DR. HILL: You used the example of a frog snout-length change, in terms of thyroid hormone or activity, if I remember right. So those are frog hormone receptors, not human receptors, frog nuclear systems with frog trans-activators and repressors and coactivators. And then you made a statement not thyroid-based activity, but then that's frogs.

So amphibians, how do you extend those results to humans unless you have transgenic frogs?

DR. MIHAICH: Actually, the systems are very well conserved between frogs and human and, in fact, interestingly enough, again this is because I was an EDSTAC groupie, there was a lot of discussion about whether or not we should do the rat study or the frog study, because you can find just about the same thing. And the key with frogs is, metamorphosis is completely controlled by thyroid so, or very much controlled by thyroid. So that's why the receptors are just about the same.

DR. HILL: Just about the same is not the same, so that's the point.

DR. MIHAICH: No, that's right, except that it -- remember these are the screens, right? So it's to give you an idea of whether or not you potentially have activity, and then you go on to do the definitive tests that'll give you the no effect level.

DR. LIEBLER: I think she's just saying it's not that much of a leap.

DR. MIHAICH: Very good.

DR. HILL: If it weren't Monday morning, I would have maybe thought of that one, too.

DR. MIHAICH: Very good.

DR. HILL: No, I -- the red flag went up because of the way you made the statement.

DR. MIHAICH: Oh, I'm sorry.

DR. HILL: Yeah, and I --

DR. MIHAICH: Yeah. Yeah, no, these are the screens so, and you know there is, as far as an amphibian goes, there is the larval amphibian growth and development assay to get at amphibians. And then, you've got the extended one-generation rat study to get at rats.

But isn't the -- even a rat can be kind of not a great predictor for humans, because of the -- yeah, I mean, it's going to over -- a rat's going to over predict for humans anyway? So yeah.

DR. HILL: There are always those issues. I mean, even in humans themselves, and you mentioned the difficulty of estrogens, is because we have things like selective estrogen-receptor modulators and selective progesterone-receptor modulators.

DR. MIHAICH: Yeah, sure.

DR. HILL: And so until you get right down to which tissue, which receptors, which other proteins in these nuclear receptor complexes, you don't know the complete picture. And so, the way you made the statement, and again, I

knew you knew this, but the way you made the statement, if somebody, not be critical of the press because, but if somebody's sitting in the room and latches on to a statement like that and takes it --

DR. MIHAICH: Oh, that happens all the time.

DR. HILL: -- just to sort of -- oh, I know it does and so --

DR. MIHAICH: Yeah. No, and that's -- and actually, the issue of -- I mean, really it comes down to, and yes there's serums and all of that, but you really have to think about the potency in all of it because, you know, you're talking about chemicals that are so low in potency that they can't really and truly do anything over and above the constitute of hormone. So it's just, you know, and we see that a lot, and that's why you don't generally, you know, you often see other mechanisms that are probably more in play than endocrine.

DR. LIEBLER: So I actually have a serious question. So about halfway through your talk --

DR. HILL: My question was serious.

DR. MIHAICH: That was --

DR. LIEBLER: My wise-ass comment wasn't so anyways, but about halfway through your talk, you referred to an acute-to-chronic ratio and it -- I've just been thinking a little bit about it, and I don't know if other people in toxicology think about this a lot, but it seems like actually a potentially useful and important concept. Could you go back and just -- you don't need to go to slide, but if you just restate what it's about and how you're using it.

DR. MIHAICH: Oh, you see that's the problem. You do -- I can flip back. Almost there. There we go. So it's really just, and it worked really well for fish, invertebrates, and algae to be able to take it apart.

DR. LIEBLER: Sorry, I --

DR. MIHAICH: Oh, sorry.

DR. LIEBLER: If you could just restate what it is? It's a ratio of what to what?

DR. MIHAICH: Oh, oh. It's the acute LC_{50} , that's the third bullet point down, acute LC_{50} to a chronic no effect level, and it's whatever your chronic no effect level --

DR. LIEBLER: I see, okay.

DR. MIHAICH: -- that survival, growth, or development, or reproduction.

DR. LIEBLER: So it can be used in a number of contexts potentially?

DR. MIHAICH: Right. I don't -- I haven't tried it with human health data, but I would think that it might be useful, too, as a piece of the puzzle from a weight-of-evidence perspective.

DR. LIEBLER: So a high -- so if you go to the next slide your three species bar charts, so then --

DR. MIHAICH: Right.

DR. LIEBLER: So then a high value for this indicates specificity for the mechanism is what you're talking about?

DR. MIHAICH: Uh-huh. If you see a big difference between the narcotic, you know, the acute narcotic effect and some other type of a, you know, whatever else is possibly causing the chronic effect, then it is likely you have a very, you know, a more specific mode of action that's occurring in the chronic.

DR. LIEBLER: I see what you're saying, okay.

DR. MIHAICH: Yeah, so whereas --

DR. LIEBLER: Because some of these effects actually take a while to manifest themselves biologically and, so, depending on what you mean by acute, you might not actually be able to have the, you know, you might not be able to have the endocrine-disrupting manifestations of something that would be a bona fide endocrine disruptor --

DR. MIHAICH: Right.

DR. LIEBLER: -- actually happen in the timeframe of your --

DR. MIHAICH: Right. And that's why the acute is typically more your narcotic mode of action that a chemical might have and, so, as compared to a more specific type of action that you would see in a chronic study that you -- where you've given it enough time.

DR. LIEBLER: Right, thank you.

DR. MIHAICH: Uh-huh.

DR. BERGFELD: I have a question. We have endocrine disruption frequently to be addressed with our ingredient reviews, and I wonder if you could give us some advice as to how to handle that, when that comes up as an issue in a report, because obviously, a million dollar testing is not going to occur.

DR. MIHAICH: Well, hopefully, it's endocrine activity first, before you decide it's endocrine disruption, even though somebody's probably already told you that it's endocrine disruption. But you will go back and look at the data, maybe think about, are they calling it an estrogenic chemical? Then let's go down that hypothesis for an estrogenic chemical and bring all your data in and see where the endpoints fit.

And if you go into the methyl tert-butyl ether or the triclosan one that will soon be published, I even went and I looked at chronic studies, where you could look at say a uterine weight and pull them in also. So you can take it -- it doesn't have to be the specific screen that is part of that 11. You can look at other data that might still be relevant for that particular hypothesis and use it.

There are some caveats to it, though. So, for example, if you were to pick for the estrogen agonist hypothesis uterotrophic study is very good in increasing uterine weight for an estrogen. But an increase in weight in a longer term study in a cycling female is going to be a lot harder to, or you need to use more caution in understanding it. I know there is one study I was looking at before, and they didn't look at body weight compared to the uterus weight, so there was not -- they didn't measure that at the time.

Same with something like preputial separation or, you know, any of those kinds of things where they might vary with the body weight. You've got to make sure the body weight information is there. So it's just a matter of trying to not lump all the endpoints together and call it endocrine disruption, you know? Try -- if you're trying to decide, take it apart, look to see, because not all endpoints weigh the same for a particular hypothesis. I don't know if that really answered your question but --

DR. BERGFELD: It makes us more cautious.

DR. MIHAICH: And I wish -- I hope so, and I wish other people were too, because it's very hard to try to go back and kind of fix what unfortunately the train has taken down the track already and, but it's not, again, in the US it's not really as big a deal and, but you know, try to take into account potency, that's really important, too. And then,

just be very clear on whether it's endocrine active or really you've identified an adverse effect that's through an endocrine mechanism and is your, you know, your lowest effect. So yeah.

DR. HILL: You say in the US it's not that important, but then there's the regulatory point of view and then there's the consumer point of view, and the persuasive degree of sort of cynicism or skepticism that becomes so problematic that you can't put any regulation --

DR. MIHAICH: That's true.

DR. HILL: -- in place.

DR. MIHAICH: No, it's true.

DR. HILL: So when you say caution she's saying in the context of not over --

DR. MIHAICH: Right.

DR. HILL: -- assess based on it might be an endocrine disruptor.

DR. MIHAICH: Right.

DR. HILL: But then the precautionary principle, on the other end, you're weighing those two things, and that's --

DR. MIHAICH: No, and it's true.

DR. HILL: -- non-trivial, right?

DR. MIHAICH: No, and it's very true. I completely agree with you. It's just that, here, we're less likely to call something an endocrine disruptor, less likely to have a category, whereas in Europe that's really being pushed hard right now, so.

Okay. Okay, question?

DR. MARKS: Did you want to make a comment, Tom? I had one last question.

DR. MIHAICH: Sure.

DR. MARKS: Great presentation, thank you.

DR. MIHAICH: Thanks.

DR. MARKS: In the beginning, it seemed like some of the let -- you were talking about regulations and legislation, and it seemed like some of the legislation was really very detailed oriented, more than I would expect legislators to be able to delve that deep. Was that true? And that was one of the comments that --

DR. MIHAICH: You know those scientists in Congress, so you know, what happened and you can go back a little bit further than that in history. It really started, you got Rachel Carson with DDT and then, Theo Colborn who kind of took in on after that, and so they were the ones that were kind of pushing a lot of this.

Unfortunately, one of the things that kind of put us over the edge on in getting those two regulations was a study out of Tulane that was ultimately retracted from science. So where it showed synergy and all sorts of other things, but it just put, like you said, you get the public going in a certain way and then, the politicians move. They were very specific to estrogen because that was the only thing that they were really hearing at that time, the legislators, and so -- and they were very specific to pesticides because that's the Food Quality Protection Act.

So that's really what got started there. And then, the Safe Drinking Water Act came in, the amendments to it and, because they were doing it on the pesticides side, they decided, okay, let's do it on the toxic side in drinking water contaminants. So, but it was really the EDSTAC, that FACA, that added way more detail to it and came up with the -- they actually came up with different screens.

One of the interesting things was they wanted a prioritization step at that time, but the only high-throughput kinds of screens we had, and really still do, came out of the pharma side of things, and they're looking for really active chemicals, and none of these are. So they weren't -- it wasn't working. So they trashed the whole issue of prioritization at the time, because it wasn't working, and went right on in to the screens. And then, they had a number of screens that could never be validated.

So they had a tadpole tail resorption assay that never quite worked out, because it was requiring too much attention right at metamorphosis, and it wasn't as helpful as you can see with frogs. You can have asynchronous metamorphosis and so, you know, legs get short while tails get long, you know, things that you wouldn't expect, and that can be an indication of a thyroid interaction. So it came more -- so there were a lot of changes throughout the program.

DR. SNYDER: So I have a comment to our Director probably not to you but --

DR. MIHAICH: Okay.

DR. SNYDER: -- I would think, it seems to me, that much of what we see in our research into the literature is endocrine activity, in what we see. And so I think that as the panel, I would recommend that we develop a boilerplate that when we do have endocrine activity that is somehow linked to our understanding, much like we do with other things like the hair dyes and things where we have this boilerplate that we understand the literature and keep that current with the literature. And what -- the difference between activity and disruption is, and formulate some kind of a boilerplate that could be linked, so it helps us then to also evaluate the literature and know what questions potentially to ask, what data sets to ask or and how to link different data sets.

Because, previously, we've been linking estrogen binding activity, not knowing whether it's inhibition or activation, and then we look at, see where is a uterotrophic assay, and if it is, if it's negative, then it's the end of the story. Well, to me, now that may not be a very good approach. So we need to probably have a better approach and, but to understand our approach, to have a boilerplate, so we know how to understand it and it'll also help our -- the people who use our documents to understand what we looked at and why we have a certain comfort level bringing in potency, et cetera.

DR. MIHAICH: That's a good point. If you go to that 2014 Borgert publication you can find all of those tables, so that, where you can see each of the endpoints that are there and what they mean. And then, the MTBE paper we had to do it, we did it more where we brought in a lot of the chronic data, too, and what you can do, and that's why these things can change so. Trying to decide on what the directionality is can be kind of challenging.

So we spent a lot of time going back into the literature to see, okay, if you've got something that's a positive and, you know, and everything seems to fit, what does it do in those studies? And so we spent a lot of time trying to gather that information so that as we looked at new chemistries we would -- and we could see which way a weight changed or whatever, does it make sense? So again, asking that, does-it-make-sense question. Uh-huh. All right.

DR. GILL: Seeing no additional questions, thank you very much.

DR. MIHAICH: All right, sure. Sure.

DR. GILL: Very interesting.

Dr. Belsito's Team

DR. SNYDER: Just interesting wording we had in there for the endocrine aspect. We didn't use endocrine disruptor, we used agonists and antagonist. Interesting.

DR. BERGFELD: I think your idea of getting a boilerplate is very good. And what are you going to suggest for this, this particular document?

DR. SNYDER: Well, I think it's worded appropriately here. We're not --

DR. BERGFELD: Okay.

DR. SNYDER: -- saying it's an endocrine disrupter. We're saying that there's activity that leans this way or that way. And I think that's the point that we would then have the boilerplate to say that it doesn't fit any of the criteria for classification as a disruption.

DR. BELSITO: So, you want that in the discussion?

DR. BERGFELD: I think so.

DR. SNYDER: I think we're okay here as it is. But I think --

DR. BELSITO: Okay.

DR. SNYDER: -- looking forward, we need -- I mean that's going to take a while to formulate that boilerplate and run through some of the duration of that. But I think the presentation today was a good foundation for all that.

DR. BERGFELD: Did you copy her slides? Is that going to be part of the record?

DR. BELSITO: Yeah.

DR. HELDRETH: Yeah, absolutely. We'll have it, and we can make sure all the panel members get a copy as well.

Tuesday, December 6, 2016

DR. GILL: Good morning. I do want to thank Doctor Emily Mihaich for her thoughtful presentation. Thank the council for the suggestion that we have that update on Endocrine activity. I did hear from a number of panel members that, CIR needed to look at developing some boilerplate language that could be useful um in the reviews. So we will prepare something for presentation to the panel at the next meeting.

142d COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

(MAIN SESSION)

Monday, April 10, 2017

PROCEEDINGS

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: Okay. This is probably, well we'll see. Maybe generate the most discussion tomorrow. And as I said, I'll go through them in no particular order, other than starting out, I think, with the introduction. Since that seems reasonable. Then the others. So the last one I have is the draft endocrine activity and endocrine disruption boilerplate. Ivan, why don't you go ahead and summarize that, and we'll get the response of our team.

DR. BOYER: Okay. This is a document that we're developing. It's the first time the panel has seen anything like this. It is more or less modeled after what you saw in the aerosol framework boilerplate document. We'd like to post this particular document that addresses endocrine disrupting chemicals and endocrine active chemicals on the website and refer to that document in our reports when it's appropriate.

And here, the document, the writing of this first draft was informed to a great extent by Dr. Mihaich's presentation at the last panel meeting and some of the key references, high-level references, that she referred to in her presentation. So we took a close look at those and prepared this document that clearly makes a distinction between endocrine active chemicals versus endocrine disrupters. It provides the definition for endocrine-disrupting chemicals that the WHO has developed and, in fact, is very similar to other definitions that have been developed and so on. It makes it very clear that it is important to know that the mechanism of action for an endocrine disrupter is known, so that you can distinguish endocrine disrupting activity as a primary effect, a direct effect, of a chemical on a whole organism. Distinguish that from maybe an indirect effect that might be attributable to some other toxicity as the primary effect and so forth. It pretty much goes down through the list of some of these key issues with respect to endocrine disrupting chemicals, and provides a summary of that topic.

DR. MARKS: Ron, Ron, and Tom, comments about this draft? It's the first time we've seen it.

DR. SLAGA: I thought it was a very nice summary.

DR. MARKS: Thanks, Tom.

DR. SHANK: I thought it was very good, very well written. The only comment I had was on page five, the second paragraph. Where it says it's been hypothesized that combining substances may be additive or synergistic. Would it be helpful to add an example or two?

DR. BOYER: Yes we can elaborate on that.

DR. MARKS: Just a little bit.

DR. BOYER: Sure.

DR. MARKS: That's under which one? Which heading, is it mechanism of modes of action, or weight of action?

DR. SHANK: It's just above mechanism of action

DR. MARKS: Okay. There we go.

DR. SHANK: It's page five, the second paragraph.

DR. MARKS: Yes, I see it.

DR. SHANK: The paragraph is fine. I was just...

DR. MARKS: It has been hypothesized, that one. So examples.

DR. SHANK: Would it be helpful to the reader to have an example or two.

DR. BERGFELD: I'd also like to ask a couple questions. Has the CIR Support Committee looked at this?

DR. EISENMANN: No

DR. BERGFELD: No. I think they need to.

DR. MARKS: Oh yeah. I assume that with all of these.

DR. BERGFELD: And the second thing, when it goes up on the website, would there be a chance for comment from whoever reads it?

DR. GILL: I'll take the second one first, there's always an opportunity for comment and feedback on our documents. This, I anticipate, like the others, will go up as draft and we would ask for comments. It's sort of like our priority list. We get the comments and see what the feedback is at the next meeting, to see if there are any changes. And then I think we make the statement online that these are living documents, they're changeable.

DR. BERGFELD: I guess on the third question would be, will the expert be presented to us get to review it?

DR. MARKS: That's what I was gonna ask Ivan. I think that would be not only common courtesy, but also very important to make sure we have her, Dr. Mihaich's, input.

DR. BOYER: And I think she would be very open to that. She'd appreciate that.

DR. MARKS: Yeah. Good. So we have some pending things coming. The Science Committee's feedback. Ron Hill, I don't want to skip you, because you didn't have a chance to comment.

DR. HILL: I'm good right now.

DR. MARKS: Okay. Good. So, I think what I'll do is just say, Ivan, good job, tomorrow. I'm not sure I'll bring up the examples. You can slip that in and we'll be seeing this again. Unless you want me, Ron Shank, or you can mention that.

DR. SHANK: My only suggestion

DR. MARKS: Okay. Science and support.

Dr. Belsito's Team

DR. BELSITO: Then we have the endocrine disruption.

DR. LIEBLER: That's in wave two. I just wrote see what Paul thinks.

DR. SYNDER: To be honest, I needed more time with that, because it was a tough one to go through. I went through it, but.

DR. BELSITO: I thought it was fine. I mean but again --

DR. LIEBLER: This is not my area.

DR. BELSITO: Yeah, it's not my area.

DR. LIEBLER: I had three tiny edits. I thought it read very nicely. Maybe laying out the issues and distinctions and definition and then describing kind of the factors that would lead to the methods of modes of action, so on. So I thought it read really well. But I also I don't feel like this is in my wheelhouse, that there might not be something in the literature that is not captured here.

DR. BELSITO: Well we had the presentation at the meeting and, I mean, I think it pretty much followed what the presentation that we got in terms of yeah, you can see these effects usually at huge doses of material. And, even then, do they actually end up having a biologic consequence to the organism? That's our point. The amount of endocrine disruption that can be observed in experiments from paraben is about the same as eating a sweet potato. Are we going to ban sweet potatoes? I remember when we looked at that data, there was actually in the draft I think a phytoestrogen dial that was derived from yam. And that actually had more uterotrophic effect than the paraben.

DR. SYNDER: And this certainly gives us the framework to address whether data we received is truly endocrine disrupting data or its activity. I think that was the biggest thing I took away from that, and from this document. So we clearly have a document that says how we're interpreting studies as to whether they represent endocrine disruption. Because I think probably, to a fault, we presumed that everything was endocrine disruption. That's not the case.

DR. BELSITO: And also our definition of endocrine disruption seems to be well supported. Now, I don't know, is this a government panel that has come up with this definition or who is that group you referred to?

DR. BOYER: The definition that we incorporated, the specific definition was the latest from the World Health Organization. And there are a number of other agencies that have developed definitions, but they're all pretty much consistent.

DR. BELSITO: But we're using agencies that aren't industry related. We're using governmental or nongovernmental agency definitions of what an endocrine disruption is. We're not just saying, oh yeah, having endocrine activity, but we're not going to call it a disruptor, we just decided to do that. We're actually using definitions that it would be hard for anyone to argue that these people are biased in any way by their viewpoints, in terms of the organizations that are coming from. So I like that. I like that a lot. I so I was fine with it.

Then the last point, yeah, I think I like the document that said what we search, that's good.

DR. SYNDER: I think it's really important that we have that. That's the whole basis for data that we're not missing data, and that we are evaluating data that are available.

MS. FIUME: So we'll start including it in our introduction?

DR. BELSITO: Yes. And that's it, right? We have nothing else to discuss. Okay, so I guess the two issues that we really don't have anything to say at this point was really the aerosol boilerplate, we're going to react somewhat to what Jim Marks says on that. And that really was it. I mean the hair dyes we're fine with. Endocrine we're fine with. So it's basically crafting the response back to Women of whatever and how we want to proceed with revamping our respiratory boilerplate.

Tuesday, April 11, 2017

DR. BERGFELD: Well, welcome everyone. We're going to begin the 142nd CIR Panel Meeting now. We have some missing people, but hopefully they'll be joining us. As the team members know, they had 15 ingredients to review yesterday. Six were final. Four drafts. And two draft tentative finals. In addition, there was another discussion that was entertained. And that was, a number of position papers. One on hair dye update. Another on aerosol. The comments regarding powders. The endocrine activity and disruption. And then, the search data of methodology. And all of you had a chance to comment, and I believe that the CIR administrative staff is open for comments to come in later as well. The endocrine activity and disruption document will also be for public review. And they'll be comments coming from the public on that one. And we're due to see that in June at our next meeting.

DR. MARKS: Next, Ivan you're up. You're up for the next three. So I'm going to proceed again in no particular order. The first one, Ivan sent a memo dated March 31, 2017, was a draft endocrine activity. An endocrine disruption background, and framework, this was in wave 2. And our panel felt that, again, this draft report or paper or boilerplate, was actually very good. We suggested that it be reviewed by the Science and Support Committee, and also by Dr. Mihaich, who you recall presented a very nice review of this issue to the panel in the past.

DR. BERGFELD: Comments by the Belsito team.

DR. BELSITO: Nope. We liked it.

DR. BERGFELD: Liked it. Moving on.

Endocrine Activity and Endocrine Disruption 09/2017 Draft

BACKGROUND

Concerns have been growing over the past several decades about the potential for exposures to some chemicals to cause adverse health effects by altering the normal functioning of the human endocrine system. The Cosmetic Ingredient Review (CIR) continually monitors developments of the research and the regulation of such substances as a matter of long-standing policy. CIR safety assessment reports include data from in vitro (e.g., estrogen-receptor binding) and in vivo (e.g., uterotrophic) assays that address the potential for ingredients to bind to and interact with endocrine receptors and other components of the endocrine system, as well as reproductive toxicity studies that identify adverse responses for safety assessment.

The CIR Expert Panel considers ingredients that have demonstrated endocrine activity in such tests as potential endocrine disrupting chemicals (EDCs), depending on the relevance, quality and concordance of the available studies, the doses and concentrations tested and the dose- or concentration-response relationships observed in such studies, the affinities of the ingredients for endocrine receptors or other components of the endocrine system, the potency of endocrine-active ingredients compared with endogenous hormones, and other important factors that contribute to an assessment of the overall weight-of-the-evidence (WoE). Such assessments depend, at the outset, on a clear definition of what constitutes an EDC, understanding of the distinction between endocrine activity and endocrine disruption, and differentiation of endocrine-mediated effects from other likely mechanisms of action (MOAs).

These factors are discussed in greater detail below.

Definitions and Distinctions

In 2002, the World Health Organization (WHO) International Program on Chemical Safety (IPCS) defined an EDC as “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.”¹ By this definition, EDCs cause adverse health effects in living organisms specifically by altering the function of the endocrine system.

This definition has three important elements:^{2,3}

- The substance must act through an endocrine MOA that alters the function of the endocrine system
- The substance must cause an adverse health effect
- The adverse effect must be causally related to, and occur as a consequence of, the altered endocrine function

All three of these elements are necessary to identify a chemical as an EDC.

The IPCS (2004) defines an adverse health effect as “change in morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influence.”² An “adverse effect” in this context means toxicity, including pathology or functional impairment, in an intact organism, their progeny or (sub)populations through a hormonal or hormone-like MOA.^{2,4}

An adverse effect reflects exceedance of the body’s normal ability to modulate endocrine function adaptively.^{2,4} An increase or decrease in endocrine activity does not indicate a health risk to a living organism, unless it can be shown to lead to harmful effects.

Endocrine disruption is distinct from endocrine activity, which is simply the ability of a chemical to interact with the endocrine system without necessarily posing a health risk.⁵ The endocrine system is designed to respond to environmental fluctuations, and the responses are considered to be adaptive when they are transient and within the normal homeostatic range.^{2,6,7} The responsive nature of the endocrine system is essential to health. Thus, the

potential for interaction with the endocrine system is distinguished from the disruption of physiological or developmental processes that may result from such interactions.

Furthermore, in vitro data alone are not sufficient to classify an ingredient as an EDC. Endocrine activity observed in in vitro tests and some in vivo assays is not sufficient to classify a substance as an EDC if the tests do not indicate whether the alterations cause actual harm in a living organism or its offspring. Such a substance may be considered endocrine-active but not an EDC.^{2,8}

Thus, for example, if the objective is to establish whether or not a test article is a reproductive EDC, it should be tested for its “reproductive” activity (i.e., the ability to alter the development or the function of the reproductive system) in vivo, rather than just for its sex-steroid activity in vitro.¹

Many endocrine active substances may lack sufficient potency, compared to endogenous hormones, or exposures may be so low that no effects occur.⁵ In other cases the body naturally adjusts, and the exposure causes no health effect.

Dose, Dose-Response and Potency

Doses administered in experimental animal studies are often orders of magnitude greater than possible consumer exposures, to produce an effect on the endpoint(s) of interest.^{2,5} Excessive doses of any chemical increase the chances of systemic toxicity and effects on endocrine endpoints that are mediated indirectly by other effects.

Results from studies in which there is systemic toxicity cannot be used to identify and characterize the endocrine activity of a test substance. For example, alterations in endocrine function may be the indirect effects of weight loss caused by exposure to the substance.

The issue of dose-response relationships for EDCs at low doses continues to be highly controversial.¹ This is because, for example, EDCs often act by mimicking or antagonizing the actions of endogenous hormones. These hormones are typically substantially more potent than exogenous EDCs and are present in the body at physiologically-functional concentrations. Thus, dose-response relationships of EDCs are often different from those of other chemicals that do not act directly on the endocrine system. Consequently, dose-response relationships vary for different chemicals, endocrine mechanisms, and timing, frequency and duration of exposure. This is true for endocrine-mediated carcinogenesis and developmental, reproductive, immunological, and neurological effects.

The reported low-dose effects of EDCs have come under intense scrutiny concerning the adequacy of traditional toxicology testing paradigms for detecting low-dose effects.¹ Participants of a workshop addressing this issue concluded that low-dose effects often are not replicated consistently, and the toxicological significance of the reported effects is often questionable.⁹

At the receptor level, potency is determined by the affinity of a substance for binding to a receptor or other endocrine-system component and the efficacy with which it activates or inactivates the component.^{2,10} Endogenous hormones characteristically exhibit strong binding affinity and high efficacy for activation of their corresponding receptors. Thus, endogenous hormones are potent modulators of endocrine function. In contrast, exogenous chemicals are rarely as potent as hormones because of lower affinity, lower efficacy, or both.^{2,11,12} The presence of exogenous chemicals generally will not alter hormone binding to any significant extent at low doses, and biological thresholds for potency can be expected.^{2,10}

The ability of a substance to produce a biological effect in vivo may be substantially different from the activity measured in in vitro assays.^{2,8} In vitro studies can be relevant for investigating MOA and the potential for endocrine activity. However, in vitro tests may not provide useful information on dose-response relationships, do not take into account the toxicokinetics of a substance in the body (i.e., absorption, distribution, metabolism and elimination), and do not account for homeostasis or other pathways and processes that may be responsive to in vivo exposures. Thus, hazard identification should be based on the ability of a substance to produce an adverse health effect in vivo, not solely on the results of in vitro tests.

It has been hypothesized that the combination of several weakly acting substances may be additive or synergistic and, thus, cause adverse effects.⁴ However, such effects are improbable, based on theoretical and practical considerations.^{4,7,13}

Assuming dose additivity for specific toxic effects presupposes that the chemicals in a mixture are true congeners, produce the same spectrum of biological effects by the same mode of action, are metabolized by the same biological processes, and exhibit parallel dose-response curves.¹⁴ There are numerous direct and indirect mechanisms by which substances may affect hormones or exert hormone-like activity, which limits the possibility of additive (“cocktail”) effects. The potential for additivity is reduced further by differences in toxicokinetic pathways, which are rarely, if ever, identical for different substances of this nature.⁴

Furthermore, there are major quantitative and qualitative differences in the affinities or activities of weak ligands for cell receptors, compared to those of strong ligands.⁴ In principle, weak ligands may occupy and trigger cell receptors at high concentrations, but low concentrations of weak ligands will not influence the receptor binding or receptor-mediated effects of strong ligands.

For example, one study investigated the estrogenic responses to mixtures of synthetic chemicals combined with phytoestrogens at several concentrations in vitro and doses in vivo. The results showed that low concentrations or doses of the chemical mixtures failed to increase estrogenic responses, in vitro or in vivo, compared with the responses to phytoestrogens alone.^{4,15} Significantly increased responses to phytoestrogens occurred only when each synthetic chemical was near or above its individual response threshold. In vitro, high concentrations of the synthetic chemicals in the presence of phytoestrogens yielded greater than additive responses, but mixtures of the chemicals in the absence of phytoestrogens produced less than additive responses. In vivo, the responses to high doses of the synthetic chemicals in the presence of phytoestrogens were consistent with additivity. The authors concluded that mixture effects are likely to be of concern only when the components of the mixture are present at or near their individual response thresholds.¹⁵

Thus, additivity may be limited to substances with moderate-to-high potencies at doses near their individual response thresholds, and is not likely for substances with low potencies or at low doses.^{3,4,14,15} There is no evidence of additivity for such substances at exposures within the range of likely human exposures, despite the presence of thousands of natural, weak hormone-receptor agonists and antagonists in food and the environment.^{4,13,16} Furthermore, there is no theoretical justification for extrapolating data from the high exposures tested in the available studies to assess the risks associated with exposures to the low doses that can reasonably be expected among consumers.^{4,14} Most mixture studies are not relevant for evaluating human health safety or risk because human exposures are typically orders of magnitude lower than doses that cause detectable responses.

Mechanisms or Modes of Action (MOAs)

As noted above, one of the three key elements of the definition of an EDC is that the chemical must act through an endocrine MOA that alters the function of the endocrine system. Thus, by this definition, it is important to know that the critical adverse effect of a chemical is caused by a primary or direct endocrine MOA, rather than the secondary or indirect manifestation of a non-endocrine MOA or non-endocrine toxicity, before it can be considered as a potential EDC.⁴

The possible primary or direct MOAs of EDCs include inhibition of hormone synthesis, transport, or metabolism and activation of receptors through processes such as receptor phosphorylation or the release of cellular complexes necessary for hormone action, in addition to direct interactions with hormone receptors.^{1,3} Furthermore, multiple receptor systems act in concert (“cross talk”) to regulate biological functions. These, and many other factors, should be considered when considering mechanistic information on EDCs to support human health safety or risk assessments. Of particular concern are species, inter-individual, and tissue specificities in endocrine-signaling pathways.

The MOAs are poorly understood for most associations reported between exposure to EDCs and biological outcomes.¹ This makes it difficult to distinguish direct from indirect effects and primary from secondary effects of exposures. Although there is considerable information on the early molecular events involved in the responses to hormones, there is comparatively little known about the relationships between these molecular events and adverse

health effects, such as cancer and reproductive toxicity.¹ This knowledge gap limits the ability to causally link an endocrine-specific MOA and an adverse effect. It will continue to be difficult to attribute adverse effects to endocrine-mediated pathways until such data become available. However, this knowledge gap does not preclude the assessment of safety or risk from appropriate studies from which relevant and reliable no-observed-adverse-effect levels (NOAELs) can be derived.

Considerable homology exists in the endocrinology of vertebrates. However, there are differences among some species in endocrine function that warrant consideration in safety and risk assessments.¹ For example, the role of specific hormones in reproductive function and development can vary substantially between human beings and non-mammalian test animals. In addition, species differences in metabolism can cause marked differences in responses to exposure. Thus, safety and risk assessments should address the significance of such differences, to the extent that the differences are known, and characterize the uncertainties associated with using data from animal studies to evaluate the potential for adverse health effects from the use of cosmetic ingredients.

Weight-of-Evidence (WoE) Assessment

A WoE assessment is essential for determining the conditions under which observed effects of exposures can be attributed to an endocrine-mediated MOA.^{1,5}

The critical elements of a WoE assessment include an assessment of the relevance, appropriateness, usefulness, quality and reliability of the studies available for informing the safety assessment process.⁵ Also important is the evaluation of the consistency of the pattern of responses across studies for or against explicitly defined hypotheses. The hypotheses are typically defined to assess the premise that a substance interacts as an agonist or antagonist with components of the estrogen, androgen, or thyroid pathways or of the aromatase or steroidogenic enzyme systems, for example. One key concern is how dose responses observed in experimental animal studies compare to potential human exposures.²

Several additional factors that have been outlined for evaluating the available data against these hypotheses in an overall WoE assessment include temporality, strength of the association, biological gradient (i.e., dose response), biological plausibility, and evidence of recovery.^{2,17-19} Furthermore, evaluating the MOA of a substance is critical because the MOA is central to the overall assessment of whether or not a substance can be considered to be an EDC.^{1,2}

All of the relevant information should be considered in an organized and structured manner. The goal of this approach is to reconcile different results from different studies. (Cook et al., 1994).^{1,20}

FRAMEWORK FOR DISCUSSION SECTIONS OF SAFETY ASSESSMENTS

[INGREDIENT NAME(S) OR GROUP NAME, e.g., Trimethyl Pentanyl Diisobutyrate] ([CONCENTRATIONS OR DOSAGES TESTED; e.g., 0.001, 0.01, 0.1 and 1 mM]) was tested for endocrine receptor agonist and antagonist activity in [NATURE OF THE TESTS, e.g., multiple cell lines]. [Provide a brief statement of the overall results, e.g., the results were positive for hER1 agonist activity and negative for mAhR, hPPAR γ , and hTR β agonist activity. All cell lines were negative for endocrine receptor antagonism]. These tests are not sufficient to characterize this/these ingredient(s) as endocrine disrupting chemicals (EDCs), based on scientific definitions and criteria developed to identify EDCs. A detailed summary and discussion of the Panel's approach to evaluating ingredients for the potential to act as endocrine disruptors is available at <http://www.cir-safety.org/cir-findings>.

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Endocrine Activity and Endocrine Disruption

Draft

BACKGROUND

Concerns have been growing over the past several decades about the potential for exposures to some chemicals to cause adverse health effects by altering the normal functioning of the endocrine system. The CIR continually monitors developments of the research and the regulation of such substances as a matter of long-standing policy. CIR safety assessment reports include data from *in vitro* tests that address the potential for ingredients to bind to and interact with endocrine receptors and other components of the endocrine system, as well as *in vivo* tests, such as uterotrophic bioassays, discovered through searches of the scientific literature and other information sources.

The CIR Expert Panel considers ingredients that have demonstrated endocrine activity in such tests as potential endocrine disrupting chemicals (EDCs), depending on the relevance, quality and concordance of the available studies, the doses and concentrations tested and the dose-response relationships observed in such studies, the affinities of the ingredients for endocrine receptors or other components of the endocrine system, the potency of endocrine active ingredients compared with endogenous hormones, and other important factors that contribute to an assessment of the overall weight-of-evidence (WoE) assessments. Such assessments depend, at the outset, on a clear definition of what constitutes an EDC, understanding of the distinction between endocrine activity and endocrine disruption, and differentiation of endocrine-mediated effects from other likely mechanisms of action (MOAs).

These factors are discussed in greater detail below.

Definitions and Distinctions

In 2002, the World Health Organization (WHO) International Program on Chemical Safety (IPCS) defined an EDC as “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.”¹ By this definition, EDCs cause adverse health effects in living organisms specifically by altering the function of the endocrine system.

This definition has are three important elements:²

- The substance must act through an endocrine MOA that alters the function of the endocrine system
- The substance must cause an adverse health effect
- The adverse effect must be causally related to, and occur as a consequence of, the altered endocrine function

All three of these elements are necessary to identify a chemical as an EDC.

The IPCS (2004) defines an adverse health effect as “change in morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influence.”² Thus, an “adverse effect” in this context means toxicity, including pathology or functional impairment, in an intact organism, their progeny or (sub)populations through a hormonal or hormone-like MOA.^{2,3}

An adverse effect reflects exceedance of the body’s normal ability to modulate endocrine function adaptively.^{2,3} An increase or decrease in endocrine activity does not indicate a health risk to a living organism, unless it can be shown to lead to harmful effects.

Comment [EM1]: You might want to turn this sentence around. Perhaps: Using systematic searches of the peer-reviewed literature and other information sources, CIR safety assessment reports include data from *in vitro* (e.g., estrogen receptor binding) and *in vivo* (e.g. uterotrophic) assays that address the potential for ingredients to bind to and interact with endocrine receptors and other components of the endocrine system, as well as reproduction studies that identify adverse responses for risk assessment. Or something like this.

Endocrine disruption is distinct from endocrine activity, which is simply the ability of a chemical to interact with the endocrine system without necessarily posing a health risk.⁴ The endocrine system is designed to respond to environmental fluctuations, and the responses are considered to be adaptive when they are transient and within the normal homeostatic range (Goodman et al., 2010; Rhomberg et al., 2012).² The responsive nature of the endocrine system is essential to health. Thus, the potential for interaction with the endocrine system is distinguished from the disruption of physiological or developmental processes that may result from such interactions.

Furthermore, *in vitro* data alone are not sufficient to classify an ingredient as an EDC. Endocrine activity observed in *in vitro* tests and some *in vivo* assays is not sufficient to classify a substance as an EDC if the tests do not indicate whether the alterations cause actual harm in a living organism or its offspring. Such a substance may be considered endocrine-active but not an EDC (EFSA, 2013a).²

Thus, for example, if the objective is to establish whether or not a test article is a reproductive EDC, it should be tested for its “reproductive” activity (i.e., the ability to alter the development or the function of the reproductive system) *in vivo*, rather than just for its sex steroid activity *in vitro*.¹

Many endocrine active substances may lack sufficient potency, compared to endogenous hormones, or exposures may be so low that no effects occur.⁴ In other cases the body naturally adjusts, and the exposure causes no health effect.

Dose, Dose-Response and Potency

Doses administered in experimental animal studies are often orders of magnitude greater than possible consumer exposures, to produce an effect on the endpoint(s) of interest.^{2,4} Excessive doses of any chemical increase the chances of systemic toxicity and effects on endocrine endpoints that are mediated indirectly by other effects. These tests cannot be used to determine whether the effects observed are specifically endocrine related or otherwise attributable to a primary endocrine effect.

The issue of dose-response relationships for EDCs at low doses continues to be highly controversial.¹ This is because, for example, EDCs often act by mimicking or antagonizing the actions of endogenous hormones. These hormones are typically substantially more potent than exogenous EDCs and are present in the body at physiologically functional concentrations. Thus, dose-response relationships of EDCs are often different from those of other chemicals that do not act directly on the endocrine system. Consequently, dose-response relationships vary for different chemicals, endocrine mechanisms, and timing, frequency and duration of exposure. This is true for endocrine-mediated carcinogenesis and developmental, reproductive, immunological, and neurological effects.

The reported low-dose effects of EDCs have come under intense scrutiny concerning the adequacy of traditional toxicology testing paradigms for detecting low-dose effects.¹ A workshop addressing this issue (NTP, 2001a) concluded that low-dose effects often are not replicated consistently, and the toxicological significance of the reported effects is often questionable.

At the receptor level, potency is determined by the affinity of a substance to bind to a receptor or other endocrine system component and the efficacy with which it activates or inactivates the component (Borgert et al., 2013).² Endogenous hormones characteristically exhibit strong binding affinity and high efficacy for activation of their corresponding receptors. Thus, endogenous hormones are potent modulators of endocrine function. In contrast, exogenous chemicals are rarely as potent as hormones because of lower affinity, lower efficacy, or both (e.g., Gaido et al., 1997; Nilsson, 2000).² The presence of exogenous chemicals generally will not alter hormone binding to any significant extent at low doses, and biological thresholds for potency can be expected (Borgert et al., 2013).²

The ability of a substance to produce a biological effect *in vivo* may be substantially different from the potency measured in *in vitro* assays (EFSA, 2013a).² *In vitro* studies can be relevant for investigating MOA and the potential for endocrine activity. However, *in vitro* tests cannot provide useful information on dose-response relationships, do not take into account the toxicokinetics of a substance in the body (i.e., absorption, distribution, metabolism and elimination), and do not account for homeostasis or other pathways and processes that may be responsive to *in vivo* exposures. Thus, potency should be determined based on the ability of a substance to produce an adverse health effect *in vivo*, not on the results of *in vitro* tests.

Comment [EM2]: I think you might just want to say activity here.

It has been hypothesized that the combination of several weakly acting substances may be additive or synergistic and, thus, cause adverse effects.³ However, such effects are improbable, based on theoretical and practical considerations (Borgert et al., 2005, 2012; Rhomberg and Goodman, 2012).³

Comment [EM3]: I know that Chris Borgert is trying hard to move people away from potency for an adverse effect (toxic potency), to pharmacological (or mechanistic) potency. I am having trouble trying to reword this. Maybe hazard instead of potency, and maybe add "alone" after *in vitro* tests.

Additivity may be limited to substances with moderate-to-high potencies at doses near their individual response thresholds, and are not likely for substances with low potencies or at low doses (Borgert et al., 2012; Charles et al., 2007).³ Most mixture studies are not relevant for evaluating human health risk because human exposures are typically orders of magnitude lower than doses that cause detectable responses.

Mechanisms or Modes of Action (MOAs)

The MOAs of EDCs include inhibition of hormone synthesis, transport, or metabolism and activation of receptors through processors such as receptor phosphorylation or the release of cellular complexes necessary for hormone action, in addition to direct interactions with hormone receptors.¹ Furthermore, multiple receptor systems act in concert ("cross talk") to regulate biological functions. These, and many other factors, should be considered when using mechanistic information on EDCs in health assessments. Of particular concern are species, inter-individual, and tissue specificities in endocrine signaling pathways.

Comment [EM4]: I am not exactly sure of the point of this section. The third paragraph seems to be headed towards adverse outcome pathway development. However, then you mention low-level exposures that seems to raise a red flag that things could be going on at low levels that we don't understand. The previous section you essentially pointed out that low exposures are unlikely to do anything because they can't overwhelm the natural ligands.

The MOAs are poorly understood for most associations reported between exposure to EDCs and biological outcomes.¹ This makes it difficult to distinguish direct from indirect effects and primary from secondary effects of exposures.

Comment [EM5]: Processes?

Although there is considerable information on the early molecular events involved in the response to hormones, there is comparatively little known about the relationship between these molecular events and adverse health effects such as cancer and reproductive toxicity.¹ This knowledge gap limits the ability to evaluate exposure-response relationships, especially at low-level exposures to potential EDCs. It will continue to be difficult to attribute adverse effects to endocrine-mediated pathways until such data become available.

Comment [EM6]: I would probably say that the knowledge gap limits the ability to causally link an endocrine-specific MOA and an adverse effect (which you do say in the next sentence). I don't really see why you can't evaluate dose-response, if there are no effects in apical studies then from a risk perspective you are protective. I would probably go on to say something about the fact that it doesn't mean that you aren't being protective, you just may not be able to definitively identify the mode of action.

Considerable homology exists in the endocrinology of vertebrates.¹ However, there are differences among some species in endocrine function that warrant consideration in safety assessments. In particular, the role of specific hormones in reproductive function and development can vary substantially. In addition, species differences in metabolism can cause marked differences in responses to exposure.

Comment [EM7]: How different, particularly for humans and rodents which would be more of the focus of CIR? As mentioned above, I am still unsure of what this section is focused on.

Weight-of-Evidence (WoE) Assessment

A WoE assessment is essential for determining the conditions under which observed effects of exposures can be attributed to an endocrine-mediated MOA.^{1,4}

The critical elements of a WoE assessment include an assessment of the relevance, appropriateness, usefulness, quality and reliability of the studies available for informing the safety assessment process.⁴ Also important is the evaluation of the consistency of the pattern of responses across studies for or against explicitly defined hypotheses. The hypotheses are typically defined to assess the premise that a substance interacts as an agonist or antagonist with components of the estrogen, androgen, or thyroid pathways or of the aromatase or steroidogenic

enzyme systems, for example. One key concern is how dose responses observed in experimental animal studies compare to potential human exposures.²

Several additional factors that have been outlined for evaluating the available data against these hypotheses in an overall WoE assessment include temporality, strength of the association, biological gradient (i.e., dose response), biological plausibility, and evidence of recovery (Bradford-Hill, 1965; Fox, 1991; Ankley et al. 1997).² Furthermore, evaluating the MOA of a substance is critical because the MOA is central to the overall assessment of whether or not a substance can be considered to be an EDC.^{1,2}

All of the relevant information should be considered in an organized and structured manner. The goal of this approach is to reconcile different results from different studies (Cook et al., 1994).¹

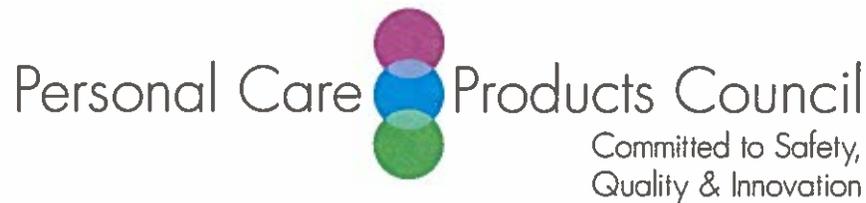
FRAMEWORK FOR DISCUSSION SECTIONS OF SAFETY ASSESSMENTS

[INGREDIENT NAME(s) OR GOU P NAME, e.g., Trimethyl Pentanyl Diisobutyrate] ([CONCENTRATIONS OR DOSAGES TESTED; e.g., 0.001, 0.01, 0.1 and 1 mM]) was tested for endocrine receptor agonist and antagonist activity in [NATURE OF THE TESTS, e.g., multiple cell lines]. [Provide a brief statement of the overall results, e.g. the results were positive for hER1 agonist activity and negative for mAHR, hPPAR γ , and hTR β agonist activity. All cell lines were negative for endocrine receptor antagonism]. These tests are not sufficient to characterize this/these ingredient(s) as endocrine disrupting chemicals (EDCs), based on scientific definitions and criteria developed to identify EDCs. A detailed summary and discussion of the Panel's approach to evaluating ingredients for the potential to act as endocrine disruptors is available at <http://www.cir-safety.org/cir-findings>.

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[You have these 4 references that seemed to match in some places where they were but you also had citations with dates in the text that aren't here.](#)



Memorandum

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

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 5, 2017

SUBJECT: Draft Endocrine Activity and Endocrine Disruption Background and Framework Document

The FDA (CDER) Guidance for Industry from 2015 titled “Nonclinical Evaluation of Endocrine-Related Drug Toxicity Guidance for Industry” (at: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm369043.pdf>) should be added as a reference.



Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)
CIR Expert Panel Members
Liaison Members of the CIR Expert Panel

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: May 17, 2017

SUBJECT: Comments on the Draft Endocrine Activity and Endocrine Disruption Background and Framework Document

We appreciate the opportunity to comment on the draft Endocrine Activity and Endocrine Disruption Background and Framework Document.

1. In the Dose, Dose-Response and Potency section the meaning of the following sentence is not clear: "These tests cannot be used to determine whether the effects observed are specifically endocrine related or otherwise attributable to a primary endocrine effect."

The sentence should be changed to: "The results from these studies cannot be used to determine endocrine activity in the presence of systemic toxicity." Also, adding an example, such as the effect of weight loss on endocrine parameters, would make the point clear.

2. Should "EDCs" be changed to "EACs" in some places, such as in the following sentence from the Dose, Dose-Response and Potency section: "The issue of dose-response relationships for EDCs at low doses continues to be highly controversial"?
3. "cannot" should be changed to "may not" in the following sentence: "However, *in vitro* tests cannot provide useful information on dose-response relationships, do not take into account the toxicokinetics of a substance in the body....."



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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Ivan J. Boyer, Ph.D., D.A.B.T.
Date: August 18, 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 *hdepi092017rep*. The previous draft was reviewed by the Panel at the April 2017 meeting. Comments on the previous draft received from the Personal Care Products Council (PCPC) Hair Coloring Technical Committee (HCTC) and from the Panel been addressed in the current draft (see highlighted text).

Also enclosed, please find the pertinent Panel meeting transcripts (*hdepi092017min.doc*), as well as comments from the HCTC (*hdepi092017HCTC.pdf*).

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

Please note that the Document may be revised again at the next few meetings, after the Panel receives the expected presentations on hair-dye chemistry and the recently completed European hair-dye self-testing study. Indeed, please consider review of these documents as an opportunity to prefigure any questions or concerns to be answered in those presentations.

142d 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 acetylators versus slow acetylators. In terms of certain drugs that have aniline-type nitrogens, or can have aniline-type nitrogens generated. That the acetylation, which is what the acetyltransferase 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. 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?

HAIR DYE EPIDEMIOLOGY – through September, 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 2010¹.

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.

Bladder Cancer

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

Ros et al. (2012) performed a population-based case-control study of hair dye use and bladder cancer in the

Netherlands.⁵ 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.⁶ 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 odds ratio (OR) and associated 95% confidence interval (CI) for women was 0.7 (95% CI 0.5-1.0), and for men 0.7 (95% CI 0.4-1.0). Because of the excellent exposure assessment, the authors were able to examine subsets of the population studied. Women who used red hair colors, for example, exhibited an OR of 0.4 (95% CI 0.2- 0.8), suggesting a significantly lower risk of bladder cancer associated with the use of such hair dyes. A similar lower risk of bladder cancer was reported for women who used hair dyes for a duration between 10 and 19 years (OR 0.5; 95% CI 0.27-0.79). As the data were further analyzed, the authors considered women with and without college degrees. Women without college degrees who used permanent hair dyes exclusively, for example, had a significantly lower risk of bladder cancer (OR 0.5; 95% CI 0.4- 0.7). Exclusive use of permanent hair dyes by women with college degrees was associated with a significantly higher risk of bladder cancer (OR 4.9; 95% CI 1.7-14.6). 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.⁷ 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

Parodi et al. (2016) performed a population-based case-control study of leukemia and non-Hodgkin's lymphoma (NHL) in Italy.⁸ 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. \geq 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.

Linnet et al (2014) conducted a meta-analysis of 19 case-control studies of NHL subtypes, focusing on follicular lymphoma (FL).⁹ 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.¹⁰ 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).¹¹ The risk ORs were adjusted age, sex, race/ethnicity, and study in the basic adjusted models of this meta-analysis. 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.¹² 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.¹³ 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.¹⁴ 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-2.¹⁵ 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 (OR 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.¹⁶ 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.¹⁷ 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).¹⁸ 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.¹⁹ 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.²⁰ 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.

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.⁶

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 GSTT1.⁶ 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).²¹ 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.²² 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).²¹

Morton et al. (2007) conducted a population-based case-control study of NHL.²³ 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).^{24,25} 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.²⁶ The study population from which the subjects were drawn was the same as that of Zhang et al. (2009)²⁵ 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 polymorphisms. 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. Recent Original Hair Dye Epidemiology Studies considered by the CIR Expert Panel.

Study Type/Methodology	Results	Reference
<i>Bladder Cancer</i>		
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) ⁵
Population-based case-control study in Maine, Vermont, and New Hampshire. Cases diagnosed 2001 to 2004 for a total of 1193 cases (911 male and 282 female) with 1418 controls (1039 male and 378 female). Genotyping done for NAT2, NAT1, GSTM1, and GSTT1.	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) ⁶
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) ⁷
<i>Lymphoma and Leukemia</i>		
Population-based case-control study of leukemia and non-Hodgkin's lymphoma (NHL)	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	Parodi et al. (2016) ⁸

in Italy. There were 161 cases (120 lymphoid and 41 myeloid) and 84 randomly-selected controls among women in the population studied.	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).	
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) ¹²
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) ¹³
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) ¹⁴
Re-evaluated tissue samples from an NHL case-control study in males from Iowa and Minnesota using FISH (fluorescence <i>in situ</i> hybridization) cytogenetic technique to evaluate both <i>t</i> -positive and <i>t</i> -negative NHL subtypes.	An association between ever/never use of hair dyes and <i>t</i> (14;18)-negative NHL (OR 2.9; 95% CI 1.6-5.0) and <i>bcl-2</i> positive NHL (OR 2.2; 95% CI 1.4-3.4), but not with <i>t</i> (14;18)-positive NHL (OR 1.3; 95% CI 0.6-2.6) or <i>bcl-2</i> negative NHL (OR 1.4; 95% CI 0.5-3.8).	Chang et al. (2010) ¹⁵
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) ¹⁶
<i>Breast Cancer</i>		
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) ¹⁸
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) ¹⁹

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Memorandum

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

FROM: Hair Coloring Technical Committee (HCTC) of the Personal Care Products Council

DATE: May 9, 2017

SUBJECT: Hair Dye Epidemiology Background Document

The Hair Coloring Technical Committee (HCTC) of the Personal Care Products Council appreciates the opportunity to comment on the Hair Dye Epidemiology background document. The Committee's input is as follows:

1. Page 1, paragraph 1, why the addition of "generally"?
2. Page 1, paragraph 5, the document states that 'selected' new epidemiology studies are reviewed. Aren't all new epidemiology studies addressing the personal use of hair dyes reviewed?
3. Page 1, paragraph 7, please note that the IARC working group also summarized the relevant studies on breast cancer, in addition to bladder and hematological cancers.
4. Page 2, 4th paragraph addressing the Parodi study, the only results reported re: hair dye use are in women, so the correct number of controls is n=120, and the number of cases of lymphoid malignancies is n=84.
5. Page 4, paragraph 7, typo in the last sentence, '...not associated with an increased risk...' (not and)
6. Page 5, 1st complete sentence at the top of the page, 'began using hair dyes in the early 1980s' should be changed to 'began using hair dyes after 1980'.
7. Page 5, Table 1, the entry for the Parodi et al. study should make it clear that the findings related to hair dye use were only in women. The correct number of controls and cases is 120

and 84, respectively. The Parodi et al. publication does not include any results for men and hair dye use.

8. Page 9, reference 25 has a formatting error.