ADMIN

Memo

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Inhalation

Re-Review Summaries

- Acetyl Trialkyl Citrates
- BHT
- EDTA and Salts
- Imidazolidinyl Urea

CIR EXPERT PANEL MEETING SEPTEMBER 16-17, 2019

Cosmetic Ingredient Review

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MEMORANDUM

To: CIR Expert Panel Members and Liaisons
From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review
Subject: 152nd Meeting of the CIR Expert Panel — Monday and Tuesday, September 16-17, 2019
Date: August 22, 2019

Welcome to the September 2019 CIR Expert Panel Meeting. Enclosed are the agenda and accompanying materials for the 152nd CIR Expert Panel Meeting to be held on September 16-17, 2019. The location is the same as the last meeting – The Westin Hotel, Washington, D.C. City Center, 1400 M St NW, Washington, District of Columbia, 20005. Phone: (202) 429-1700.

The meeting agenda includes the consideration of 16 reports advancing in the review process, including 3 final reports, 6 tentative reports, 3 draft reports, and 4 re-reviews. Also, on the agenda are 4 re-review summaries and a new draft of the Inhalation Precedents document.

Schedule and hotel accommodations

We have reserved rooms for the nights of Sunday, September 15th and Monday, September 16th at the Westin Hotel. If you encounter travel problems, please contact Monice on her cell phone at 703-801-8156.

Team Meetings

Draft Reports - there are 6 draft reports for review. – Sufficient data to proceed or issue an IDA?

1. Adenosine – This is the first time the Panel is reviewing the safety of Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate.

   The report includes the following unpublished data: use concentration data; a summary of a Magnusson Kligman assay using a trade name mixture containing 15% mannitol and 15% Disodium Adenosine Triphosphate; 0.5% (intracutaneous induction) and 10% (epicutaneous induction and challenge) aqueous dilutions of the trade name mixture were used; a summary of a phototoxicity assay using a 10% aqueous dilution of a mixture consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate; a summary of a photosensitization test using a 2% aqueous dilution of a trade name mixture consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate; a summary of a 48-hour patch test performed on 10 subjects using a test substance containing 0.2% Adenosine; and a summary of an HRIPT performed on 205 subjects using a test substance containing 0.2% Adenosine.

   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, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

2. Wheat – This is the first time the Panel is reviewing the safety of most of these wheat-derived ingredients as used in cosmetics. Most of the 27 wheat-derived ingredients detailed in this safety assessment are reported to function in cosmetics as skin conditioning agents, while some are reported to have other functions, such as abrasives, absorbents, antioxidants, bulking agents, film formers, flavoring agents, hair-conditioning agents, and viscosity-increasing agents. It should be noted that the accepted scientific name for both *Triticum vulgare* and *Triticum spelta* is *Triticum aestivum*; however, the Dictionary lists ingredients using all three nomenclatures.

   This report includes three ingredients that have been previously reviewed and re-reviewed by the Panel: Triticum Vulgare (Wheat) Kernel Flour, Triticum Vulgare (Wheat) Gluten, and Wheat Germ Glycerides. These ingredients were found to be safe as used in cosmetic products; reports on these ingredients were originally published in 1980, and their safety was reaffirmed in a re-review that was published in 2003. Because it has been more than 15 years since the safety of these ingredients was last reviewed, these ingredients are included in this safety assessment for re-review.

   In addition to information found in the publicly available literature, this report contains unpublished concentration of use survey data; human dermal irritation and sensitization data on Triticum Vulgare (Wheat) Germ Extract; and composition and method of manufacturing data on Triticum Vulgare (Wheat) Bran Extract.

   According to the results of the concentration of use survey, Triticum Vulgare (Wheat) Germ Extract has the highest concentration of use in a leave-on formulation; it is used at up to 13% in face powders. The maximum concentrations of use for the remaining ingredients are much lower, with the next highest concentration of use reported for products resulting in leave-on dermal exposure is 0.6% in Triticum Aestivum (Wheat) Germ Extract in “other” skin care preparations. A concentration of use survey is currently being conducted on Triticum Spelta Seed Water; Triticum Vulgare (Wheat) Bran Lipids; Triticum Vulgare (Wheat) Gluten; Triticum Vulgare (Wheat) Gluten Extract; and Wheat Germ Glycerides.

   If no further data are needed to reach a conclusion of safety, 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. Scutellaria – This is the first time the Panel is seeing a safety assessment on 4 *Scutellaria baicalensis*-derived ingredients. A Scientific Literature Review (SLR) was announced on June 20, 2019. In addition to data found in the published literature, this report contains the following unpublished data: use concentration data; method of manufacture data on Scutellaria Baicalensis Root Extract; chemical characterization data on Scutellaria Baicalensis Root Extract trade name mixture; impurities data on a Scutellaria Baicalensis Root Extract trade name mixture; and human skin irritation and sensitization data on Scutellaria Baicalensis Root Extract trade name mixtures.

   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, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

Draft Tentative Reports – there are 6 draft tentative reports (including two amended reports).

1. Mannitol – At the April 2019 meeting, the Panel issued an IDA for this ingredient group. The Panel requested phototoxicity data at leave-on use concentrations and irritation and sensitization data at maximum use concentrations. Since the April Panel meeting, the following unpublished data have been received:

   - A summary of a Magnusson Kligman assay using a trade name mixture containing 15% Mannitol and 15% disodium adenosine triphosphate; 0.5% (intracutaneous induction) and 10% (epicutaneous induction and challenge) aqueous dilutions of the trade name mixture were used.
   - A summary of a phototoxicity assay using a 10% aqueous dilution of a mixture consisting of 15% Mannitol and 15% disodium adenosine triphosphate.

- A summary of a photosensitization test using a 2% aqueous dilution of a trade name mixture consisting of 15% Mannitol and 15% disodium adenosine triphosphate.
- An HRIPT using a body lotion containing 3% Xylitol.

After reviewing these documents, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or insufficient data conclusion. Additionally, Discussion items should be identified.

2. MCI/MI – At the June 2019 meeting, the Panel issued an IDA and requested an inhalation study of at least 3 months in duration that is in accordance with the Organization for Economic Co-operation and Development (OECD) test guideline (TG) 413. This request is in response to reports of adverse events observed in infants following inhalation exposure to humidifier disinfectants that contained this preservative mixture.

   Additional data concerning the adverse events occurring in South Korea from exposure to humidifier disinfectants containing MCI/MI have been incorporated into the report since the last review. However, no data have been received in response to the IDA.

   The Panel should carefully consider and discuss the data (or lack thereof) and the draft Abstract and Discussion presented in this report, and issue a Tentative Amended Report with the appropriate conclusion.

3. Pomegranate – At the April 2019 meeting, the Panel issued an IDA for these 18 ingredients. The Panel's data needs were:

   a) Dermal irritation and sensitization data at maximum leave-on use concentrations for all ingredients, except Punica Granatum Pericarp Extract.
   b) A no-observed-effect-level (NOEL) for skin lightening effects.
   c) The generally recognized as safe (GRAS) status for the pomegranate plant parts not usually consumed (e.g., the bark, flower, root, stem, and leaf).
   d) Method of manufacturing for the extracts, especially with regard to solvent-type used.
   e) Composition and impurities data for Punica Granatum Bark Extract, Punica Granatum Bark/Fruit Extract, Punica Granatum Callus Culture Extract, Punica Granatum Flower Extract, Punica Granatum Fruit/Root Stem Powder, and Punica Granatum Leaf Cell Extract.

   Since the April Panel meeting, CIR has received the following data, which have been incorporated into the report:

   a) Summary of an HRIPT on a leave-on product containing 0.1% Punica Granatum Fruit Extract.
   b) –
   c) –
   d) Method of manufacturing with solvent type for Punica Granatum Pericarp Extract.
   e) –

   Additional composition data from the published literature have also been incorporated in the report and designated appropriately. The Panel should carefully consider and discuss the data (or lack thereof) and the draft Abstract and Discussion presented in this report, and issue a Tentative Report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion.

4. MIPA – At the April 2019 meeting, the Panel issued an IDA, requesting the following:

   - skin sensitization data for Cocamide MIPA, at maximum leave-on use concentrations
   - 28-day dermal toxicity study on Cocamide MIPA
     - if positive, additional data may be requested

   The only new information submitted since the IDA was issued, was concentration of use survey data for Peanutamide MIPA; no use data were reported for this ingredient. Please note that INCI definitions have been updated; the ingredients have been redefined based on structure.

At the April meeting, the Panel discussed including data on lauramide DEA for weight of evidence, but ultimately decided to not include these data. The CIR report on diethanolamides (published in 2013) has been included with this submission, in case the Panel determines information on diethanolamides is useful.

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

5. Capryloyl Salicylic Acid – At the June 2019 meeting, the Panel issued an IDA on this ingredient with the following data requests:

    - Impurities
    - Phototoxicity

    To date, there has been no response to this IDA on Capryloyl Salicylic Acid. The Panel should carefully consider and discuss the data (or lack thereof) and the draft Discussion presented in this report, and issue a Tentative Amended Report with a safe, safe with qualifications, unsafe, or insufficient data conclusion. If the data remain insufficient for making a determination of safety, then the Discussion should include a listing of the remaining data that are needed.

6. Palm – At the April 2019 meeting, the Panel issued an IDA with the following data needs:

    - For all 8 ingredients
        - 28-day dermal toxicity

    - Euterpe Edulis Fruit Extract and Euterpe Edulis Juice Extract
        - Method of manufacture
        - Skin sensitization data at maximum use concentrations
        - Genotoxicity
        - Confirmation that these ingredients are foods

    - Euterpe Oleracea Seed Powder and Hydrolyzed Euterpe Oleracea Fruit
        - Method of Manufacture

    - Euterpe Oleracea Palm Heart Extract
        - Skin irritation and sensitization data at maximum use concentrations

    To date, there has been no response to this IDA on palm tree-derived ingredients. A request from the Council that the title of this safety assessment be changed to Palm (acai and juçara)-Derived Ingredients, was received after the April Panel meeting.

    After reviewing these documents, if the available data remain insufficient, the Panel should issue a Tentative Report with an insufficient data conclusion, specifying the data needs in the Discussion. However, 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.

Draft Final Reports - there are 3 draft final reports for consideration (including two amended reports). After reviewing these drafts, especially the rationales provided in the Discussion sections, the Panel should issue them as Final Reports, as appropriate.

1. Silica – At the June 2019 meeting, the Panel issued a Tentative Amended Report for public comment with the conclusion that Silica and Hydrated Silica are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating. However, the Panel determined there were insufficient data to determine the safety of the remaining 22 ingredients. The additional data needs were:

- Chemical characterization (structure), composition, and impurities data for the silicate ingredients.
- Method of manufacturing and/or source data for the silicate ingredients.
- Depending on the information provided, additional data on toxicological endpoints may be needed.

Since the June Panel meeting, no new unpublished data have been received. However, comments received in August suggest that some of this may be forthcoming. The Panel should review the Abstract, Discussion, and Conclusion and issue a Final Amended Report.

2. Parabens – At the June 2019 meeting, the Panel evaluated the recently discovered biomonitoring and epidemiological data on these ingredients and issued a Revised Tentative Amended Report with a conclusion of safe as used for 20 of the 21 parabens (excluding Benzylparaben), when the sum of the combined concentration of parabens in any given formulation does not exceed 0.8%. Since the June meeting, an additional three references were suggested for inclusion in the Parabens report; comments from Jinqiu regarding these studies and suggestions are provided in the report package. The Panel should consider whether these studies warrant inclusion in the CIR report.

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

3. Brown Algae – At the April 2019 meeting, the Panel concluded that 32 of the 82 brown algae-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment. The Panel came to this conclusion by assessing the systemic toxicity potential (either in repeated dose studies or GRAS status/use in food) and sensitization data of the ingredients; both types of data were needed for a conclusion of safety to be reached. As for those ingredients that are formulated differently, but are derived from the same genus and species, and therefore are expected to be similar in composition (e.g. Laminaria Digitata Extract and Laminaria Digitata Powder), the Panel confirmed that if there are sufficient data to support the safety of one of these ingredients, all related ingredients of the same genus and species would be considered safe.

   The Panel concluded that the data are insufficient to determine the safety of the remaining 50 ingredients under the intended conditions of use in cosmetic formulations. As an alternative method for determining safety, the Panel suggested that representative data for each genus (rather than both genus and species), if submitted, may be used to formulate decisions regarding other ingredients of the same genus. Therefore, the Panel requested data regarding the possible constituents of concern of these brown-algae derived ingredients (e.g., specific terpenoids and flavonoids, and concentrations of such).

   A table has been provided presenting each ingredient, as well as a notation of the presence or absence of systemic toxicity data (repeated dose studies or use in food/as a GRAS substance) and sensitization data.

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

Re-Reviews – there are 4 Re-Reviews. Do the data, or other changes since prior review, warrant re-opening?

1. Quaternium-18 – The Panel first reviewed the safety of Quaternium-18 and Quaternium-18 Bentonite in 1982. The Panel concluded that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration, as described in that report. In 2003, after considering new studies and updated use data on these ingredients, the Panel determined not to re-open the safety assessment.

   It should be noted that Quaternium-18 Hectorite was also included in the 1982 safety assessment and previous re-review. However, Quaternium-18 Hectorite is not included in this current re-review because it was recently (2013) part of a separate assessment (Safety Assessment of Ammonium

Hectorites as Used in Cosmetics). In that assessment, Quaternium-18 Hectorite was determined to be safe as used in cosmetics in the present practices of use and concentration.

Because it has been at least 15 years since the first re-review summary was published, in accord with CIR Procedures, the Panel should again consider whether the safety assessment of Quaternium-18 and Quaternium-18 Bentonite should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1995 forward. No relevant published data were found; however, unpublished data were provided regarding Quaternium-18 Bentonite.

Since the initial re-review was considered, frequency and concentration of use have decreased for both ingredients. In 2001, the maximum concentration of use for Quaternium-18 Bentonite was reported to be 9% in leave-on products, while in 2018, maximum concentration of use was reported to be 2.5% in leave-on products. A decrease in concentration of use was also reported for Quaternium-18; the reported maximum concentrations of use in 2001 and 2018 were 2% and 0.95%, respectively.

If, upon review of the new studies and updated use data, the Panel determines that a re-review is warranted, a full draft amended report will be presented at an upcoming meeting.

2. Sodium Polynapthalenesulfonate – The final safety assessment on Sodium Naphthalenesulfonate and Sodium Polynaphthalenesulfonate was published in 2003 with the conclusion that these ingredients were "safe as used in cosmetic formulations intended to be applied to the skin. The available data, however, are insufficient to support the safety for use in cosmetic products which may contact mucous membranes or be ingested." Because it has been at least 15 years since the report was published, in accord with CIR Procedures, the Panel should consider whether the safety assessment of Sodium Naphthalenesulfonate and Sodium Polynaphthalenesulfonate should be re-opened.

   An exhaustive search of the world's literature was performed for studies dated 1997 forward. According to VCRP data, Sodium Polynaphthalenesulfonate was reported to be used in 50 formulations in 1998. In 2019, VCRP data indicate that Sodium Polynaphthalenesulfonate is used in 12 formulations. The current maximum concentration of use in leave-on products (0.1%) is slightly lower than that reported in 1999 (0.3%). While no uses were reported by the VCRP in products that may be used on mucous membranes or may be incidentally ingested, a concentration of use was reported in products that may come into contact with mucous membranes (bath soaps and detergents at 0.0074%). Uses were neither reported in 2003 nor 2019 for Sodium Naphthalenesulfonate.

   If, upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a full draft amended report will be presented at an upcoming meeting.

3. Isopropyl Lanolate - The Panel first published the safety assessment of Isopropyl Lanolate in 1980. The Panel concluded that "on the basis of the information available, which the Expert Panel believes to have been accumulated in a reasonable manner, it is concluded that Isopropyl Lanolate is safe as currently used in cosmetic products." In 2003, after considering new studies and updated use data, the Panel determined to not re-open the safety assessment.

   Because it has been at least 15 years since the first re-review summary was published, in accord with CIR Procedures, the Panel should again consider whether the safety assessment of Isopropyl Lanolate should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1995 forward, but no relevant new data were found.

   Both, the frequency and maximum concentrations of use, have decreased significantly since the initial re-review was considered. According to VCRP data, Isopropyl Lanolate was reported to be used in 415 formulations in 2001, but is only reported to be used in 122 formulation in 2019. The maximum reported concentration of use decreased from 26% in 2001 to 14.5% in 2019.

   If the Panel determines that a re-review is warranted, a full draft amended report will be presented at an upcoming meeting.

4. Sulfites - The Panel first reviewed the safety of Sulfites in 2003. The Panel concluded that Ammonium Bisulfite, Ammonium Sulfite, Potassium Metabisulfite, Potassium Sulfite, Sodium Bisulfite, Sodium Metabisulfite, and Sodium Sulfite are safe as used in cosmetic formulations. Because it has been at least 15 years since the safety assessment was published, in accordance with CIR Procedures, the Panel should consider whether the safety assessment of Sulfites should be reopened.

   An exhaustive search of the world's literature was performed for studies dated 1998 forward. The frequency of use for Sodium Sulfite has increased from 911 to a value of 1679 reported uses. A substantial decrease in the use from 348 to 2, however, is reported for Sodium Metabisulfite. Of the ingredients reviewed in the 2003 report, Sodium Metabisulfite had the second highest use concentration (14% in rinse-off products). In 2019, this ingredient is reported to be used at substantially lower concentrations, of up to 0.6% in these products. Ammonium Bisulfite was reported to be used at a concentration of 32% (rinse-off product) in the original report; this was the highest reported sulfite concentration at that time. No concentration of use is reported for this ingredient in 2019. The sulfite with the highest reported use concentration in 2019 is Sodium Sulfite; it is reported to be used at concentrations up to 3% in rinse-off products. This was also the highest use concentration of Sodium Sulfite in the 2003 original report.

   If upon review of the new studies and updated use data, the Panel determines that a re-review is warranted, a full draft amended report will be presented at an upcoming meeting.

Administrative Items - there are 4 re-review summaries and 1 precedents document.

Re-Review Summaries - The Panel considered the re-review of these ingredients at the June 2019 meeting, and determined that these reports should not be re-opened. The re-review summaries are included for Panel review:

1. Acetyl Trialkyl Citrates
2. BHT
3. Imidazolidinyl Urea
4. EDTA

Precedents Document

1. Inhalation – This document (Respiratory Exposure from Cosmetic Ingredients) has been reorganized to address the comments received on the document to date. At the December 2018 meeting, the Panel concluded that, while particle/droplet size is an important parameter, the physicochemical properties of ingredients in a spray formulation, as well as the realistic exposure factors under in-use conditions, also play significant roles in evaluating inhalation safety of ingredients as spray formulations. When spray parameters are absent or provide an insufficient basis to support a robust inhalation exposure assessment, the Panel would request additional information from industry and further evaluate the sufficiency of other exposure data that may be available on a case-by-case basis.

   In addition, the Panel recommended changing the document title from "Aerosols" to "Respiratory Exposure from Cosmetic Ingredients." The Panel noted that particle size distributions are product specific; however, data are currently insufficient to assess the inhalation exposure of some types of cosmetic sprays. The Panel requested collection and analysis of particle size distributions-consumer use data of such spray products. To date, CIR has not received such relevant information.

   The Panel should determine how, and to what extent, the attached draft of the CIR Precedents – Respiratory Exposure from Cosmetic Ingredients document should be revised further, based on the currently available particle size data and inhalation exposure parameters of sprays; or, can this document be finalized.

Full Panel Meeting

Please 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 3 reports to be issued as final safety assessments, followed by the remaining

reports advancing in the process (including the tentative reports, draft reports, and re-reviews), re-review summaries and precedents document. 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
152nd Cosmetic Ingredient Review Expert Panel Meeting
September 16th - 17th, 2019

The Westin Hotel
1400 M Street, NW,
Washington, District of Columbia, 20005

Monday, September 16th

8:00 am	**CONTINENTAL BREAKFAST**	
8:30 am	**WELCOME TO THE 152nd EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Heldreth**
8:45 am	**TEAM MEETINGS**	**Drs. Marks/Belsito**

Dr. Marks Team		**Dr. Belsito Team***	
RRsum (PC)	EDTA	RRsum (CB)	BHT
TR (PC)	Mannitol	RRsum (CB)	Imidazolidinyl Urea
DR (PC)	Adenosine	RR (CB)	Sodium Polynapthalenesulfonate
RR (PC)	Quaternium-18	DR (CB)	Wheat
FAR (PC/JZ)	Parabens	TAR (CB)	MCI/MI
FR (PC)	Brown Algae	TR (CB)	Pomegranate
TAR (WJ)	Capryloyl Salicylic Acid	FAR (CB)	Silica
TR (WJ)	Palm	Admin (JZ/BH)	Inhalation
DR (WJ)	Scutellaria	RRsum (PC)	EDTA
RR (WJ)	Sulfites	TR (PC)	Mannitol
RRsum (WJ)	Acetyl Trialkyl Citrates	DR (PC)	Adenosine
RR (MF)	Isopropyl Lanolate	RR (PC)	Quaternium-18
TR (MF)	MIPA	FAR (PC/JZ)	Parabens
RRsum (CB)	BHT	FR (PC)	Brown Algae
RRsum (CB)	Imidazolidinyl Urea	TAR (WJ)	Capryloyl Salicylic Acid
RR (CB)	Sodium Polynapthalenesulfonate	TR (WJ)	Palm
DR (CB)	Wheat	DR (WJ)	Scutellaria
TAR (CB)	MCI/MI	RR (WJ)	Sulfites
TR (CB)	Pomegranate	RRsum (WJ)	Acetyl Trialkyl Citrates
FAR (CB)	Silica	RR (MF)	Isopropyl Lanolate
Admin (JZ/BH)	Inhalation	TR (MF)	MIPA

The purpose of the Cosmetic Ingredient Review is to determine those cosmetic ingredients for which there is a reasonable certainty in the judgment of competent scientists that the ingredients are safe under intended conditions of use.

FR: Final Report // FAR: Final Amended Report // TR: Tentative Report // TAR: Tentative Amended Report // DR: Draft Report // DAR: Draft Amended Report // RR: Re-Review // RRsum: Re-Review Summary // SM: Strategy Memo // Admin: Administrative item

(CB): Christina Burnett || (BH) Bart Heldreth || (MF): Monice Fiume || (PC): Priya Cherian || (WJ): Wilbur Johnson || (JZ) Jinqiu Zhu

*Team moves to breakout room.

Tuesday, September 17th			
8:00 am	**CONTINENTAL BREAKFAST**		
8:30 am	**WELCOME TO THE 152nd FULL CIR EXPERT PANEL MEETING**		**Dr. Bergfeld**
8:45 am	Admin	**MINUTES OF THE JUNE 2019 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

FAR (CB)	Silica – *Dr. Marks Reports*
FAR (PC)	Parabens – *Dr. Belsito Reports*
FR (PC)	Brown Algae – *Dr. Marks Reports*

Reports Advancing

TR (PC)	Mannitol – *Dr. Belsito Reports*
DR (PC)	Adenosine – *Dr. Marks Reports*
RR (PC)	Quaternium-18 – *Dr. Belsito Reports*
TAR (CB)	MCI/MI – *Dr. Marks team Reports*
DR (CB)	Wheat – *Dr. Belsito Reports*
TR (CB)	Pomegranate – *Dr. Marks Reports*
RR (CB)	Sodium Polynapthalenesulfonate – *Dr. Belsito Reports*
TR (MF)	MIPA – *Dr. Marks Reports*
RR (MF)	Isopropyl Lanolate – *Dr. Belsito Reports*
TAR (WJ)	Capryloyl Salicylic Acid - *Dr. Marks Reports*
TR (WJ)	Palm – *Dr. Belsito Reports*
RR (WJ)	Sulfites – *Dr. Marks Reports*
DR (WJ)	Scutellaria – *Dr. Belsito Reports*

Other Items

RRsum (WJ)	Acetyl Trialkyl Citrates – *Dr. Marks Reports*
RRsum (CB)	BHT – *Dr. Belsito Reports*
RRsum (CB)	Imidazolidinyl Urea – *Dr. Marks Reports*
RRsum (PC)	EDTA – *Dr. Belsito Reports*
Admin (BH)	Inhalation – *Dr. Marks Reports*

ADJOURN - *Next meeting Monday and Tuesday, December 9-10, 2019, at The Westin Washington, D.C. City Center, 1400 M St NW, Washington, District of Columbia, 20005*

On the basis of all data and information submitted, and after following all of the Procedures (https://www.cir-safety.org/supplementaldoc/cir-procedures), the Expert Panel shall determine whether each ingredient, under each relevant condition of use, is safe, safe with qualifications, unsafe, or there are insufficient data or information to make a determination of safety. Upon making such a determination, the Expert Panel shall issue a conclusion and/or announcement.

FR: Final Report // FAR: Final Amended Report // TR: Tentative Report // TAR: Tentative Amended Report // DR: Draft Report // DAR: Draft Amended Report // RR: Re-Review // RRsum: Re-Review Summary // SM: Strategy Memo // Admin: Administrative item

(CB): Christina Burnett || (BH) Bart Heldreth || (MF): Monice Fiume || (PC): Priya Cherian || (WJ): Wilbur Johnson || (JZ) Jinqiu Zhu

Commitment & Credibility since 1976

ONE HUNDRED FIFTY-FIRST MEETING

OF THE

EXPERT PANEL

June 6-7, 2019

The Westin 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

Alexandra Kowcz, M.B.A.

Government

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

Adopted (Date)

Wilma F. Bergfeld, M.D.

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Others Present at the Meeting

Alice Akinsulie	CIR
Christina Burnett	CIR
Priya Cherian	CIR
A. J. Cuevas	Henkel
Carol Eisenmann	PCPC
Michael Fevola	Inolex
Monice Fiume	CIR
Eileen Francis	HBW Insight
Kevin Fries	CIR
Bart Heldreth	CIR
Carla Jackson	CIR
Wilbur Johnson, Jr.	CIR
Brett Jurd	W. R. Grace
Demetrius Michos	W. R. Grace
David Plimpton	Inolex
Teresa Washington	FDA
Keith Wyatt	FDA

MINUTES FROM THE 151st CIR EXPERT PANEL MEETING

CHAIRMAN'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 151st meeting of the CIR Expert Panel, and thanked the CIR staff for their excellent work in preparing documents for Panel review. The work of the CIR Science and Support Committee was also acknowledged. She noted that 16 ingredient reports, 5 of which are final reports, and the New Priority List were reviewed in Teams on the preceding day. Dr. Bergfeld added that reports on the Silicates, MCI/MI, the Parabens, and botanicals were particularly challenging to the Panel.

Dr. Bergfeld stated that the CIR guidance document has been expanded to document CIR report conclusion qualifications, such as, safe when formulated to be non-irritating and safe when formulated to be non-sensitizing. Additionally, regarding sensitization potential, language relating to use of the QRA is another conclusion qualification. Dr. Bergfeld stated that the Panel is also adding inhalation restrictions to report conclusions. This is consistent with the Panel's concern about aggregate exposure.

Regarding CIR report comments that have been received, she noted the contributions of industry, Women's Voices for the Earth, and other groups. Dr. Bergfeld stated that all comments received are taken very seriously.

APPROVAL OF MINUTES

The minutes of the April 8-9, 2019 (150th) CIR Expert Panel meeting were approved.

DIRECTOR'S REPORT

Dr. Heldreth expressed gratitude for the Panel's and other stakeholders' continued support of the Cosmetic Ingredient Review program. He also reported on a status change for 12 ingredient conclusions. In 2017, the Panel issued a final report on the Safety Assessment of Citrus Plant- and Seed-Derived Ingredients as Used in Cosmetics. The Panel reviewed the available data presented and concluded that 18 of these ingredients are safe in the present practices of use and concentration when formulated to be non-irritating and non-sensitizing. However, the data for the remaining 12 ingredients were insufficient to determine safety. Since the 2-year clock has expired, those 5 ingredients reported to be in use at the time are thus moved to the "use not supported category" and those 7 with no reported uses now fall under the "zero use" categorization.

Citrus Aurantifolia (Lime) Oil
Citrus Aurantium (Bitter Orange) Oil
Citrus Aurantium Dulcis (Orange) Oil
Citrus Aurantium Sinensis Powder
Citrus Limon (Lemon) Flower/Leaf/Stem Extract
Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder*
Citrus Grandis (Grapefruit)*
Citrus Iyo Oil*
Citrus Limon (Lemon) Flower/Leaf/Stem Oil*
Citrus Limon (Lemon) Leaf/Peel/Stem Oil*
Citrus Nobilis (Mandarin Orange) Water*
Citrus Unshiu Extract*

**zero use.*

Final Safety Assessments

Alkoxylated Fatty Amides

The Panel issued a final report with the conclusion that the 40 ingredients named below are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

PEG-2 Cocamide
PEG-3 Cocamide
PEG-4 Cocamide*
PEG-5 Cocamide
PEG-6 Cocamide
PEG-7 Cocamide*
PEG-11 Cocamide*
PEG-20 Cocamide*
PEG-3 Cocamide DEA*
PEG-20 Cocamide MEA*
PEG-6 Hydrogenated Palmamide*
PEG-50 Hydrogenated Palmamide
PEG-13 Hydrogenated Tallow Amide*
PEG-5 Lanolinamide*
PEG-2 Lauramide*
PEG-3 Lauramide
PEG-5 Lauramide*
PEG-6 Lauramide
PEG-11 Lauramide*
PEG-3 Oleamide*

PEG-4 Oleamide*
PEG-5 Oleamide*
PEG-6 Oleamide*
PEG-7 Oleamide*
PEG-9 Oleamide*
PEG-4 Rapeseedamide
PEG-4 Stearamide*
PEG-10 Stearamide*
PEG-15 Stearamide*
PEG-50 Stearamide*
PEG-5 Tallow Amide*
PEG-8 Tallow Amide*
PEG-50 Tallow Amide
PEG-2 Tallowamide DEA*
Polyglyceryl-4-PEG-2 Cocamide*
PPG-2 Cocamide
PPG-1 Hydroxyethyl Caprylamide*
PPG-2 Hydroxyethyl Cocamide
PPG-2 Hydroxyethyl Coco/Isostearamide
PPG-3 Hydroxyethyl Soyamide*

**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 ingredients included in this family are structurally related as *N*-alkoxylated simple amides. The Panel determined that the information on the mono-*N*-alkoxyl-substituted ingredients informs the safety of the di-*N,N*-alkoxyl-substituted ingredients that are included in this report. Also, the Panel determined that the information on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide (which are the two ingredients with the highest reported frequency of use) could be read-across to other members of the group. The Panel remarked on the lack of carcinogenicity data; concerns for this lack of data, however, were mitigated by the sufficient, negative genotoxicity studies and the lack of structural alerts for carcinogenicity. Additionally, the margin of exposure (MOE) for PEG-4 Rapeseedamide (calculated by NICNAS) and PPG-2 Hydroxyethyl Cocamide (calculated by the CIR SSC) were acceptable; therefore, concerns regarding systemic toxicity following dermal exposure were mitigated.

There was a concern that the potential exists for dermal irritation with the use of products formulated using alkoxylated fatty amides. As a result, the Panel specified that products containing alkoxylated fatty amides must be formulated to be non-irritating.

The Panel also discussed the issues of impurities that could be of concern with this group of ingredients. The possible presence of 1,4-dioxane as an impurity is one concern, and the Panel stressed that the cosmetics industry should continue to use the necessary procedures to limit this impurity in alkoxylated fatty amide ingredients before blending them into cosmetic formulations. Additionally, manufacturers should minimize primary amine impurities, and the Panel specified that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed.

Basic Red 76

The Panel issued a final report with the conclusion that Basic Red 76 is safe as a hair dye ingredient in the present practices of use and concentration described in the safety assessment. Basic Red 76 is currently reported to be used as a hair coloring agent (48 formulations), as well as a component in nail products (2 formulations). This ingredient is not an approved color additive by the US Food and Drug Administration (FDA), and thus use in a nail product is considered adulterated; however, hair dye use is exempt from such color additive regulations. The Panel recognized the use of this ingredient in nail products, but noted that evaluating the safety of this ingredient in formulations other than hair dye uses is outside of the Panel's purview. The results of the concentration of use survey conducted by the Council indicate that the highest concentration of use reported for Basic Red 76 is 0.35% in hair dyes and colors.

Alkanoyl Lactyl Lactate Salts

The Panel issued a final report with the conclusion that the 10 alkanoyl lactyl lactate salts listed below are safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating and non-sensitizing, which may be based on a QRA or other accepted methodologies.

Calcium Stearoyl Lactylate	Sodium Cocoyl Lactylate*	Sodium Oleoyl Lactylate*
Sodium Behenoyl Lactylate	Sodium Cupheoyl Lactylate*	Sodium Stearoyl Lactylate
Sodium Caproyl Lactylate	Sodium Isostearoyl Lactylate	
Sodium Caproyl/Lauroyl Lactylate	Sodium Lauroyl Lactylate	

**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*.

Alkyl lactyl lactate salts are the carboxylic acid salts of diesters that are formed between a fatty acid group and two equivalents of lactic acid. Acknowledging positive sensitization data on alkyl lactyl lactate salts, the Panel noted that the potential for induction of skin sensitization varies depending on a number of factors, including the area of product application; thus, formulators should assess the potential for final formulations to induce sensitization using a QRA or other accepted methodologies. The Panel was also concerned that the potential exists for dermal irritation with the use of products formulated using alkyl lactyl lactate salts. Thus, the Panel specified that products containing alkyl lactyl lactate salts must be formulated to be nonirritating.

Polyaminopropyl Biguanide

The Panel issued a final report with the conclusion that Polyaminopropyl Biguanide is safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating and non-sensitizing, which may be based on a QRA or other accepted methodologies. However, the Panel also concluded that the data are insufficient to determine the safety of Polyaminopropyl Biguanide in products that may be inhaled. The Panel determined that the following data are needed to determine the safety of Polyaminopropyl Biguanide in products that may be inhaled:

- Consumer use data on pump and propellant hair sprays, for use in determining the extent of exposure to Polyaminopropyl Biguanide during product use. As part of this data insufficiency, use concentration data on this ingredient in aerosolized products and the particle size that is associated with the spray product are needed if Polyaminopropyl Biguanide is used in products that could be inhaled.

Due to concern over the skin sensitization potential of Polyaminopropyl Biguanide, the Panel previously requested the following data in addition to the above data request: HRIPT on Polyaminopropyl Biguanide involving a diverse population (i.e., with a range of Fitzpatrick skin types) of 100 subjects tested with a dose of 1000 μg/cm^2 (and recommendation to test at 500 μg/cm^2 as well). In response to this request, an HRIPT on 1% Polyaminopropyl Biguanide involving 108 subjects (Asian (~2%), biracial (~3%), Black (~ 23%), Caucasian (~ 33%), and Hispanic (~39%); Fitzpatrick skin types not stated) was provided. Polyaminopropyl Biguanide did not induce dermal sensitization in the subjects tested, and, using the results from this study, a QRA yielded a NESIL of 750 μg/cm^2. However, other data included in this CIR safety assessment indicate the potential for sensitization to Polyaminopropyl Biguanide, specifically in an LLNA, HRIPT, and in guinea pig maximization tests. Acknowledging the positive sensitization data on Polyaminopropyl Biguanide, the Panel noted that the potential for induction of skin sensitization varies depending on a number of factors, including the area of product application and final formulation; thus, formulators should assess the potential for final formulations to induce sensitization using a QRA or other accepted methodologies.

Tentative Safety Assessments

Silica & Synthetic Silicates

The Panel issued a tentative amended report for public comment with the conclusion that Silica and Hydrated Silica are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating. However, the Panel determined there were insufficient data to determine the safety of the remaining 22 ingredients listed below:

Aluminum Iron Calcium Magnesium Germanium Silicates*
Aluminum Iron Calcium Magnesium Zirconium Silicates*
Aluminum Iron Silicates*
Aluminum Silicate
Ammonium Silver Zinc Aluminum Silicate
Calcium Magnesium Silicate*
Calcium Silicate
Lithium Magnesium Silicate
Lithium Magnesium Sodium Silicate
Magnesium Aluminometasilicate
Magnesium Silicate
Magnesium Trisilicate
Potassium Silicate
Sodium Magnesium Aluminum Silicate*
Sodium Magnesium Silicate
Sodium Metasilicate
Sodium Potassium Aluminum Silicate
Sodium Silicate
Sodium Silver Aluminum Silicate*
Tromethamine Magnesium Aluminum Silicate*
Zinc Silicate*
Zirconium Silicate*

Ingredients in red were previously reviewed by the Panel.
**Not reported to be in use.*

The Panel emphasized that this report reviews the safety of synthetic amorphous Silica and synthetic amorphous silicate ingredients. Crystalline silica is not toxicologically similar to amorphous silica and would need to be reviewed separately.

The Panel reviewed the current safety test data on amorphous Silica and Hydrated Silica and determined that these two ingredients do not pose an inhalation safety risk. The exposures that were tested in inhalation studies were at much higher concentrations than those possible with cosmetic use, and had very few adverse effects. The carcinogenicity study used such high concentrations of Silica that the noted effects on the lymph nodes were due to the overload of the animal system: incidental inhalation of Silica in cosmetics is not a concern.

The data on the remaining ingredients were considered insufficient to determine the conclusion on safety. The additional data needed for the 22 silicate ingredients comprise:

- Chemical characterization (structure), composition, and impurities data for the silicate ingredients
- Method of manufacturing and/or source data for the silicate ingredients
    - Depending on the information provided, additional data on toxicological endpoints may be needed

Parabens

The Panel issued a revised tentative amended report for public comment with the conclusion that the following 20 alkyl parabens are safe in the present practices of use and concentration described in the safety assessment when the sum of paraben concentrations in final formulation does not exceed 0.8%.

Butylparaben
Calcium Paraben*
Ethylparaben
Isobutylparaben
Isopropylparaben
Methylparaben
Potassium Butylparaben*
Potassium Ethylparaben*
Potassium Methylparaben*
Potassium Paraben*
Potassium Propylparaben*
Propylparaben
Sodium Butylparaben
Sodium Ethylparaben
Sodium Isobutylparaben
Sodium Isopropylparaben*
Sodium Methylparaben
Sodium Paraben
Sodium Propylparaben
4-Hydroxybenzoic Acid*

**Not reported to be in current use.*

Because of the extensive metabolism of parabens, the Panel determined that safety data for one of these alkyl parabens can be used to support the safety of the other alkyl parabens.

However, the Panel concluded that the available data are insufficient to determine the safety of Benzylparaben. (This ingredient is not reported to be in use.) The data needed to determine the safety of this ingredient comprise a no-observed-adverse-effect-level (NOAEL) derived from developmental and reproductive toxicity (DART) studies.

Insufficient Data Announcements

Caprylhydroxamic Acid

The Panel reviewed the safety of Caprylhydroxamic Acid for the first time and issued an insufficient data announcement (IDA). Several human repeated insult patch tests (HRIPTs) were included in the draft report, that described testing at various concentrations of Caprylhydroxamic Acid. Although the test results are largely negative, there were some alerts for sensitization in HRIPTs on formulations containing less than the maximum reported use concentration of Caprylhydroxamic Acid. Because the potential for sensitization could not be ruled out completely based on the reactions observed in the HRIPTs, combined with reactions reported in patients following the use of Caprylhydroxamic Acid in a reformulated moisturizer in Finland, and the absence of a local lymph node assay or guinea pig maximization test to demonstrate a lack of sensitization potential, the following data were requested:

- Human repeated insult patch test at maximum use concentrations
    - a minimum of 100 subjects, preferably with Fitzpatrick skin types 1 – 4
    - based on these results, a QRA should be performed, and a no-expected-sensitization-induction-level (NESIL) should be determined

The Panel noted that Caprylhydroxamic Acid penetrates the skin. However, the negative results reported in a 13-week oral repeated dose toxicity study, an oral developmental and reproductive study, and in vitro genotoxicity studies included in the report, mitigated concerns about systemic toxicity.

Hydroxamates, as a class, are chelating agents, and some are capable of the inhibition of a variety of enzymes, including ureases, peroxidases, and matrix metalloproteinases. However, based on the structure of Caprylhydroxamic Acid, it is not expected to be an effective inhibitor; none of the effective inhibitors contain a straight alkyl chain.

Additionally, the Panel also noted that nitrosamide formation is theoretically possible. However, they also noted that such formation is highly unlikely with Caprylhydroxamic Acid.

Capryloyl Salicylic Acid

The Panel issued an IDA with the following data requests on Capryloyl Salicylic Acid:

- Impurities
- Phototoxicity

The CIR Expert Panel published a safety assessment of Salicylic Acid and 16 salicylates in 2003. That safety assessment included Capryloyl Salicylic Acid, which was included in the grouping because, at the time, it was mischaracterized and defined as an ester. However, it is now known that this ingredient is a ketone. This is the first time the Panel has reviewed this ingredient as a ketone.

According to the Dictionary, Capryloyl Salicylic Acid is reported to function as a skin conditioning agent. Capryloyl Salicylic Acid is used in 104 cosmetic products (93 leave-on and 11 rinse-off). This ingredient is used at concentrations up to 0.5% (in moisturizing products, not spray), the highest reported maximum use concentration

for leave-on formulations. In rinse-off products, Capryloyl Salicylic Acid is used at concentrations up to 0.4% (in paste masks and mud packs).

The Panel discussed the issue of skin sensitization potential for this ingredient. Capryloyl Salicylic Acid induced skin sensitization in guinea pig maximization tests at challenge concentrations of 0.5%, 2%, and 5%, but not at 1%. However, in HRIPTs, cosmetic products containing 0.5% or 2% Capryloyl Salicylic Acid were classified as non-sensitizing. After reviewing the HRIPT results and considering that the highest reported maximum use concentration of Capryloyl Salicylic Acid is 0.5% in leave-on cosmetic products, the Panel was reassured that the sensitization potential of exposure to this ingredient via cosmetic use is not a risk.

Glycerin Ethoxylates

The Panel issued an IDA for the following 8 glycerin ethoxylates ingredients:

Glycereth-3	Glycereth-12	Glycereth-26
Glycereth-7	Glycereth-18	Glycereth-31
Glycereth-8	Glycereth-20	

The Panel reviewed the safety of these glycerin ethoxylates for the first time, and found the data were insufficient to determine safety. The results of a concentration of use survey conducted by the Council in 2018 indicate that Glycereth-26 is used at up to 1% in body and hand spray formulations which may result in incidental inhalation exposure. The Panel discussed the issue of incidental inhalation exposure from aerosol spray moisturizers, and body and hand products. The Panel also asked to see data from similar alkoxylated ingredients for potential inference. In order to determine the safety on these ingredients, the following data were requested:

- Impurities
- Method of manufacture
- Inhalation toxicity data

Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI)

The Panel issued an IDA for the cosmetic use of the ingredient mixture, MCI/MI. (This report was initiated as a re-review.) The Panel requested an inhalation study of at least 3 months in duration that is in accordance with the Organization for Economic Co-operation and Development (OECD) test guideline (TG) 413. This request is in response to reports of adverse events observed in infants following inhalation exposure to humidifier disinfectants that contained this preservative mixture.

The Panel noted the results of a QRA for skin sensitization performed by the CIR Science and Support Committee. The results indicated that some leave-on products with MCI/MI, at the recommended safe concentration of 7.5 ppm, may increase the risk of sensitization induction. In most rinse-off products, 15 ppm MCI/MI was not associated with a potential increased risk of skin sensitization induction. Regarding safety of topical (non-inhalable products), the Panel found that MCI/MI should be formulated to be non-sensitizing in dermal applications based on the results of a QRA or other similar methodologies. The Panel cautioned that following these recommendations may not necessarily prevent the elicitation of allergic reactions in individuals who are already allergic to MCI/MI. Individuals previously sensitized to MCI/MI should avoid products that contain this ingredient mixture, or either constituent.

Soy-Derived Ingredients

The Panel issued an IDA for the following 28 soy-derived ingredients:

Glycine Max (Soybean) Callus Culture	Glycine Max (Soybean) Leaf Cell Extract
Glycine Max (Soybean) Callus Culture Extract	Glycine Max (Soybean) Leaf Extract
Glycine Max (Soybean) Callus Extract	Glycine Max (Soybean) Phytoplacenta Conditioned Media
Glycine Max (Soybean) Fiber	Glycine Max (Soybean) Phytoplacenta Extract
Glycine Max (Soybean) Flower/Leaf/Stem Juice	Glycine Max (Soybean) Pulp

Glycine Max (Soybean) Seed Extract
Glycine Max (Soybean) Seedcake Extract
Glycine Max (Soybean) Seedcoat Extract
Glycine Max (Soybean) Seed Powder
Glycine Max (Soybean) Sprout Extract
Glycine Soja (Soybean) Extract
Glycine Soja (Soybean) Fiber
Glycine Soja (Soybean) Flour
Glycine Soja (Soybean) Germ Extract
Glycine Soja (Soybean) Hull
Glycine Soja (Soybean) Lipids
Glycine Soja (Soybean) Phytoplacenta Extract
Glycine Soja (Soybean) Seed
Glycine Soja (Soybean) Seedcake Extract
Glycine Soja (Soybean) Seed Extract
Glycine Soja (Soybean) Seed Powder
Glycine Soja (Soybean) Seed Water
Glycine Soja (Soybean) Sprout Extract

The Panel noted the lack of genotoxicity and carcinogenicity data, but considered the lack of those data to be mitigated as these ingredients are commonly ingested as food and food products, and exposure via oral ingestion would be much higher than exposure from cosmetics. The much greater exposure via food and food products, and the lack of adverse events resulting therefrom, also mitigated the concern for possible estrogenic effects. In addition, the Panel noted an occupational exposure study in which workers displayed asthmatic symptoms after inhalation exposure to soy. The Panel attributed the respiratory symptoms therein to the prolonged duration of exposure, which would not be a relevant issue with cosmetic use. Tyrosinase inhibition was apparent in a study involving Glycine Soja (Soybean) Sprout Extract; however, the Panel decided that this was not of concern as this was an in vitro study and the doses used in this study were much higher than what would be used in cosmetics. The possible tumor-promoting effects of soy were evaluated and were mitigated, as persistent activation of certain pathways would need to occur before tumor promotion could be a concern.

However, in order to make a conclusion of safety on these ingredients, the Panel requested sensitization data on Glycine Soja (Soybean) Seed Extract at the current maximum use concentration of 2%. In addition, the Panel requested data identifying the composition, method of manufacture, or general characteristics of the callus ingredients.

Vanilla-Derived Ingredients

The Panel issued an IDA for the following 9 vanilla-derived ingredients, from *Vanilla planifolia* and *Vanilla tahitensis* plants:

Vanilla Planifolia Fruit Extract
Vanilla Planifolia Flower Extract
Vanilla Planifolia Fruit Oil
Vanilla Planifolia Fruit Water
Vanilla Planifolia Leaf Cell Extract
Vanilla Planifolia Seed
Vanilla Planifolia Seed Powder
Vanilla Tahitensis Fruit Extract
Vanilla Tahitensis Seed

The Panel issued the following data requests on Vanilla Planifolia Flower Extract:

- Composition
- Method of manufacture and impurities
- Concentration of use
- 28-day dermal toxicity
    - Depending on the results, other toxicological endpoints may be needed (e.g., genotoxicity and DART)

According to 2019 VCRP data, Vanilla Planifolia Fruit Extract is reported to be used in 370 cosmetic products (232 leave-on products, 133 rinse-off products, and 5 products that are diluted for (bath) use). Of the vanilla-derived ingredients reviewed in this safety assessment, this is the greatest reported use frequency of use.

The results of a concentration of use survey conducted by the Council in 2017 indicate that Vanilla Planifolia Fruit Extract is used at maximum concentrations of up to 0.33% in leave-on products (face and neck products) and maximum use concentrations up to 0.25% in rinse-off products (skin cleansing products). These are the highest use concentrations in leave-on and rinse-off products reported for the vanilla-derived ingredients that are reviewed in this safety assessment.

Re-Reviews

Acetyl Trialkyl Citrates

At the December 1999 Panel meeting, the Panel concluded that Acetyl Triethyl Citrate, Acetyl Tributyl Citrate, Acetyl Trihexyl Citrate, and Acetyl Trioctyl Citrate (now known as Acetyl Triethylhexyl Citrate) are safe as used in cosmetic formulations, and issued a final report. The final report was published in 2002. Because it has been at least 15 years since this report was published, in accordance with CIR Procedures, the Panel again considered whether the safety assessment of these 4 ingredients should be reopened. After considering new studies and updated use data on these 4 ingredients, the Panel determined to not re-open the safety assessment.

After reviewing assays involving cell models with reporter genes (i.e., in vitro cell reporter assays), the Panel noted that Acetyl Tributyl Citrate and Acetyl Triethyl Citrate may produce adaptive effects or trigger activation of reporter constructs. However, the Panel stated that toxicity cannot be concluded unless the effect is evaluated in vivo. In other words, these assay results are not evidence of a toxic effect, and the results would have to be validated in vivo to determine whether or not the effect observed is actually a toxic effect.

Acetyl Tributyl Citrate is being used in leave-on products at concentrations up to 8.9% (7% in the original report), and the frequency of use of this ingredient has increased significantly since the initial review of this ingredient group. Acetyl Triethyl Citrate is reportedly used in rinse-off and leave-on products, but current use concentration data were not reported. Acetyl Trihexyl Citrate and Acetyl Triethylhexyl Citrate are not reported to be in current use.

BHT

The Panel first published a review of the safety of BHT (Butylated Hydroxytoluene) in 2002, concluding that, “BHT is safe as used in cosmetic formulation,” as described in that report. Because it has been at least 15 years since the report was published, in accordance with CIR Procedures, the Panel considered whether the safety assessment of BHT should be re-opened.

The Panel reviewed data that have been published since the last review, as well as updated frequency and concentration of use data. The frequency of use has increased significantly. The available studies, along with the case literature, demonstrate no significant irritation or sensitization. Recognizing the low concentration at which this ingredient is currently used in cosmetic formulations and the lack of case reports in spite of the increased use, the Panel reaffirmed the original conclusion, and determined to not re-open the safety assessment.

EDTA & Salts

The Panel first published a review of the safety of EDTA and its corresponding salts in 2002. The Panel concluded that EDTA, Calcium Disodium EDTA, Diammonium EDTA, Dipotassium EDTA, TEA-EDTA, Tetrasodium EDTA, Tripotassium EDTA, Trisodium EDTA, HEDTA, and Trisodium HEDTA are safe as used in cosmetic formulations. Because it has been at least 15 years since the publishing of this report, in accordance with CIR Procedures, the Panel considered whether the safety assessment of EDTA and its corresponding salts should be re-opened.

The Panel reviewed the data that have been published since the last report, as well as the updated frequency and concentration of use data. The frequency of use of several of these ingredients increased significantly. The Panel noted the potential for phototoxicity from a study involving protoporphyrin, but concerns were mitigated as the concentrations of EDTA used in that study were extremely high. In addition, the Panel noted the lack of genotoxicity and clinical effects in studies involving these ingredients. Therefore, the Panel reaffirmed the original conclusion, and determined to not re-open the safety assessment.

Imidazolidinyl Urea

The CIR Expert Panel first reviewed the safety of Imidazolidinyl Urea in 1980, concluding that this ingredient was “safe when incorporated in cosmetic products in amounts similar to those presently marketed.” In 2001, after

considering new studies and updated use data on this ingredient, the Panel determined to not re-open the safety assessment. Because it has been at least 15 years since the first re-review summary was published, in accordance with CIR Procedures, the Panel again considered whether the safety assessment of Imidazolidinyl Urea should be re-opened.

The Panel reviewed data that have been published since the last re-review, as well as updated frequency and concentration of use data. The frequency of use has decreased significantly. The Panel noted that Imidazolidinyl Urea is a formaldehyde-releasing preservative and use of these types of ingredients as a whole has decreased. The Panel determined that there were no new relevant data that would inform a new review of this ingredient. Therefore, the Panel reaffirmed the original conclusion, and determined to not re-open the safety assessment.

Re-Review Summary

Squalane and Squalene

The Panel approved the re-review summary of Squalane and Squalene, reaffirming that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration. This conclusion was originally published by CIR in 1982. Limited new data that were identified in the published literature, as well as updated information regarding frequencies of use, provided by the FDA, and maximum use concentrations of use, provided by the Council, were reviewed by the Panel.

Final 2020 Priorities

The CIR Procedures require preparation of the Draft 2020 Priority List for public comment by June 1, 2019. The Draft 2020 Priority List was issued for public comment earlier (March 2019) in the process to allow more time for the acquisition of data. Comments at the April 2019 Expert Panel meeting were considered and incorporated, where appropriate, into a Draft Final 2020 Priority List. Comments at the June 2019 Expert Panel meeting, on that Draft Final version, were considered and incorporated here, in this Final 2020 Priority List. The list is based on stakeholder requests; frequency of use data (FOU) from FDA's Voluntary Cosmetic Registration Program (VCRP), received from the FDA on February 13, 2019; and on CIR staff and Panel workflow. The Final Priorities for 2020 are essentially the same as those finalized for 2019; however, this list has been updated with 2019 frequency of use data, a report in progress (Caprylhydroxamic Acid) has been removed from the list because it is already under review, an ingredient (Benzisothiazolinone) was removed for zero FOU, and an ingredient (Calcium Sulfate) was removed for significantly declining FOU (between years 2018 and 2019). Additionally, three items were suggested for incorporation in this list. However, each was deferred to future prioritization, in order to gather more information.

While this Final Priority list below includes only the lead ingredients, groupings are provided for each in the final document (https://www.cir-safety.org/sites/default/files/CIR_Final_2020_Priorities.pdf) There are 23 reports covering 185 ingredients on the Final 2020 Priorities List. Reports previously prioritized and on the CIR docket at the end of 2019, as well as a number of re-reviews of previous assessments, will supplement the total number of ingredients to be assessed in 2020. Interested parties are encouraged to submit pertinent data to the CIR, as soon as possible, for use in the development of the Scientific Literature Reviews for these ingredients.

Final 2020 Priorities List

Ingredients	*Frequency of Use (FOU)*
For cause	
BASIC BROWN 17 – a hair dye	51
Per FOU	
HONEY	1002
SACCHARUM OFFICINARIUM (SUGARCANE) EXTRACT	447
EQUISETUM ARVENSE EXTRACT	338
SACCHARIDE ISOMERATE	455
PORTULACA OLERACEA (PURSLANE) EXTRACT	481
UBIQUINONE	374
DIATOMACEOUS EARTH	213
SODIUM LEVULINATE	390
GLUCONOLACTONE	369
ACETYL HEXAPEPTIDE-8	379
HONEY EXTRACT	359
CHONDRUS CRISPUS EXTRACT	350
ROSA DAMASCENA FLOWER OIL	328
SALVIA OFFICINALIS (SAGE) LEAF EXTRACT	325
ROSA DAMASCENA FLOWER WATER	331
DICAPRYLYL ETHER	344
PEG/PPG-8/3 DIISOSTEARATE	290
POLYQUATERNIUM-51	310
DIACETONE ALCOHOL	223
ACETYL GLUCOSAMINE	276
POLYQUATERNIUM-6	280
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	279

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, CIR Toxicologist
Date: August 22, 2019
Subject: Draft Revised Respiratory Exposure from Cosmetic Ingredients Precedents Document

Enclosed is a draft of the CIR Precedents – Respiratory Exposure from Cosmetic Ingredients document (*resp092019rep*) and the transcripts of the discussion of the CIR Precedents document (*resp092019min*).

This document has been reorganized to address the comments received on the document to date. At the December 2018 meeting, the Panel concluded that, while particle/droplet size is an important parameter, the physicochemical properties of ingredients in a spray formulation, as well as the realistic exposure factors under in-use conditions, also play significant roles in evaluating inhalation safety of ingredients as spray formulations. When spray parameters are absent or provide an insufficient basis to support a robust inhalation exposure assessment, the Panel would request additional information from industry and further evaluate the sufficiency of other exposure data that may be available on a case-by-case basis.

In addition, the Panel recommended changing the document title from "Aerosols" to "Respiratory Exposure from Cosmetic Ingredients." The Panel noted that particle size distributions are product specific; however, data are currently insufficient to assess the inhalation exposure assessment of some types of cosmetic sprays. The Panel requested collection and analysis of particle size distributions-consumer use data of such spray products. To date, CIR has not received such relevant information.

The Panel should determine how, and to what extent, the attached draft of the CIR Precedents – Respiratory Exposure from Cosmetic Ingredients document should be revised further, based on the currently available particle size data and inhalation exposure parameters of sprays.

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Day 1 of the April 10-11, 2017 CIR Expert Panel Meeting – Dr. Mark's 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 nanoparticulates 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 nanoparticulates 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…

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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 you7 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…

Day 2 of the April 10-11, 2017 CIR Expert Panel Meeting – Full Panel

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 pharmaceutics 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…

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DR. MARKS: Ivan, just your reaction with that in terms of his presentation today. And that just because a product is not labeled as being nano product, that they're nano particles in there. Do you have any first blush of how the document would be revised?

DR. BOYER: Well, his focus was on very small particles.

DR. MARKS: Right.

DR. BOYER: I mean, when he mentioned of course particles and so forth it was still within a fairly narrow small particle range and so forth. He provided us with a good deal of information about aggregation and glomeration and I think that probably needs to be addressed in a little bit more detail in this document.

The issue of just what the exposure is -- is really a critical one. It's one thing to say that there's the fine particles, the very fine particles -- nanoparticles and so forth are ubiquetas regardless of how a product is labeled. But it's another thing to evaluate just how much of the material actually gets into the respiratory tract and how much of it is deposited, particularly in the pulmonary region. So I think the discussion is going to have to be updated to address that. Also, we're right now, the way the boilerplate reads, we make the statement that um, that in fact, the amount of respiral particles and people would be exposed to through their cosmetics. Through the products and the powder products is -- would be a negligible amount or it would not be a significant amount.

And so, I think we'll have to rethink that after we gather the data and take a close look at it. So we've Doctor Nazarenko's data that we need to take a closer look at and incorporate and summarize in some way. Maybe in this document or in a supplementary document. And we're also going to have to do a better job I think in terms of characterizing the data that we've been using up till now, to support the framework.

MR. MARKS: And I kind of felt that Doctor Singal's presentation was more translational. Taking basic science and then trying to apply -- you mention exposures. How -- is there anything in particular that you include from her presentation or...?

DR. BOYER: Well, I think she did a good job in terms of evaluating some of the other elements that go into exposure assessment.

DR. MARKS: Okay.

DR. BOYER: Again, particle size is just one of those parameters --

DR. MARKS: Right.

DR. BOYER: -- I just one of those. I should say more specifically, particle size distribution. But there's you know, a lot more that goes into the evaluation of exposure. Exposure assessments and risk assessments and so forth.

DR. MARKS: Right.

DR. BOYER: And many other parameters. And those are important to take into consideration. And we have some of that information already in the framework document. But I think we could, you know, based on the context that both presentations provided we can revise the

document and it'll be a better document.

DR. SLAGA: So we'll deal with that the next time or...

DR. BOYER: Well, whenever we see the next document.

MS. FIUME: Sometime in the near future, I promise it for next meeting.

DR. BERGFELD: When is your departure Ivan? You see your workload here.

DR. BOYER: I am supposed to leave the 27th of this month.

DR. BERGFELD: Um-hum.

DR. BOYER: I do have a lot of vacation time built up, so I'm going to try to work some of that into the timeframe. And in fact, I'm starting my new position on the 28th, the next day.

DR. MARKS: You were going to comment?

MR. GREMILLION: I wanted to follow up on the, I guess the comment on the Women's Voices for the Earth letter. They had picked out this sentence the panel noted, the droplets particles from cosmetic products would not respirable to any appreciable amount. And I'm looking at the document now, it says, that's been changed to note that most aerosol droplets particles incidentally or -- I guess, kind of a more qualified sentence says, they would not be respirable to any appreciable amount. However, some of the droplets particles are respirable including up to five percent of the particle size, is that right? Was that responsive to their concern?

DR. BOYER: Actually, that's -- I believe what you just read was the original language and we haven't really changed that. That's the language that I think that the panels are going to have to take a closer look at. As a result of some of the new data that's been presented and so forth.

MR. GREMILLION: So the letter from the Women's Voices (inaudible) that's kind of paraphrasing the current policy.

DR. BOYER: That's right.

MR. GREMILLION: Okay.

DR. MARKS: Okay. Any other comments? If not, we look forward to seeing the revised document with the input from the presentations today. Are the presentations today going to go online? What do we do with those? They had a -- was a very slide show.

DR. FIUME: We do capture them with our announcement. And we do capture them for in the office.

DR. MARKS: Okay.

DR. FIUME: So and often we do post them online.

DR. MARKS: Okay.

DR. BERGFELD: I like to ask a question. When we revise this particular aerosol -- I guess what you call precedent, is that what you're calling it? What will we do with old documents where we have made other types of statements.

DR. SHANK: Good question.

MS. FIUME: I think that's something we'll need to think about for when we bring this back in the near future. Have some recommendations as to what we do, there has been things in the past where our language has change or how we handle things have change.

We generally announce it with the post meeting announcement and we hope that gets disseminated and then we go forward with it. We can't really do anything with those that have already been published in the IJT. But we may also sometimes make a statement that goes into the IJT, that there's been a change to some language and it applies to all documents. So we can look into something like that.

DR. BERGFELD: Okay.

DR. MARKS: Thank you Wilma.

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DR. BELSITO: Yeah. I thought most of them were, which was why I was like totally confused. Okay. Anything else on the endocrine? Okay. So, aerosols. That's before endocrine? After endocrine?

DR. LIEBLER: Yes. It is

DR. BELSITO: So we were asked to potentially make some changes based upon the

DR. LIEBLER: PDF 53

DR. BELSITO: materials that were presented today. I mean, I think one of the issues is we found that even if it doesn't say that it's

DR. SNYDER: Size distribution thing, I think is still problematic.

DR. BELSITO: Yeah.

DR. LIEBLER: Right. That's my main concern here.

DR. BELSITO: Yeah.

DR. SNYDER: We don't know what it is.

DR. LIEBLER: So this is PDF 55. This is the data, or the idea that the propellant hair sprays have a median particle dander of 35 microns, where as the deodorant propellant sprays are 10. And they have the same co-efficient of variation. And first of all, I wonder how reliable those differences are. I don't know how good the data are, and I couldn't look at the references to determine what method was used to measure the particle sizes. And this is why I had a question for Dr. Nazarenko this morning about how the analysis platform influences the measurement. And how the chemical composition of what's been sprayed influences the measurement. And whether these distributions really are different or not. And we've got, you know, three measurements of a deodorant and three of a hair spray, or something like that. And we haven't really seen the data, and so it's very hard for me to determine whether or not that's a significant difference or not. But, if we say 10 microns is the magic number, and we know it's about distribution, but if we say, 10 microns is sort of a gold standard for deposition into the distal airways, or into the alveoli, then with this deodorant, propellant deodorant spray, we've got half of these particles are below the median. And so, the respirable fraction should be approximately 50%. And that's not what was used in the calculations here. I mean, that's what the note from the woman, Ms. Scranton, from Women's Voices for the Earth pointed out in her memo. So I think she's still got a valid point and we haven't dealt with it.

DR. BOYER: Well actually, if you look at some of the yellow highlighted text, I did re-calculate everything. And from that documentation that communicates 10 microns as a medium for deodorant sprays, they also indicated that there's a maximum of like 33% or so. And so I re-calculated everything based on 33%. And I went ahead and did the calculation also assuming 50% respirable particles. And so the results are now in this document.

DR. LIEBLER: Yeah, and you offer those as sort of alternate calculations at the end. This is on PDF 57, where you've got a series of bullets then the yellow highlighted section there. And you've got the respirable fraction in the last bullet as 5%. And I think that still has to be wrong, has to be 50%.

DR. BELSITO: What page are you on, Dan?

DR. LIEBLER: PDF 57.

DR. BOYER: I just can bring up that calculation. Assuming 50%. I can just bring that up.

DR. LIEBLER: No, that's fine. And the thing is, so that, I think is just a either a

typo or an error.

DR. ANSELL: Because that changed in the yellow part.

DR. BOYER: Well, it's actually what we received the calculations as. Assumed 5%.

DR. LIEBLER: Okay. But that might have been an error that propagated through somewhere. Because if it's median is 10, then you know, if it's a symmetrical distribution, and we don't know that. But let's just assume it's the simplest thing, then half of the particles are less than 10.

DR. NAZARENKO: Well, is it the number metric, or mass metric, or surface air? If it's number metric, it depends on how low you measure. If you measure down to 20 nanometers, then ten nanometers is drastic.

DR. LIEBLER: Yeah. You're talking about the shape of the tail of the distribution all along, right?

DR. NAZARENKO: Because there are so many particles in this nano size range, that if you measure from 20 nanometers up to 20 micrometers, you measure from 10 nanometers up to 20 micrometers, it's a very small change in the size lever,

DR. LIEBLER: Yeah

DR. NAZARENKO: but there will be a huge difference in the number of particles. Not so much in mass, but

DR. LIEBLER: Yeah, no, I think we're concerned with total mass of matter that was deposited.

DR. NAZARENKO: It's important to know

DR. LIEBLER: But we can't assess how low they were able to measure without knowing what platform they used. And so, that's why, and I couldn't check that. I saw it referenced there and it was some report from the council or something like that.

DR. BELSITO: Are we still using assays that are based on the 70s? We seem to be.

DR. LIEBLER: I just don't know what platform was used. So I don't know if these numbers are very useful or not.

DR. BOYER: Okay.

DR. BELSITO: So where did you think the 57, Dan, was? In the last bullet? Respirable fractions: 5%, 1%

DR. LIEBLER: Yeah, I think that first one, 5% should be 50%. If the median is 10.

DR. BELSITO: The bullet there is

DR. LIEBLER: It's an approximation, correct.

DR. BELSITO: 50%?

DR. SNYDER: 1% and 5%.

DR. LIEBLER: But that should be checked. This is the same thing that Alexandra Scranton noted in her memo to us. And she thought it might be a typo, she said. So, and I thought, yeah, it might be a typo. Because, you know, if you think about the median being 10. If we just talk about the mass distribution.

DR. ANSELL: I think the part that Marta tried to get to in her presentation this morning was that, you know, that the exposure is still going to be extremely low, even if we use respirable fractions of 5% or 50% or 100% available as some of the modeling used. That what we're interested in is a risk assessment, not the methodological measurement of part and size, per se.

DR. LIEBLER: So, I agree with that. But if we're showing numbers that are wrong

DR. ANSELL: Right

DR. LIEBLER: it makes us look bad. So, I agree. I think I agree with where we're going with this, but we need to have a better handle on the data that we're using to make these assessments, these risk assessments.

DR. BOYER: Okay. And with that, actually comes from a RIFIM document. And it's, what I can do is, I can make that available and pull that down. I believe it also has the individual data points.

DR. LIEBLER: And maybe something about the platform that was used?

DR. BOYER: Not a lot, but at least it contains something. I don't remember off hand.

DR. LIEBLER: In the presentation from Dr. Nazarenko this morning, I mean it looked like depending on the platform you could get maybe a two-fold variation in measured parameters.

DR. BOYER: Right

DR. LIEBLER: And you know, a two-fold would be where we are almost, with this difference between the deodorant aerosols and the hairspray, or the deodorant propellant sprays and the hairspray propellant sprays. And I don't know if those should be different. You know? If the chemistry of the solutions that are being sprayed should make them different.

DR. ANSELL: A lot of it is the work-up. I mean, the samples require significant manipulation to be assessable by the internet, which is why the photographic PDM gave much different results that were gravimetric or those which used mass

DR. LIEBLER: Right. Exactly. And I include that work-up as part of the platform to measure. The method of measurement, broadly speaking, from droplets in the air to data on a piece of paper.

DR. NAZARENKO: Well, I would like to just comment that there are specific approaches to formulate the products, to change the sprayer dye and the way they are applied, to reduce inhalation exposure. It's always a concern that there's inhalation exposure. And if it's possible to reduce it, then manufacturers should reduce it, and use those. And that's also the final comment in this letter. Panel noted that droplet/particles produced would not be respirable to any appreciable amount. So this is a very vague statement. And of course, you know, the research is not there to specifically talk about quantification of every product. But it's possible to recommend that manufacturers make every reasonable effort to employ the existing technological approaches to minimize inhalation exposure.

DR. LIEBLER: Right. That's a good comment. And we often, our panel often operates in that way, we get the best available data, we note that if it, you know, if it suggests there's a potential for risk or hazard, and then we make a recommendation. And I think where we're stuck right now is we're not sure how good our data are.

DR. NAZARENKO: Well, in my opinion, there's specific quantitative data for some products. So some ranges in terms of when the date of exposure, those, you know, could be cited.

DR. LIEBLER: They could. Although, I noticed in your presentation you didn't have anything about like, deodorants, for example.

DR. NAZARENKO: No.

DR. LIEBLER: And our, you know, red flag is on a deodorant. That's why I was looking and I was a little disappointed with no deodorant there. So anyway, there may be data, I mean, there are data. We need better description of the data so that we can comment on that. And then I think we need to, you know, take the most conservative approach and recommend that manufacturers can take steps to control the particle size.

DR. SINGAL: Sorry. One of things, speaking from a consumer product

perspective, and working on the inhalation tox aspects of a lot of these products, one thing we find is that often the tools to be able to assess the particle size distribution doesn't exist across the board. So, larger companies will have access to these resource, smaller companies may not have access to these resources. So they are left to conduct their risk assessments without the benefit of having droplet size distribution information. Certainly I agree with Dr. Nazarenko, if we can quantify that and refine our assessments based on droplet size distribution, that would be ideal. It would be a complete data set. Unfortunately, that isn't always available. And then taking a step aside from this, so that's just one comment that I do have and want to keep in the back of our minds. The other is with regards to the distinction between propellant and pump sprays, which is vastly different. The propellant alone, as being a constituent of the formulation, actually drives part of the breaking apart if you will, for lack of a better term, of the aerosol into smaller droplets so that the surface area is much larger and the droplet sizes are much smaller. Something about the force of it coming out of that specific nozzle. So there is some technology that goes into the design of that pump, or that spray, device is designed in order for the propellant to work with it to propel it out. And then from a pump spray perspective, on average, these are about anywhere from 50 to 80 microns in diameter. And those are pretty consistent across different companies is what you'll see. Propellants definitely, propellant based aerosols, generally about 14 to 15 microns in diameter. So there are some general cut-offs that you will observe if you were to take a survey across those product categories.

DR. BELSITO: 14 to 15 is much lower than what we've been being told.

DR. SNYDER: I have a naïve question. So we talk about aerodynamic equivalent diameters in our measurements and things but we don't talk anything about MMADs or GSDs. Should that? Which is better?

DR. SINGAL: Well, I think the terminology often times, the aerodynamic equivalent diameter often is almost a misnomer for the mass aerodynamic diameter. So, to someone like myself, those almost equate to the same thing. But I understand from folks who may not be as familiar with the terminology the mean the same thing. It's almost like getting information from a Malvern that says DB50. Someone is looking at that and saying, well, I don't know what a DB50 is. Well, DB50 is your MMAD, so that's where we get that information. But it does require an understanding that there are synonymous terms across different data sets. So as long as we have a value by which to ground ourselves and have that distribution built around, that's where we need to start.

DR. SNYDER: So would you suggest that we have in parentheses or something what that means? Or how we're using that data in today's current understanding?

DR. SINGAL: Yes. Absolutely.

DR. SNYDER: Okay.

DR. LIEBLER: Yeah. Having context, and I think that's one of the drivers for some of the comments within the precedence document is that the data is viable, it just really needs context to help it along and make it much more easy to understand across the board, and be more applicable across different product categories.

DR. LIEBLER: Okay, so I think where we are overall here is that we've got a statement that we've been blithely using for a long time, which is, the CIR Expert Panel noted that in practice, 95 to 99% of droplet particles released from cosmetic sprays have aerodynamic equivalent diameters greater than 10 microns. And then we use that basically to end discussion. And the data that we're showing so far in this boilerplate document don't support that. So we need more data before we continue using that statement. And this needs more work with you, more data and better characterization of the data that we have. And I don't think we can finalize this document until we're there.

DR. BELSITO: Well and, I mean, it goes back to the point that we asked Will

before, is that, we go out and A, use current instrumentation to measure particle size and pull off a bunch of products off of the shelves. I mean, we're basing this based on three products that were looked at using 1970 technology. Which I think is totally inappropriate, you know, particularly based upon what we heard today that whether it's labeled as nannoparticle or not, a lot of these have nanoparticles. And that leads me to my last point if we're raising all these questions in the calculations on PDF 57 for both respirable components, particularly the propellant sprays are not valid. Or we're not sure whether they're valid.

DR. LIEBLER: We're not sure.

DR. BELSITO: And even for the loose powder products, we're not sure.

DR. LIEBLER: Correct.

DR. BELSITO: So, those two paragraphs of calculations, I think we need to go back and get data and recalculate.

DR. LIEBLER: Right.

DR. KLAASSEN: I'd like to emphasize the top half of page 57, which isn't yellow. But I think we need much better data, at least from what I can gather from this. And now, Ivan can help with this, but, you know, all of the spray enters the breathing zone, exposure duration is 20 minutes. I mean, how realistic is this for the cosmetics that we're using? So, most of our discussion today is what happens once the chemical gets into the nose, from your nose to the alveoli. I think an equal problem, if not even a bigger problem, is how much gets to the nose. And I think maybe some, I don't know what the data is out there, and the literature. You inhalation people probably know better than I do, but, you know, this is quite different than occupational exposure. I mean, it's a little squirt and then you're done. How much of it when you put in your armpit ever gets close to your nose? And it sure isn't that concentration for very, very long. You know, probably a minute instead of 20 minutes. So, I would like to see this redone. And I think someone has something to say?

DR. SINGAL: Yeah. Actually to your point, and that's an excellent point, certainly one of the things that we took into consideration during our initial assessments at RIFIM and certainly something that we carry through in a lot of our assessments is consumer habits and practice data, which attest to that, that very point. Not all products are used the same way. Different regions have different habits and use practices. For example, propellant deodorant are more often used in Europe than they would be in the United States. That's just one distinction. So maybe their use parameters are going to be different there than they would be here. How often in a day would they be spraying a particular product, that would change the usage and then the eventual exposure. So, we do take these parameters into account. The last time I think this was undertaken was in the mid 2000s, so it may be due again. That consumer habits and practice data be reevaluated. I believe EFAT tried to do this at one point in the late 2000s. You know, when I say late 2000s, I mean 2013, 2012.

[laughter]

DR. SINGAL: You know, so, you know, we're still in the early 2000s. But, yes, they did try to look at this. They did have a contract with ISPRA to collect this kind of information. But, their study might have been a bit biased because they were working with consumers who had known issues with, or complaints with, using certain personal care products. So that may not be the most representative of a cross-section of individuals who are both consistent users as well as consistent non-users.

DR. BELSITO: But we could actually get 95% use concentration possibly?

DR. SINGAL: Mm hmm

DR. BELSITO: Potentially? Purchase it from RIFIM? Or ask them for it?

DR. SINGAL: Mm hmm

DR. BELSITO: Because they now have this company called Crème Global in

Dublin.

DR. SINGAL: Yep.

DR. BELSITO: That is looking at this. And D.O.s are one of its specific product categories that are looked at in QRA.

DR. SINGAL: Mm hmm

DR. BELSITO: And so they would have information on the 95th percentile maximum use and they have that information for both US and Europe population. And if we're interested in the aggregate, we could do the aggregate. We could ask just for the U.S. since we regulate only for the U.S. And I can't say that RIFIM would share that data because they've paid a lot of money to accumulate it, but perhaps we can ask to purchase some of it. But that data exists.

DR. SINGAL: Yeah.

DR. BELSITO: And this company, Dan and I visited them in May. These guys are brilliant.

DR. KLAASSEN: I would definitely support that. I mean, I think we need to have some idea, or a better idea of what the exposure is. Right?

DR. BELSITO: So I would contact Ann Marie and you know, let her know that we're looking for this data. And see whether they'd be willing to share it, whether we could purchase it, or however we could go about it. But we could get information on pump sprays. We could get information on propellant sprays. They have all of that information available. Anything else on these? Okay, I think we'll end here. Because we are now 23 minutes past our set lunch hour. Can we do lunch in 30, well 1:15, 1:05.

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DR. BERGFELD: Okay. The aerosols. I'm not sure, Dr. Marks, what we would discuss on that since we've had two presentations and obviously the document has to be -- have this information included into it.

DR. MARKS: That's exactly what our team concluded, that revision to the document would occur including the nanoparticles and the exposure parameters from this meeting's presentations yesterday by Dr. Nazarenko and single. And that the Women's Voice of the Earth letter of April 3rd was addressed. And as I did at the last meeting, is there anybody from the Women's Voice of the Earth here that would like to express any comments?

So we'll await the revised document. We appreciated the presentations yesterday, particularly the basic science on nanoparticles.

DR. BERGFELD: I don't think we need to vote on that. We can move on. It seemed obvious that it needs to be updated. The present --

DR. BELSITO: Just another comment --

DR. BERGFELD: Okay.

DR. BELSITO: -- from our team. First of all, a correction on page 57, where it has respirable fraction for deodorants, pump hair and propellant hair sprays, we thought the deodorant was 50 percent and not 5 for respirable fraction. And when redoing the boilerplate, particularly based upon the information that we got from Dr. Nazarenko, we are recommending that PCPC or someone go out and measure using the latest tools the distribution of particle size in propellants and in pump sprays because the particle sizes that we're referencing here, at least based upon yesterday's presentations, clearly are not accurate. And we had made that recommendation before that they pull some ingredients off the shelf and use modern technology beyond the technology of 1970 that was in our report.

DR. LIEBLER: In fact, more than one platform.

DR. BELSITO: yes.

DR. LIEBLER: Because Nazarenko's presentation yesterday indicated that there's a platform-to-platform difference that's fairly substantial in these measurements. So we need better data upon which to base our assessment of the approach to these. And it's not going to probably be as straightforward as it used to be.

DR. BERGFELD: Any other comments? Ron Shank, Tom, Curt?

DR. KLAASSEN: No.

DR. BERGFELD: No. Tom, Paul?

DR. SNYDER: No comments.

DR. BERGFELD: All right. Dr. Belsito, comments on the endocrine activity report.

DR. BELSITO: Okay. Let me find it.

DR. HILL: I will while he's saying -- I did have a comment about the aerosols. I felt like, other than the question mark about what we mean by respirable fraction. I looked at what we wrote in the triglycerides report, and I think it still stands up really well, even in light of what we heard all yesterday in terms of the rationale that's written there. So while our reference document obviously needs a lot of work, I felt like what we had in that and some other documents really still stands up quite well.

DR. BERGFELD: That's good to hear because we have to go back and look at those. Yes. Thank you.

DR. BELSITO: Okay. So the endocrine document, by and large, we're very pleased with the corrections that Ivan had made to that document. We had one correction to the text. I believe Dan is going to do that on PDF page 103 having to do with hazard. Weren't you drafting some language for that, Dan?

DR. LIEBLER: Yes. I'm just (inaudible). It's the last sentence on page --

DR. BELSITO: Mic.

DR. LIEBLER: Sorry. Last sentence, PDF page 103. And it says, "thus hazard identification." And I deleted the rest of that sentence and substituted for it, "hazard identification may employ in vitro screening tests. But evidence of these effects must be verified in vivo." It's just a little more succinct and clearer statement of what's in that sentence. That's all.

DR. HILL: I like it.

DR. LIEBLER: Thank you.

DR. BERGFELD: Any other comments? I think then, we'll move ahead.

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DR. BELSITO: Okay, aerosols. We got, again, in an email, some papers out of tox letters and Food and Chemical Toxicology, looking at cosmetic powders, deodorants and antiperspirants that were aerosolized. Sprayed consumer products. And then we got a rather lengthy letter from Women's Voices for the Earth, that are still with concerns about our boilerplate languages.

I looked at this. I thought it was good, but I just thought it needed to be toned down a lot. You repeatedly say throughout the document, "particle droplet-sized data, under consumer use conditions, are rarely needed when assessing inhalation safety of an ingredient in a spray product. A tiered approach to the exposure assessment."

I don't think it's rarely needed. I think that it should say something like, "particle and droplet-sized data, under consumer use conditions, need to be considered when assessing an inhalation study of an ingredient in a spray cosmetic. However, a tiered approach to the exposure assessment of spray products."

To say that we don't give a darn about particle size, I think, is really overstepping what we really mean. I mean, I agree with this tiered approach, but we want to know particle size as well. That was my biggest

issue with this whole report. And that language occurs several times throughout the report. It's on PDF 103, PDF 104.

DR. EISENMANN: What that statement is referring to -- in many cases, the concentrations are used at such low levels that you can assume everything is absorbed and it's still safe. That's why the particle size wouldn't be needed. But your statement would be fine.

DR. LIEBLER: I think instead of saying the particle size information is not needed, I think it's better to say that the particle size information may not actually be available. Because we do have sort of data that is thought to be representative of differences between pump and deodorant sprays, let's say. With a finer particle distribution being with the deodorant propellant sprays.

But we also acknowledge that under the conditions of use, and in the formulations actually used in cosmetics products, those particle size distribution may be different. But we really won't know how different, and we won't be able to routinely measure those.

So, we may not have the particle size distribution information available to us when we make a safety assessment. What we will have, is that sort of limited data that suggests that the propellant deodorant sprays are smaller particles, more within the respirable range.

If we make that the introductory comment, as opposed to we don't need to know particle size. It's a little bit different. Instead of saying, we don't need to know, say, we often won't have that information. Therefore, a tiered approach allows us to begin with a most conservative assessment. But if we have additional information, we can go on to these tiers, two and three, to incorporate the additional information into our assessment.

DR. GREMILLION: Kind of building on that. It seems like one the main points in that letter was that particle size information is a lot easier to obtain now. And so, maybe the statement should be, in the past particle size hasn't always been available, and so we've taken this approach.

I guess I was curious as to the reactions of that. She's asserting that the industry kind of knows -- has very granular information about the particle size in those products. Is that accurate?

DR. BELSITO: The information that we were provided, in these papers from Food and Chemical Toxicology, and toxicology letters, gave us some ranges of what one would expect in a powder and a spray. I think we do have some information on that. I mean, the cosmetic powders was just published in 2018. The deodorants and sprays were from 2012. And the pump sprays was from 2014.

So, I mean, we have, I think, what is the most current data in terms of the delivery systems. I agree that a tiered approach is good, because sometimes we have data that clears it even when it's respirable. Then we don't really care about what the particle size is in a cosmetic product, because it doesn't present a toxicologic concern, even when you are putting animals and they're inhaling particle sizes that are 4 microns or 10 microns. Then we can clear it just based upon that.

I think what is problematic, is when we don't have inhalation data and it's used in aerosols. So, that's what I think this document is really meant to look at, all of those possibilities, when we have data, when we don't have data.

But I just thought that saying we don't really care about particle size was just a little too strong a language, because we sort of do. Oftentimes, we don't have inhalation data. And we're clearing it, based upon the fact that we know the range of particle sizes that are in a pump, that are in a spray, that are in a deodorant, that are in a powder. And so, then we are looking at particle size to clear it.

I just thought that that wording was too strong, and needed to be toned down, from my perspective. Before we get into the comments from Women's Voices for the Earth, just looking at that. And then I think we need to go through -- we'll let Council -- because we got a Wave 4 here this morning. Let you talk about that, and then perhaps we should go through Ms. Scranton's letter and go from there. So, Council, what were your concerns here?

DR. EISENMANN: I think we agree with what you've said already. One paper that we provided, that is described in the report, that I would really like you guys to read at some point, is this Schwartz et al (phonetic), paper where they did -- I don't know if you got that paper.

DR. BELSITO: We did not.

DR. EISENMANN: Right. So maybe between now and the next time. It's where they actually did a more refined exposure assessment, and measured aluminum in an antiperspirant product. So, they not only measured particle size, they measured the amount of aluminum in the particles, and then they carried it on.

And the other point of this paper was that the difference in particle size, if you sprayed it at a surface versus just spray it directly into the air. The exposure was much lower if you sprayed it at a surface. I thought that paper might be of interest to you, to see more details of that.

DR. BELSITO: So, we need to see that paper in the next iteration.

DR. EISENMANN: Right.

DR. BELSITO: Okay.

DR. ZHU: Do we need a whole paragraph to introduce a study? I mean, more details on the study?

DR. EISENMANN: I think a little more detail. I think it would be important for them to read it, so they get the impression of what a more detailed exposure assessment would be like. And when the exposure would go for that. And I'm not sure you'd need a whole lot more in the report, but I think it's important for the panel to read that paper.

DR. ZHU: But that paper is focused on exposure to aluminum chlorohydrate.

DR. EISENMANN: Correct. It would be considered OTC here. But I still think it would be a useful paper for you to read.

DR. BELSITO: That delineates the tiered approach that we're talking about.

DR. EISENMANN: Correct.

DR. BELSITO: Right. So, I think that would be very helpful. I don't think you need to expand the document. But I think the panel needs to understand what you mean by tiered approach.

DR. EISENMANN: Right. And how it causes the -- if you do a higher tier of the exposure, it's much lower than if you make conservative assumptions.

DR. BELSITO: Right. Okay. So, let's go through the comments that were placed by Women's Voices for the Earth. Obviously, the first is that we're still making broad assumptions, and conclusions of safety, about inhalation cosmetics that are not supported by the data. The particle size in deodorant spray is actually coming from the same source as hairsprays, and should be given equal weight and credibility.

Basically, sort of the same point keeps coming up, over and over, about particle size. But I think that, clearly, the papers that we got can address the fact that we haven't updated the data since 1979. That's one of her points. "The boilerplate language, regarding exposure to cosmetic powders, has not been updated and still reflects assumptions based solely on talc data from 1979.

DR. ZHU: Actually, we updated the data. We have the data to show that exposure to silica in face powder. That data is from a Danish EPA report. So, the exposure amount ranges from 73 to 85 milligram per day. It's on PDF Page 102. We just updated that data.

DR. BERGFELD: The date on that was what? The publication?

DR. ZHU: Publication?

DR. BERGFELD: Yes.

DR. ZHU: It's from the Danish EPA report. It's government issued.

DR. BERGFELD: Danish?

DR. ZHU: Yeah, Danish.

MS. FIUME: 2015?

DR. ZHU: 2015.

DR. BELSITO: So, did she see this document? Do we know? Because, again, some of the points she's making have been addressed in this document. Or did she just see what was in the last iteration that we looked at?

DR. ZHU: I think she saw this documents.

DR. BERGFELD: I think we've had a policy to get back to her every time there's been a letter,

and go through the itemized list. Yes. We can look at that.

DR. BELSITO: I understand. But I mean, these comments don't seem to be addressing what we're seeing here right now.

MR. GREMILLION: Can I ask, when you said the Danish data, that supports the -- when you say, "conservative estimates of inhalation exposure to respirable particles during the use of loose powder, cosmetic products, are 400 fold to 1000 fold less than protective regulatory and guidance limits." That's citing the 1979 study. And you're saying the Danish -- there's a newer Danish study that --

MS. FIUME: Yeah, the 2015.

DR. BELSITO: Her comment in 1979, was exposure to cosmetic powders in terms of what is the actual exposure when you use a cosmetic powder. And on PDF 102, there is updated exposure on literature reports, use amount for one day, application of a loose face powder range from 73.1 to 85 milligrams. So, we've updated the exposure. That's the Danish study that's being referred to.

DR. ZHU: Yes. So if you compare the old data from 1979, which is 0.1 to 1 microgram per kilogram per day, and the new data which is 0.9 microgram per kilogram per day, and another data from the paper the council provided, exposure to the powder, the amount is 0.084. So, the older data still represent a very conservative assumption. So, in the boilerplate we keep using that conservative value.

DR. KLAASSEN: I have a general question to my colleagues. If you have a one-fold increase, what does that mean? You double it, right? What's a 400 fold decrease? Can you have more than a one-fold decrease? We keep using, like, he just read, and we use in these documents; they might have said that, but I don't think we should continue to say -- how about 1/400th the amount if that's what's meant.

DR. ZHU: So that conclusion is based on comparison. Based on the new paper, published in 2018, the exposure to aluminum chlorohydrate, where inhalation, after a tier approach is applied, the exposure amount is less than 0.5 microgram per application, per day. And if you compare this value to the occupational permission limit, that is about 18 milligram per day. If you compare these two values, they differ by four orders of magnitude.

DR. KLAASSEN: Okay. Well, the term that's been used in our reports today, and tomorrow, it always says a 400-fold decrease. And I would prefer that to be changed to 1/400th.

DR. ZHU: So, it's based on you compare this value to what value?

DR. KLAASSEN: It's just the wording that I object to. I just don't like the terminology, 400-fold decrease. Because I think you can only have a 1-fold decrease, because then you're zero.

DR. ZHU: I see.

DR. KLAASSEN: I would prefer using the word 1/400th the amount.

DR. LIEBLER: Or 0.25 percent.

DR. KLAASSEN: Or make it a percent or something.

DR. ZHU: Sure.

DR. BELSITO: Number two has to deal with her assumption, or her claim, that there are many different types of cosmetic sprays. And in that, I'm not an expert. We talk about pumps, we talk about aerosols, we now talk about propellants.

DR. SNYDER: That comment I think was appropriate, and I think that we need to capture use data based upon however we're going to look at them, you know, pump sprays, propellant sprays, powders. I think we do that already, and I think we need to continue to do that because that drives our interpretation as to what data we need or what data we have.

DR. ZHU: But in truth, you know, besides the hairsprays and the deodorant sprays there were discussed in the document, we do not have the data for the other new type of sprays indicated by the WVE. You know, such as the suntanning, the hair color spray. The airbrush makeup, lotion spray, et cetera. We do not have data for those kind of sprays.

But our boilerplate language do address the deodorant sprays, separately, from other types of sprays. We have one question for the panel, whether in information on hairsprays can be included as a worst-case scenario; and therefore, included in the boilerplate language to represent cosmetic sprays other than deodorant

sprays?

MS. FIUME: I believe, as Jinqiu said, her point wasn't pump versus aerosol, it was hairspray, versus spray tanning, versus foot spray, versus airbrush, as those type of applications, not pump versus aerosol.

It appears that it defaults to hairspray, but does our language -- as Jinqiu said, can it be used as a worst-case scenario for those other type of sprays, when we use the boilerplate language in the cosmetic use section and the discussion section? We do break out deodorants, because we have that information. But we don't always, specifically, have that information if it's a spray tan versus a hairspray.

MR. GREMILLION: Can I ask why are the deodorants broken out?

DR. ZHU: Because we have data to show that up to 50 percent particle, from deodorant sprays, are respirable. But that's a very conservative assumption.

MR. GREMILLION: That says based on the particle size the deodorants are broken out?

DR. ZHU: Based on particle size distribution, yes.

MR. GREMILLION: Okay. That's interesting. Yeah, I mean, it sounded like cosmetic sprays is really a big category and, particularly, some of the airbrush things is really a different kind of exposure then what's contemplated in this document.

MS. FIUME: I'm not familiar enough with the technology of what's used to distribute those sprays or anything. But generally, from a writer's standpoint, if there's any type of spray product, we use the standard paragraph. If deodorants are known to be a spray, then we add the deodorant language. If we know there's powders, then we add the powder language.

I guess we're asking the panel, do we need to address it differently? Do we need to ask for information? What do we need to do to make sure that when we're using that language, that it actually applies to the product types that are sprays, that might be a face spray or a hand and body product?

DR. BELSITO: Again, I'm not an expert in spray technology either. Maybe we need to have someone come in and address that. But I think the point is, up until recently, to my knowledge, we weren't looking at deodorant antiperspirant sprays any differently than we were looking at other spray products.

MS. FIUME: But we did have separate language. And that's the other point; is that we use that language when it's a known spray. So, when we look at the VCRP data there are certain categories that we're going to assume are sprays. There are some that could possibly be sprays. And until we get use data, saying that, yes, these are used in a spray, we don't necessarily consider them sprays until it's confirmed.

But if VCRP says it's used in a hairspray -- whether or not we have concentration of use data, if VCRP says it's a hairspray, then we know it's a spray product and we'll use the boilerplate language. If VCRP says it's a deodorant, but we don't confirm that it's a spray, we don't necessarily add that deodorant language. Because the attitude was we didn't want to create concern where there really -- concern wasn't confirmed.

But then if we if we received concentration of use data that says, yes, this deodorant is used in a spray, then that separate deodorant language would be included in the cosmetic use section. There's always been two sets of language. And then powder was the third set of language. So, it all depends on the information that we get.

DR. BELSITO: But the reason why we had that is particle size in deodorant sprays are smaller than particle size in hairsprays.

MS. FIUME: Right.

DR. BELSITO: Okay. But then I think her point is, do we know anything about particle size in these other types of sprays? And we don't.

DR. BERGFELD: We don't have exposure time either.

DR. SNYDER: Yeah, that was going to be my comment. So, the consumer use conditions are going to be drastically different for a deodorant, versus a hairspray, versus a tanning spray, versus an airbrush. And so, I mean, it becomes quite problematic. Because consumer use conditions are important, because it relates to exposure.

DR. BELSITO: But should we at least know particle size? I mean, one would hope the manufacturers of these airbrush makeup applicators, that I've never heard of, would have some sense of particle

size.

MS. FIUME: Can we ask, Council, does that information exist as far as you know?

MS. KOWCZ: Well, they're not members of the council so we can ask. But there's only one primary manufacturer, and I think one of them is a third party, so.

MS. FIUME: What about the suntan sprays or face and body sprays; do we have that type of information?

DR. EISENMANN: The thing is, I suspect they're going to be pretty variable. I think this is a difficult case in that you're charged with ingredient safety, and the companies are responsible for product safety. Other than you saying that your expectation is that the particle size should be whatever, and you're reviewing as reported -- so in some ways some of those products, like the airbrush that hasn't been reported to you, so, you're really not assessing whether or not that's safe. That's how I see it.

But I don't think we'd really get that -- and if we got that information, it's likely to change. Somebody will create another product and it will change. I don't have necessarily a good solution other than you expect those products not to have respirable -- I mean, to have a small fraction of respirable particles.

MS. KOWCZ: But I also think what's important, is what Paul said, is the consumer use conditions are very important. So in a sunless tanner, if anybody's ever had it, it's very different from salon, to salon, to salon. I think that's a difficult one.

And then the air spray, there is one major manufacturer right now, company that's distributing that. So, it's going to be difficult because it depends on how the consumer uses the product.

DR. SNYDER: To be honest, when I read this, I thought we could no longer use a boilerplate statement. That I think that we're almost obligated, depending upon the use conditions, and taking into consideration particle size distribution, the formulation of the product -- because the formulation can also impact the absorption and other issues.

I was becoming quite concern whether we could even have a boilerplate that would cover sprays. And we should just ask for the data and interpret the ingredient based upon data. So, that was my concern as I went through all this. Because otherwise, it's getting to be like the one we just did with all these different -- the algae, with all these different conditions and all these different things.

And I'm not certain that we can globally categorize them. We can use the same argument, if it's a deodorant; because we know the deodorant and worst-case scenario and all that. We can put that in the report. But again, I was not aware of all these other sprays. I mean, face spray, tanning sprays, airbrush.

I think that having a boilerplate that covers all of that, I think will be quite cumbersome. I'm not even certain it can be done.

DR. LIEBLER: Yeah. I'm not sure that we need to try and extend our boilerplate to all these other product types or spray types that we have no characterization on. I'm not sure that we can use our boilerplate to cover all these other things; which in many cases, I've not seen reported to us as ingredients that we need to consider in any of our report so far.

So, I think it's not that we -- maybe I misunderstood you, Paul, I don't think you were saying jettison the boilerplate entirely. But I think we can't wrap all of these other --

DR. SNYDER: Under that one heading.

DR. LIEBLER: I hate to use the term one-offs. These other types of less-frequently encountered spray products, into a boilerplate that's really designed to help us deal with much more frequently-encountered spray products, for which we do have some data.

MR. GREMILLION: Is there data on the frequency of use? The products that are targeted by the boilerplate now, actually, are more frequently used?

DR. LIEBLER: I don't even know if they're reported as such.

DR. BELSITO: What would an airbrush face makeup be reported under?

MS. FIUME: I wouldn't use the airbrush as a good example. Because as Carol said, we would probably have no idea that it's an airbrush makeup unless we were maybe -- and this is just my guess -- to receive concentration of use information, under the category foundation, that says it's a spray. So to me that would give an

indication that it's an airbrush makeup. But that would just be my guess.

But we do often receive information that says a face and neck product, whether or not it's a spray, and sometimes it is. Or a tanning product, and it's a spray. So, there are other categories that can be sprays and that we find out, through the concentration of use survey, whether or not they're a spray or a powder. They could also be powders.

And sometimes it will say not spray, but then we don't know whether or not it's a powder. So there are a number of categories, that aren't hairsprays or aren't deodorants, that can be spray products.

DR. BERGFELD: We could probably do that in the introduction, say what this is covering.

DR. LIEBLER: Right. I think we just have to draw limits around what this spray/aerosol boilerplate covers. And it covers the relatively, frequently-encountered ingredients in formulations that we handle on this panel. But it's not comprehensive to all possible respirable ingredients.

And the panel's aware that there are other delivery formats and ingredients, for which sufficient information isn't available for us to determine how to encompass into this precedence document. The panel will consider those on a case by case basis, with the available data when they occur.

DR. BELSITO: Would we even know, from the product category, that it was used in a sunless tanning product?

DR. EISENMANN: There is an FDA product category called indoor-tanning products.

DR. BELSITO: Okay.

MS. FIUME: The concentration of use data that you received, as unpublished data, is very detailed to that information. You wouldn't know from the VCRP data whether or not it's a spray, because that's just a number. But the accompanying concentration of use data would tell you whether or not it's been reported to be used in a spray, when the survey gets returned.

DR. LIEBLER: Are there tanning sprays that are propellant, and tanning sprays that are pump?

MS. FIUME: Are those separated out, Carol?

DR. EISENMANN: I don't think the indoor-tanning products are necessarily separate. They've asked me to separate out the suntanning product. I'm not sure if they went as far as the indoor-tanning products out. Sometimes some people tell me whether or not they're sprays. But I don't always get it.

DR. BELSITO: There are the rub on ones. And then there are the ones where you literally go into a chamber, and you have your whole body sprayed at a salon.

MS. FIUME: But that's also available -- I mean, you can buy a spray on indoor tanner.

DR. BELSITO: Right.

MS. FIUME: In the store. I know my sister, that's the type she uses, is the spray on rather than a rub on.

DR. KLAASSEN: Does she have any health problems?

MS. FIUME: Not from that, that I know of. But to me, think of the face and neck. The sunless tanning, I'm hoping a lot of people aren't spraying at their face, because that would be very difficult to control. But the face and neck products are designed, specifically, to be aimed at the face and neck, per the name of the product. And those are available in sprays.

DR. BELSITO: I agree with Paul, it's very complex. I think the issue is very complex. More of it depends upon how it's used, frequency, duration of exposure. It's almost like we can create the boilerplate, but then we have to adapt it for all those other issues.

DR. LIEBLER: I think we can use the boilerplate to help guide our approach. We can't use the boilerplate as we have in the past to essentially foul off pitches.

DR. BERGFELD: But, essentially, we've not been faced with this dilemma before, with the different types. This is being brought up by the Women's Voices.

DR. BELSITO: Right.

MR. GREMILLION: I just want to reiterate. I think one of the points she's making here, is that you're distinguishing deodorant sprays on the basis of particle size, and now it's much easier to determine. It seems like the manufacturers know the particle size of the products, because they're specifically telling the people they're

sourcing from what particle size they want. And so, having that information in here --

DR. EISENMANN: You have to remember, there's a big difference between the particle size of an ingredient and the particle size of what's in the product. Because you're not necessarily going to get just the little particles of whatever, kaolin, or something, coming out. It's going to be mixed with other things, and then put it in the product to spray out. So, the particle size of the ingredient will not reflect what the particle size in the product is.

MS. FIUME: Which was why I was --

DR. LIEBLER: We tend to think of particles -- I mean, I think, the way you're looking at particles is I've got this stuff I'm going to put into this deodorant, so I take a teaspoon and dump it in. And then that's the particle size that comes out the nozzle.

But actually, the particle size of what comes out the nozzle is influences by the nozzle physics; and the identities of all the other chemical substances that are part of that, that influences the stickiness and adherence of any particulate matter, or any liquid matter, to make these little droplets.

And so we don't think of particles just as these little hard particles that went into the initial formulation. But the particles are what comes out of the nozzle. That's really the particle size.

MR. GREMILLION: I guess it's not appreciably easier, today, to update kind of the particle size numbers that we have in this document?

DR. LIEBLER: Realistically, if you've ever had a can of anything that sprays and you use that can when you just first open it; and then you notice when the can's almost empty the spray seems different. You know, bigger -- it looks like --

MR. GREMILLION: I mean, there's particle size numbers in this document. And I thought she was saying -- you're making a distinction on the basis of particle size, and now it's easier to do that --

DR. LIEBLER: No, it's not that easy. That's the fundamental fact, it's just not that easy.

MR. GREMILLION: Okay.

DR. LIEBLER: It doesn't work like that. Yeah.

DR. SNYDER: It's going to be just similar to how we approach everything else. In the absence of inhalation data, when we know we have an aerosol use, we need other data. And if we get particle distribution data, in the final product formulation, that makes us comfortable that it's not going to be respirable, that checks it off. If it's an exposure situation that will not result in systemic toxicity, greater than systemic toxicity data that we already have, we're comfortable.

I mean, I can clearly see how we're going to evaluate the data. And it's just a different approach that we're going to have to take now. We just can't broadly categorize these into broad assumptions of a spray versus a propellant deodorant.

DR. LIEBLER: Right. And I think this is where the tiered approach helps us. Because it will be cases where we can use the most conservative assumptions, that everything is respirable, and it still doesn't present a risk. And then we'll have things where the particle size information that we do have to go on, suggest it might be respirable, the concentration might be enough to present a risk. That's tier two. And then tier three is where we need real data on the product under conditions of use.

We'll never be able to resolve those in advance with a boilerplate. Those will be battles we'll have to fight, every time, when we have an ingredient to review.

DR. ZHU: May I ask one question? In a situation when the industry does not provide particle size distribution data, for all those new types of sprays, would the data then be considered to be insufficient to determine the safety of an ingredient?

DR. LIEBLER: We won't know that until we have the actual ingredients and their use concentrations to work with. In other words, we can't say industry always need to provide us particle size distribution for their product under use conditions. We won't know if we need that. I mean, if they automatically do that, wonderful. But if they don't do it, it doesn't mean it's insufficient, until we know more about the use concentration and the use practice.

DR. ZHU: So, we would need to address that issue in the boilerplate language?

DR. LIEBLER: No, I don't think so. Because I don't think we could provide useful enough

guidance in a boilerplate anyway.

DR. BERGFELD: Again, I think clarification at the beginning and maybe the end. Some of these will have to go under specific review.

MS. FIUME: So, for now the hundred thousand dollar question that I really, really don't want to ask, but will. Just about every report we have has ingredients that are used in some type of spray; that it's known to be used in some type of spray. Are there changes that need to be made now? Are there changes that need to be made, once you get more information or see a revised version of the aerosol language? How do you want us to proceed in all of those reports right now?

DR. LIEBLER: I think we continue to use the language we've been using, until we can finalize this aerosols precedence document. And we don't really have good information to suggest that our approach has been wrong.

MS. FIUME: As we go forward and announce the different versions, are there any request that you have of industry, that would help answer the questions that we could put out with our post-meeting announcement? Or is there anything specific that can be asked for?

DR. LIEBLER: Does it seem like our main issue is propellant sprays?

MS. FIUME: I don't know. Because I don't know when they talk about the face products, if those are propellant or if they're a pump. Carol?

DR. EISENMANN: Well, it's also category. If I understand, it's a type of bag-on-valve type of spray where --

MS. KOWCZ: It's a forced air. It's a forced pressure, basically. Because you're trying to keep two types of ingredients separated. So, one ingredient needs to be protected from the rest of the formula. And the bag-on-valve is just keeping one type -- let's say the DHA is very reactive with the reset of the formula. So, DHA is in one part, the formula's in the other, and it's a forced airbag, and it forces it through the nozzle.

Then there's a propellant where you're actually mixing it all together, in the formula, and then you're aerosolizing it, and then it comes out. So, that's two very different types. And that would determine, definitely, a different particle size distribution, uses, conditions, all that.

DR. BELSITO: Is such a person available, to come address the panel, on the aerodynamic diameters of these various types of sprays that are used in cosmetics? So we can get some sense of that.

MS. KOWCZ: I'm sure there are suppliers that have information. Most of the industry that deals with any of these systems, there are experts in particle size. You know, what type of spray pattern you want to have, what the particle size distribution is. There are many experts on that.

DR. LIEBLER: You're talking about having somebody come in and give us a seminar?

MS. KOWCZ: A talk.

DR. BELSITO: A talk, yeah.

DR. LIEBLER: Yeah. I mean, that will just kick this down the road further in terms of time, though. We schedule them for April? We talk about what they have to tell us, then we revise this thing again. We see it again in June. We maybe finalize it then?

DR. BELSITO: I just don't know anything about these sprays. And we're being asked to determine safety and this is going to be an increasing issue. And clearly, it's an issue that Women's Voices for the Earth will continue to bring up and we're not resolving it. And I just think that we need greater expertise, or a greater understanding among ourselves, as to what we're talking about here.

I mean, up until this letter, with these various different types of sprays, I was unaware of that. I don't use any spray products. So, I'm not cognizant of it.

DR. SNYDER: We're obligated to change our boilerplate anyway, based upon what we learned about the distribution of particle size measurement. That there's new technology that now capture the full spectrum. We are in the process of revising that. I just would prefer if before we get to another revised boiler, that we at least have some idea that we're not overlooking something or misstating something.

I mean, I appreciate the comments, holding our feet to the fire, so to speak. But we just can't use these broad assumptions. And we were using some very broad assumptions. And I think we can no longer continue

to do that.

MS. FIUME: No. But to clarify, for now I was under the impression that we will use the language, until we know for sure why it's not appropriate. Correct?

DR. BELSITO: Yes.

MS. FIUME: So the report language will not change until we have reason to change it.

DR. BELSITO: Exactly. Right.

MS. FIUME: Okay.

DR. BERGFELD: Or I think the caveat would be, that if we find that we have a spray that doesn't fit, that we will look at it individually.

MS. FIUME: So, what doesn't fit? Because in all of the past reports it didn't have to be a hairspray. Sometimes it was a face spray. So, what doesn't fit?

DR. BERGFELD: Well, here is the problem. The panel is going to have to decide that when they look at the ingredient and the chemical. Decide if it pulls out of the routine boilerplate for whatever reason.

MS. FIUME: Okay.

DR. LIEBLER: You're asking, right now, do we change all the reports that are in process? And my suggestion is no we don't, until we figure out how we're going to handle this.

MS. FIUME: Thank you. That's the answer I was looking for.

DR. BERGFELD: Who's reporting on this?

DR. SNYDER: Dr. Marks.

DR. BERGFELD: It might be well that this particular team has a response, what they think that ought to be done here, succinctly stated.

DR. BELSITO: Well, I think, what we're saying is, is that the language doesn't change. And at least, what I heard is that there is some support to get an individual to give a brief talk at the panel, outlining the various aerodynamic particle size of different types of sprays. And what the common types of sprays are; because again, I wasn't aware that there were things different from propellant and a pump.

That's what we've been working on. And now we're being told there are airbrush sprays. And I don't understand what that is, and how that makes the sizes different. So, I think we need a better understanding of what's out there for cosmetic spray application. And I don't know.

DR. BERGFELD: But you're also saying that the intent is to change the boilerplate to adapt it to the current uses, to understand better the delivery systems. And hopefully, in the future, be able to have a broader perspective on how we deal with these sprays.

DR. BELSITO: Mm-hmm. Okay. So, where are we with the comments?

DR. SNYDER: Number three. The updated language on exposure for powder.

DR. LIEBLER: Say that again, Paul.

DR. SNYDER: We just covered the cosmetic sprays. The third point was the updated language regarding exposures.

DR. BELSITO: Well, we do have the update on the cosmetic powder exposure. That's why I was asking whether she saw this most recent document. That's there.

DR. SNYDER: Okay.

MS. FIUME: And I believe that's what she's responding to. So, I don't know why that question was in there. Because most of the other questions seem specific to the document.

DR. BELSITO: Right. Okay, number four, citations for several of the newly included calculation examples do not correspond to the relevant papers and should be corrected.

MS. FIUME: Jinqiu, you responded to these, correct?

DR. ZHU: Oh, yeah. Actually, all these exposed dose amount are accurate. So, first, for the use amount of deodorant sprays, it's actually coming from the SCCS Notes of Guidance. But in the previous version we cite one paper. But, actually, this SCCS Notes of Guidance need to be cited as well.

And secondly, if you look at Table 2, again, the exposure amount of face powder range from 73 milligram to 85 milligram. The data is coming from Danish EPA's report. And, actually, this data also coming

from review paper. So, if you look at the table in the review paper, it shows that the face powder, the dose at 85 milligram, is coming from Loretz paper; 2008 paper. After carefully checking the original paper article, we found that this kind of data is actually from another paper. So this citation we will correct that.

And thirdly, for the paper, again, the face powder, the exposure to the silica is from Danish EPA's report. So, in that document, Danish EPA cited the SCCS Notes of Guidance as the data source. But in the SCCS Notes of Guidance, there is no category for the face powder. So, in that document the use amount at 510 milligram per day refers to liquid foundation.

I double checked the original Danish EPA's report, and the SCCS Notes of Guidance, these two values are equal. But the Danish EPA seems to use the liquid foundation use data, at 510 milligram per day, to represent the worst-case scenario for exposure to face powder. And that data clearly stated it in the Danish EPA's report.

DR. BELSITO: Okay. Then the fifth point I think we've already discussed, ad nauseum, that we downplay the particle size as a consideration, but tiered approach is how we go. Anything else on the aerosols?

So, we're holding with what we have for now. We're going to try and get a better speaker, or information, so that the panel has a better understanding of the various types of delivery systems, and particle sizes that those delivery systems produce. And then, based on that, we may consider changing this boilerplate.

And I guess Paul's point is, how does this work as a boilerplate? Are we not going to -- because up until now we've simply been using it in the cosmetic use section. Is this just going to be like we'll refer to it, like we do for hair dye epi, and then look at it case by case within the report itself, based upon what it's used? How do we use this boilerplate?

MS. FIUME: I would like to point out, in the discussion, we do refer to the resource document with a link, as we do with the hair dye epi. So, we do that currently. I guess, I was sort of interested to see -- and maybe an expert can tell us -- in those other spray types, maybe, because often they're heavier products that might affect the particle size, can the hairspray be used as a worst-case scenario? And, as Dan said, build off our current language that way? Or do we really need exposure type for each individual type of product?

DR. BELSITO: No. And that's what I would hope the expert would tell us. That, okay, we can pick a delivery system that's a worst-case scenario and work off of that.

DR. LIEBLER: And I think we can check the commonly used delivery systems that sort of dominate spray products/pumps. The forced air and the propellants. To the extent that we have some data for those, build our boilerplate around those. And then say we are aware that there are other types of devices, but if we don't have data for them, we really can't assess them. So, this precedence document only applies to the types of delivery devices for which we can evaluate.

MS. KOWCZ: Can I just ask a question? The objective of having an expert come, Dr. Belsito, is it really to just discuss the different product forms and the potential different spray patterns, particle sizes, whatever? Or is it really to help you determine the safety of different type of product from?

Because I have to say that depending on the formula, knowing a different particle size of use will not help you. Because it really is dependent on each formula. I'm just trying to figure out what would be the objective for getting an expert on sprays?

DR. BELSITO: Well, I'm assuming that the spray, regardless of what is put into it -- if you take a specific formula and put it into different types of packaging, your aerodynamic size may vary a little bit, but maybe I'm wrong.

MS. KOWCZ: So that's what you want to confirm or?

DR. BELSITO: Yeah. I mean, I guess what I'd like to know is, in general, if you use a pump spray, if you use a typical hair aerosol spray, versus whatever these other types of delivery systems are, are you changing the aerodynamic particle size of what's coming out of those sprays. I would like to get a better handle on that.

Because what we seem to be being critiqued on are that we don't look at airbrush spray. Is an airbrush spray -- does that give a finer particle size than a hairspray? I don't know.

MS. KOWCZ: Okay, that's a whole packaging issue, also, as well. So, it's not just the particle

size that's distributed. And the end result will be an entire -- it does depend on the type of packaging, the nozzle, the diameter. There's a whole physics to the packaging mechanisms as well.

DR. KLAASSEN: I think we want to know that. And also, I think it's been emphasized, today, that the formulation is important. That's something that we have zero information on at the present time. So, how does the particle mass, diameter, et cetera, change with different formulations? Is it a 10 percent change or a 3-fold change? What's happening?

So, we need to have a better feeling for these cosmetics, as they're used, of basically the size of the particles that are being sprayed. That's what we would like to have that person educate us on. What are the main things? So, if you're using hairspray and it's not spraying right, you put a paperclip in there and does that change things or not?

DR. BELSITO: Well, we don't really care about that. I mean, we can't look at consumer abuse of the product.

DR. KLAASSEN: No. But we need to know what does vary it. What does vary it.

DR. SNYDER: It could simply turn out that if we use the deodorant propellant spray, which we have good data on, particle size, distribution and all of that in a worst-case scenario, that they could say if you use that as your default, that will broadly cover all the rest of the sprays.

We don't have the data, that's what Alex is saying. You don't have data to support your statement. So, if we had somebody that could come and tell us, or give us that data, to say that these other spray types all would fall well within that, then we're fine. But we don't have the data.

DR. KLAASSEN: And what we would really like to know is, with those various systems, what percentage of the product is less than 10 microns? Because we kind of use as a cutoff if things are less than -- they aren't going to get down into the respirable track if they're not less than 10 microns. So, that's the part that we're really interested in.

DR. LIEBLER: Do we think an expert's going to come in and give us new data that we haven't seen?

DR. KLAASSEN: Yes.

DR. BELSITO: I don't know what airbrush technology is.

DR. LIEBLER: Yeah. Right. I used an airbrush when I was a kid to paint model planes. I mean, I think it's the same device.

DR. BELSITO: I don't know, she's claiming it's a different device.

DR. LIEBLER: No, airbrush is an airbrush.

DR. BELSITO: No, I understand. But that the aerodynamic particle size of an airbrush may be different from a hair pump.

DR. LIEBLER: Oh, who knows? It might be. It might be. I'm just wondering if we're just sort of following this off by saying we're going to get an expert to come and size this up for us -- no pun intended -- instead of figuring out what questions we need to have them address. I think we shouldn't invite anybody until we can tell them exactly what questions we need to have answered.

DR. BELSITO: For me, what are the different types of sprays that are used generally in cosmetic products? And what are the average aerodynamic particle size that comes out of that type of spray application use?

DR. LIEBLER: Well, if we can get somebody that can tell us that, let's bring them in.

DR. BELSITO: Yeah. You know say, okay, these are the six types of -- here's an airbrush spray, here's a pump spray. Here's a da-da-da DO spray. And these are the average aerodynamic particle size. Here's the distribution. And like Paul said, it maybe that a DO spray has the smallest and we just use that as a default. If it clears that, then we don't need to worry about it.

Or it may turn out that the airbrush is smaller and if we use that, we don't have to worry about it. But I don't know that. Because like I said, I don't use any spray products, other than the occasional cleaner in the house. And I don't really care about that. I don't understand these different spray systems.

But I would imagine an airbrush spray probably has a smaller aerodynamic particle size than a hairspray. But I don't know.

DR. LIEBLER: This issue has us fogged in, circling the airport.

DR. BELSITO: So, we stay with the current statement as is. That's my recommendation. Is everyone happy with that?

DR. SNYDER: With the modification of 5 percent to 50 percent, all those modifications, right?

DR. BELSITO: Right.

DR. SNYDER: Worst-case scenario.

DR. LIEBLER: No wait a minute. You're talking about changing all reports in the use section where we currently say in practice?

DR. SNYDER: I thought we found out that we were under estimating the exposure. We were saying it was 5 percent and the conservative was better at 50 percent. Was that not right?

DR. BELSITO: Where are you, Paul?

DR. SNYDER: Let me find it here.

DR. ZHU: Okay, the 50 percent is for the deodorant spray, right. And the 5 percent is actually for the hairspray. We addressed that separately. But the Women's Voices for the Earth suggested that the boilerplate language include information for the deodorant spray. You know, clearly, stated that up to 50 percent of airborne particles are respirable.

But right now, in our boilerplate language, we do not indicate that. So, do we need to do that? Up to 50 percent of particles are respirable?

MR. GREMILLION: And then you also have -- in your response to her, you say recent studies indicated that most of the mass, 85 percent to 93 percent of inhaled airborne particles released from cosmetic powders, is deposited in the head airway, not the pulmonary region. And that implies 15 percent, at least, if you don't want to go to the 50 percent associated with deodorants.

DR. ZHU: Yeah. But actually, we discussed that issue in the document. Even though up to 50 percent of particles are respirable, we need to consider the product parameters of the formulation, the nozzle size, type of propellant, as well as the exposure parameters, including spray type, frequency, spray direction, et cetera.

So, when a tiered approach is applied, the actual amount that -- in the deep-lung region will be dramatically decreased. And in our boilerplate language, we do state that the data is insufficient to determine the extent of lung exposure that resulted from the use of deodorant sprays, compared to other cosmetic sprays.

The only thing we do not clearly state is that up to 50 percent of the particles are respirable. So, do we need to do that in the boilerplate? That's the point from the Women's Voices for the Earth.

DR. BELSITO: On page PDF 100 --

DR. ZHU: 103. I mean, the boilerplate. And 100 is the discussion in the document.

DR. BELSITO: Right. Page 100 of the PDF, the first full paragraph deals with, the conservative estimation indicates up to 50 percent of particle size distribution, released from propellant deodorant sprays, consist of respirable particles. And then it goes on to different patterns of use. How you're spraying. The angle of the spray. The size of the room, da-da-da. Respiratory rate of the person applying it.

But I think we have been looking at deodorant sprays differently than hairsprays. So, I don't think we need to change things.

MR. GREMILLION: I guess, when you see on Page 100, you say 95 to 99 percent of the droplet particles released -- the CIR Expert Panel previously notice that in practice, 95 to 99 percent of the droplets released from cosmetics -- not the deodorants, the cosmetics -- have less than 10 microns. And then, in your response and in other places too, you have this 85 percent to 93 percent, which seems like a difference between 5 percent to 15 percent is respirable.

DR. ZHU: We actually discussed that already.

MR. GREMILLION: I don't understand why the factors that you cited don't apply to the 5 percent as well as the 15 percent. Just for the record.

DR. BELSITO: I'm not exactly following where you're at, here, in this report.

MR. GREMILLION: I was looking at the response to comment three. In the first, second, third, fourth paragraph. "In addition, recent studies indicated that most of the mass, 85 percent to 93 percent of inhaled

airborne particles released from cosmetic powders is deposited in the head airway, not the pulmonary region."

It seems like that indicates that 95 to 99 -- that's kind of at odds with the 95 to 99 percent of the droplets released from cosmetic pump and propellant. Is it different for powders than pump and propellants? I thought we just talking about cosmetics versus deodorants. But that's a lower number than the 95 to 99 percent.

DR. BELSITO: Which point are you on?

MR. GREMILLION: Number three.

MS. FIUME: Powders are different than the sprays.

MR. GREMILLION: All right. Well, I'll leave it there.

DR. BELSITO: The powders were addressed. Perhaps you didn't get the email from Kevin. So, there were three separate papers that were sent out that are summarized. But they couldn't actually send the papers because of copyright issues, so they emailed them to us. The powders are different in terms of size and sprays.

MS. FIUME: And powders are always addressed separately in the cosmetic use boilerplate language. If it's known to have a powder use, that's separate language that's added to the document.

MR. GREMILLION: I'll check my notes and circle back.

DR. BELSITO: Okay. Anything else? Okay so we're staying with what we have. And then try to get a better understanding of the types of sprays that are available for cosmetics and the aerodynamic particle size that each of those would typically generate.

MS. FIUME: Yes.

DR. BELSITO: Okay. Pretty good. It's lunch time. Should we have some brown algae?

Day 1 of the December 3-4, 2018 CIR Expert Panel Meeting – Dr. Mark's Team

DR. MARKS: Ron Shank, there is a memo -- is that dated today also? Yes. And this memo is from the Sciences and Support Committee also. And key issues are mentioned, there's three of them. And let me see, that's Page 67, and the edits are 96. Jinqiu, we made it easy for you, didn't we, for the hair dye, after all that discussion. Other than you went through the work of forming the discussion, but that's okay.

So, I think tomorrow if the Belsito agrees, we probably will just move on to that's the final resource document. I'm not sure we'll need to see it again. But we'll see what happens tomorrow.

Okay. So, tomorrow, Ron, Ron and Tom, there are lots of edits that Jinqiu made. And then there's in Wave 3, the Women's Voices for the Earth letter. And, Jinqiu, your response is, maybe we need to go over those individually. And then lastly, what we received this morning from the Science and Support Committee. And that's on Page 96, are the edits.

Where should we begin? Should we begin with the edits? How do they look? And then go to the Women's Voices and finish up with the council? Does that seem reasonable? Ron, Ron and Tom, there are lots of edits. Was there anything that stood out that you felt should be changed?

DR. SHANK: I think it depends on what our intent is. Between the council's comments, the Women's Voices for the Earth comments, and our documents, we seem to be going back and forth talking about particle size and inhalation. That's sort of been our major focus.

Actually, from an inhalation toxicology point of view, that is a naive approach. Particle size is only one part of that which governs what comes from the air into the whole respiratory tract. From the nose to the alveoli. Many, many different factors. I'm not going to name them. I can, but.

So, what are we trying to do here? Talk about aerosols and pump sprays, which is basically delivery of ingredients and formulations, and then the exposure. Or are we really interested in what governs the deposition of material in the respiratory tract.

One document, the latter, is a very large document. You can talk about humidity, solvents, airborne time, baby lungs, adolescent lungs, old people lungs. The list is very long. And just the definition of the different measurements for particle size and characteristics of particles in food dynamics.

So, I think we need to decide what is the purpose of the document. Because everybody's having

different suggestions, at different levels, and it becomes a very mixed bag as far as the science of respiration of chemicals. So, Council wants to tell us or --

DR. ANSELL: Well, we agree, absolutely. We think that the original document, which focused exclusively on particle size, really needed to be updated. The Women's letter said that they found papers, which showed particle size greater than the particle size that was in the boilerplate. And I think what that brought to light was that we're missing -- what we're really interested in is exposure.

DR. SHANK: Right.

DR. ANSELL: And which particle size is only one element. And so, what we tried to bring in, in our comments, is really the risk assessment that how under may exposure scenarios, the exposure is so low that even presuming 100 percent respirable fraction would not present a concern. The data typically is generated with all respirable size, six hours a day for multiple times. And we're talking about 15 second exposures, maybe a couple times a day.

But I do think that's where we've ended up, is we now have a paper which is neither fish nor fowl. We have the risk assessment discussions added, but we still have a lot of this, quite literally, boilerplate; that depending on this scenario, you'd pick this language.

And we think that this is getting closer. Certainly, it goes to exposure and not just particle size. Although certainly, it doesn't get into the box models and all the other elements. Well, actually we do talk about one and two box models. It's trying to portray that it's a much richer discussion than simply particle size.

And so, maybe we need to do another iteration, looking at some of the older stuff carried through. Does it still suggest that this is too particle driven?

DR. HILL: I think part of it is, is that if you got something like the silica we were talking about earlier, and particles are the problem, potentially, in developing something like silicosis, that's a very different toxicology scenario than something like the polyaminopropyl biguanide that we were discussing. Where there's clearly that communitive exposure, but it's really things that get in there as a liquid, not particles that matter. But what size of the droplets and how deep in the lungs can they get.

And then we have other things that's strictly that exact same deal, but the mechanisms of toxicology are how big a concentration can you develop, or how long, and where, in the respiratory tract.

So, you can try to mix apples and oranges for something that's true particle scenario, where it's a solid that's being deposited in the lungs. And can we clear it or not. Versus something like a formaldehyde, which is just an upper respiratory tract irritant unless you breath too much of it. And it's gaseous and we're breathing something volatile, in which case it's going everywhere in the lungs.

As a reviewer on the panel, every time we get to this language, the scenario is we have potential inhaled routes of exposure, do we have data or not? Do we think the inhalation toxicology data is relevant, or is it not? If we don't have it at all and then we use it as a write off, is that document that we're referencing -- I mean, this is where I get through 99 percent. And we have language that we've used in some documents that says something to the extent that -- and relates it to occupational exposure that's language related to particulate problem. When in fact, the ingredient we're reviewing has nothing to do with particulates at all, because it's in a liquid droplet or it's not there at all.

So, that's what we're trying to get at, is if we're going to use it to dismiss, we don't need inhalation toxicology and here's why. What do we have in place to refer to? Because it sure doesn't help to have something in place that refers to particulate associated toxicology if the ingredient usage, at hand, has nothing to do with that.

We're talking about small droplets that can get into the deep lung of spray colognes. There's no particulates there, or there are if stuff evaporates and we end up with solid. Because as particles are flying through the air, for sure the liquid evaporates and it happens pretty quickly.

And ultimately, what we can say is there's still big gaps in science. But at least what we can do is say, what kind of exposure are we talking about in any particular case. If this stuff gets into the lungs, so what. Where in the lungs? Where in the respiratory tract? Because that, so what, is different depending on what those ingredients are. Is it a clay? Then it's a solid exposure scenario. Is it something in small liquid droplets like the

polyaminopropyl biguanide? You get my point. Is it a reactive? Is it something volatile like a salicylate, where it's the vapor of the salicylate itself that goes?

DR. MARKS: So, how would you, Ron Shank, or Tom, or Ron Hill, guide Jinqiu in terms of editing this? Again, what I heard is the most important factor in all of this is, what is the exposure to the respiratory tract of these ingredients? And then, Ron Shank, you elucidated a number of factors that are concerning not only exposure, but also the risk assessment of it.

So, it's sort of how do we -- as you said it before it was particle size because that's where we were really focused. But now it's not. And I think of how the Science and Support Committee keeps using the word "tiered" approach. I guess we could further elucidate, what does that mean as a tiered approach?

DR. ANSELL: We discussed it in some detail. I wonder if it's just literally editorial. Because we didn't really object to any of the statements. But maybe if we took it out of this, if then, type of format.

DR. HILL: But in context with all I just said, I pretty much agree with the tiered approach. I mean, maybe the specifics change, depending on what ingredient we're talking about, but I pretty much agree with it.

DR. ANSELL: And there's nothing in here which disagrees with the tiered approach. I think you excellent draft discusses that, and talks about how it's a tiered approach. But then we go into some pertinent tox results examples that they note -- a lot of the -- "No maximum use concentrations in spray and/or loose powders" examples. And then you put in exposition. And maybe if we just keep the exposition, we'll have a resource document that points out our feeling -- which reserves the factual elements and conclusions, that at least the council agrees with.

It's a tiered approach. The exposures had to be very short. It's complicated in the first instance. We do a tier one assessment. It's all defaults, and that it could require, depending on the conclusions, becoming more and more precise in data inclusion.

DR. HILL: And I guess the other part of it is, if we want something to use as a boilerplate per se, then we might need to have 16 different scenarios where under this circumstance you use this. Because I'm, all the time, finding myself, I get to the end and we have this bit of discussion which we can't put in the discussion, because we can't put references there.

And we're talking about things that have no relevance to solid, particular toxicology. And then now, suddenly, I encounter a boilerplate that's written based on exposure to particles in the workplace. So that can't persist. It compromises credibility, massively.

And then depending on who the writer is, they adopt -- or depending on our feedback, then it gets refined, based on what's the actual issue with that particular set of ingredients, under those particular uses. Well and good. But the first draft goes out on the website, just as well as the third draft goes out on the website. And it would be nice if our credibility wasn't compromised with the first draft.

DR. MARKS: So, actually, going in to the precedence document that's presented here from Jinqiu, I heard, Jay, you say, from a council's point of view, you're pretty happy with the way it is. Now, there's a lot of highlights in here. Ron Shank or --

DR. ANSELL: We're happy with the factual part.

DR. MARKS: The factual?

DR. ANSELL: Yeah. I understand Ron's point. It still has a lot of boilerplate parts to it, the boilerplate structure to it.

MS. FIUME: I remember how this all came about; is that after reviewing it, these ingredients are used in sprays and things like that, and we don't really address it. So, we need boilerplate language to address it, and we don't have specific data to address inhalation toxicity, is how that boilerplate language came about. And still with a lack of, you know, type of inhalation toxicity, we need something in the report to address that information. And unfortunately, it does come down to the boilerplate language, because that's all we have.

DR. HILL: Or we insist, uniformly, that if you have inhaled products, we want to see your data. Or convince us why we don't need to see your data. And that has to come from the people marketing those things, ultimately. And otherwise, we say insufficient and let the chips fall.

DR. ZHU: So this information need to be included in the boilerplate language? I mean, for we needing the data?

MS. FIUME: I didn't hear the question.

DR. MARKS: Does that information need to be in the boilerplate?

DR. ZHU: Yeah. Needed to be in the boilerplate. I mean, we needing the data for specific spray types?

MS. FIUME: That is going to have to be a panel decision, I believe.

DR. MARKS: Right.

DR. HILL: Right.

DR. SHANK: This isn't the boilerplate.

MS. FIUME: This leads up to the boilerplate. So, the boilerplate language is included --

DR. SHANK: In here.

MS. FIUME: On page 103 it shows -- it's very difficult to use -- the writers have managed to narrow it down. This is how it was written years ago, when it was first done. But, basically, the premise of the boilerplate language starts -- is on about Page 103, PDF Page 103.

DR. MARKS: And what is proposed as the new -- as it's referred to -- precedence? But it will be the new boilerplate? Because if I heard correctly, Ron Shank, the focus, previously, or the emphasis was on particle spray.

DR. SHANK: Particle size.

DR. MARKS: Particle size, whereas now we want to be more nuanced. That tiered approach that you mentioned is in the revision here. Tier 1, tier 2, tier 3. I get the sense that, Ron, and, Ron, you like this tiered approach?

DR. HILL: I think the general idea behind the tiered approach is right. I'm looking at the boilerplate, and I need to be able to articulate well my places where I have doubts about the implementation. But then, frequently, how this goes, is we go ahead and implement and we try it out in the context of actual ingredients and see how it works, and if not, come back and revisit again.

DR. MARKS: But, basically, we're devising the new boilerplate, correct? That's what this precedence is about.

DR. HILL: So, if you have language -- I'm looking at the bottom of Page 104, where it says -- I can see how this might end up being used. "Droplets/particles from cosmetic pump and propellant hairsprays would not be respirable to any appreciable amount." I don't know that that's an accurate statement.

Again, the droplet size, as they leave the device that's delivering, is not necessarily the same as the droplet size when it reaches the person's face. Because, hey, it's a liquid and it's going to evaporate flying through the air at a high rate of speed. And so exactly what comes into the consumer's lungs might be very different than what comes out of the tip of an aerosol or a pump spray. And that's the point. We have gaps in the science.

So, using an overall exposure, just here's how much is coming out of the spray and it's delivered 15 seconds, maybe maximally 10 times a day, to be conservative; the mass transfer rate idea, I think, is good, since there's only so many micrograms that can be delivered here.

We still, of course, may need to know if we've got a substance that's potentially reactive in the lungs. What is the toxicologic significance of that? If you have zero inhalation toxicology data, depending on the nature of the compound, we might say, who cares. Because there's no structural hits, no structural alerts, no reason to think that this is going to present any toxicological concern, particularly if we're not accumulating the appreciable amount.

Or yes, there are these substances in there, I think, reactive monomers -- residual monomers left over from polymerization, that we may or may not know are released from polymers under conditions of use. What's the significance of that? Usually, the answer to that is very, very small amount for which we can defend ourselves; because we're not defenseless for such compounds in our biochemistry. We can start with mass-transfer rate and make conservative estimates.

DR. MARKS: What recommendations do you have, Ron Shank, at this point?

DR. SHANK: Probably change the title. That would be very simple. What's here, I think, is very good.

DR. MARKS: Yeah, okay.

DR. SHANK: I like it. No changes. But it's basically an analysis of particle size, and the importance of particle size on distribution in the respiratory tract, overall. And what it's called --

DR. MARKS: Aerosol.

DR. SHANK: Aerosol Precedent. Well, first place, it's not limited to aerosols, if you mean an aerosol; which is a specific kind of formation of material as opposed to a pump spray, as oppose to evaporation. This doesn't include gasses at all. Or is it supposed to? It doesn't now.

So, expand the title, or something, to say, this may need consideration of aerodynamic particle effects on exposure. Something like that.

DR. MARKS: So, you wouldn't even use -- it could be analysis of particle size in aerosols and its effect? Or you don't even like to use the aerosol?

DR. SHANK: You don't have to use aerosol, because then what about pump sprays.

DR. MARKS: Yeah. Analysis of particle size.

DR. HILL: What if maybe -- let me just start it as an extreme, and then you might can back into it. What if you just call it Incidental Inhalation Exposure something. If we're only restricting to particles, then the language can't include inhaled liquid droplets. Although, the tiered approach definitely does. I mean, they're good about that, they use particles/droplets, consistently; which I think is right.

Of course, if you evaporate all the solvent from a droplet, you have a particle; which can happen as things are flying through the air. That's how exactly an atmospheric pressure mass spect works, LC-MS.

DR. SHANK: That's all on here. I think broaden the title to focus on, the main concern here is particle size. The importance of particle -- I don't like saying size, but particle aerodynamic properties on exposure. That's too nerdy?

DR. HILL: Distribution?

DR. MARKS: Analysis of particle --

DR. SHANK: Particle Aerodynamic Properties on Exposure.

DR. HILL: So, would you include droplets as part of the particles?

DR. SHANK: Sure.

DR. HILL: Because I don't think of a droplet as particle. I think of particle as being a solid and not a liquid.

DR. MARKS: That's a big title, Analysis of Particle -- so this is going to be, aka, the particle boilerplate then. So, Analysis of Particle aerodyn --

DR. SHANK: But that's what it is, really.

DR. MARKS: Yeah. Yeah. Analysis of Particle Aerodynamic -- how did you word that?

DR. SHANK: Properties.

DR. MARKS: Properties.

DR. SHANK: On Exposure.

DR. MARKS: Respiratory --

DR. SHANK: I guess you could say Respiratory Exposure.

DR. MARKS: You want to put Respiratory Exposure? Because I know, in the past, Tom's made the point that you can get carcinogen exposure into -- it may not reach the lungs, but it can be in the larynx, the upper respiratory tract.

DR. HILL: Nasopharyngeal.

DR. SLAGA: Nasopharyngeal, all the way down.

DR. MARKS: So, this would pick that up.

DR. ANSELL: What do you think about striking everything, but the last two words, Inhalation Exposure?

DR. MARKS: Well, Respiratory Exposure.

DR. HILL: That's what I said. It's Incidental --

DR. ANSELL: Yeah, Respiratory Exposure.

DR. MARKS: Get rid of that?

DR. HILL: Incidental Respiratory Exposure.

DR. ANSELL: No. That's the whole title. Because, otherwise, you know, we have gasses, particles, fogs, all which have unique definitions. What we really want to get to is how to assess respiratory exposure.

DR. SHANK: But that's what you just eliminated.

DR. ANSELL: No, no, I wanted to eliminate everything up to that.

DR. SHANK: Oh.

DR. MARKS: But the emphasis of this, to follow Ron Shank's reasoning is, there's a lot more involved in respiratory exposure than just particle size. And this document is really addressing particle size.

DR. SHANK: I think so.

DR. ANSELL: I think CIR has done a better job at expanding it beyond particle size. That there is now discussions about duration. There is exposure about modeling. So, maybe we need more of that, but --

DR. ZHU: So, the tiered approached still need to be incorporated in the document? Or that's separate, i.e., a supplemental document. The whole inhalation risk assessment, that part, if this document is just focused on the particle size distribution.

DR. SHANK: Well, to me it seems basically particle size --

DR. ANSELL: Yeah, there's still a lot.

DR. SHANK: -- is the driving force in the document. And we certainly need to acknowledge all of the things that were -- or many of the things that govern exposure. But this really concentrates primarily on particle size.

DR. LORETZ: I think comments from the CIR SSC, we're trying to move away from that and not be so heavy on particle size.

DR. SHANK: I see.

DR. LORETZ: I think kind of the new editions tend to be outside of just particle size, of what was left over from before; it was heavy on particle.

DR. SHANK: Okay.

DR. MARKS: And that's in this precedence document, titled Aerosols Precedence Document. That's reflected in the document that --

DR. LORETZ: For example, the tiered approach was straight from the CIR SSC. That was what the recommendation was.

DR. MARKS: Well, are we back to the Aerosols as the title, or just Respirator Exposure? I kind of like the respiratory exposure part of that, because that's what we're really concerned about.

DR. SLAGA: What we're really dealing with.

DR. MARKS: And if we're more broad, then we not just limit it to particle aerodynamic properties.

DR. SHANK: Well, yeah, if you don't want to emphasize the particle size, and get away from that, then respiratory exposure to --

DR. ANSELL: Yeah. And roll in a discussion about critical parameters. And it does include exposure duration.

DR. SHANK: Yeah. It's here, just modify the title. Respiratory Exposure to --

DR. HILL: Do you think that respiratory has any connotation to respirable? Because respiratory tract is, obviously, all the structures by which inhale anything entering our bodies.

DR. SHANK: Right.

DR. HILL: But if we're not strictly focused on what gets into the alveoli, or the bronchial, and we are including things like nasopharyngeal passages, does respiratory include that enough?

DR. SLAGA: To me it does --

DR. HILL: It should.

DR. SHANK: Respiratory would include nose to alveoli.

DR. SLAGA: -- (Inaudible) it covers the whole thing.

DR. HILL: It's what? If you say respiratory toxicology, what do you think of?

DR. SHANK: Respiratory system.

DR. HILL: The entire -- okay.

DR. SHANK: Thing.

DR. SLAGA: Yeah.

DR. HILL: Okay, great. I know that. I just want to make sure that's how everybody thinks about it. Because we've talked about respirable particles and those are the ones that are able to enter the deep lung.

DR. MARKS: It's interesting. Ron, I come back to your title, originally, and is there a way to make it a little bit broader. Analysis of Particle Aerodynamic Properties, as well as other Factors on Respiratory Exposure. It's a longer title, but --

DR. SHANK: I like that. But that emphasizes -- if I understand, that emphasizes particle size and the council would like to get away from that narrow consideration.

DR. SLAGA: Yeah.

DR. MARKS: Yeah.

DR. ANSELL: It's the other we want to amplify on. It isn't other -- particle size and aerodynamic behavior are parts of the other. It's not the elite feature.

DR. MARKS: So, getting away from the aerosols, is the title Respiratory Exposure?

DR. ANSELL: Assessment of?

DR. HILL: I'm still thinking something like consideration. Except that you need something to allow for the fact that there's going to be boilerplate language. Because otherwise, I'm still thinking in terms of something like, considerations in the assessment of incidental inhalation exposure as the perspective toxicological issue -- issues. Not a good word, but.

DR. MARKS: How about this? Let me see. Analysis of Respiratory Exposure From Cosmetic Ingredients.

DR. SHANK: There you go. Nice and broad.

DR. HILL: How about Assessment? Instead of Analysis? Because if it's going to be a full analysis, we'll be --

DR. MARKS: Ron Shank, I'll ask you. You're the one that came up with Analysis. I'm not sure there's much difference between Analysis versus Assessment.

DR. SHANK: You can leave off Analysis of, and just what you had.

DR. MARKS: Just Respiratory Exposure From Cosmetic Ingredients? Leave it at that?

DR. MARKS: Yeah.

DR. ANSELL: I also think we're going to see this again.

DR. MARKS: I'm sure. So, the main change that we've come with, looking at what the Women's Voices for the Earth, the council's input and, Jinqiu, your edits are, we want to change the title to Respiratory Exposure From Cosmetic Ingredients, and what has been presented in the document, as it stands, is very good at this point.

DR. SHANK: And it addressed the Women's Voices.

DR. SLAGA: Right.

DR. MARKS: Your letter. So, is this going to be the final document with just the change in title?

DR. SLAGA: No.

MS. FIUME: No.

DR. HILL: And I also wonder, can we separate out anything like boilerplates? The boilerplate-type language, which is appropriately called "precedence" in a sense that it would be a living document, every time you do one of these that has inhalation, if there's something new and unique, you would add to that. I don't see why that has to be publicly available. I feel like it could be an internal document, subject to additional change as

you go.

And then the resource document -- not for whitepaper, not a full review -- the resource document would go on websites, to which you can refer when you put language in. So, the language that you use in the documents now is fine. I think you refer the reader to, here's how the CIR and the expert panel think about assessment of inhalation toxicology as it relates to cosmetic use. But the boilerplate language, I don't think needs to be in there at all. I think you could have that as an internal document.

I don't even feel like I would need access to it, because I'm either going to see it in the documents or I'm not. I mean, you definitely need that, as far as I'm concerned, to continue to operate. But I don't know why it needs to be public per se. Because that way you can go in and delete if something is old and we said, don't use that anymore; you can just take it out and there's no consequence to that.

MS. FIUME: I talked with Bart about it. Often, when we do have set language that we use, we've been asked to please publish it so that the SSC, or someone, could make comments on what we use as boilerplate. So, that the public is informed as to what some of our standardization is.

DR. HILL: But I assert that they don't need that. They're seeing it document by document which, to me, is the highly appropriate way of looking at it, because it's always in the context of what ingredients are there, what is the art of use. That way if a company is selling a particular product, delivered by a particular way, and they want to provide information, here's what we see in our pump spray, and here's -- that provides latitude, and we're not somehow tied to language in some boilerplate somewhere.

We always modify it anyway. But I don't know why -- I mean, SSC could get at the internal document, I'm not saying CIR only. But our Science and Support Group, for the trade organization, it's our interface to industry. But I don't why anybody in Europe needs to get at that boilerplate language, or any other organization, Watchdog, whoever.

That should be internal because it's coming into the documents in the proper context, as opposed to potentially taken out of context if somebody else sees it. That's how I view it.

MS. FIUME: Okay. I will pass that along to Bart.

DR. HILL: And then if you separate it, you do have a precedence document, but that's internal, and here you have a, like, here's how we view the whole big picture, here, in a nicely constructed document; that's not a review article, not a full whitepaper, but something you can refer the reader to without having to put all of that in the document, which I like.

DR. MARKS: So, specifically I heard, nope, this isn't it. We are going to have edits for the next revision. So, what edits are we going to suggest to Jinqiu for the next edition?

MS. FIUME: You haven't done it yet. You may want to go through the Women's Voices for the Earth comments and see if this prompts any additional discussion as well.

DR. HILL: Beyond what's already proposed in Wave 3?

MS. FIUME: Beyond Jinqiu's responses, yes.

DR. HILL: Yes. Because I thought those were pretty well thought out and pretty tight. I don't remember any big issue.

DR. MARKS: So, one of the edits would be address the --

DR. SHANK: You've already addressed the Women's --

DR. MARKS: Yeah, that's the sense I got.

DR. SHANK: And I thought it was very good. Far more than was necessary, but you gave it all to them.

MS. FIUME: Well, this hasn't gone out to Women's Voices for the Earth. This is prepared for the panel. So, I guess one specific concern that will probably need discussion is -- let me see which comment it was.

DR. ZHU: The broad assumption?

MS. FIUME: I think it is actually comment number two, was the one that I was thinking of. Where the cosmetic sprays are being talked about in the boilerplate language. Jinqiu's response in the Wave 3 memo, to the Women's Voices for the Earth comments.

DR. MARKS: This is the one that's -- yeah, "cosmetic sprays incorporate numerous different products not considered by this analysis." And then, "as discussed above, other types of cosmetic sprays" -- dah, dah, dah -- "on hair color are not specifically discussed, due the lack of particle size distribution data." We're back to particle size again.

MS. FIUME: Well, it actually goes beyond that. What they're saying is you're either talking about cosmetic sprays, which they are saying are hairsprays, or sometimes interpreting meaning hairsprays versus deodorants. Where when the writers include that boilerplate language, cosmetic spray is not only being used if it's a hairspray being reported; but if there's a face and neck spray or some indoor tanning spray, it goes beyond hairspray.

So, I want to see how your team feels. Does that language need to change? Is it a worst-case scenario so it covers those other types of documents? But we don't have what the exposure might be, or the particle size distribution, based on those other types of products. And is this problematic that it's in our cosmetic use section, and it's not only referring to a hairspray?

So, that's what they're bringing up. And I don't think we've discussed that earlier. Or if we did, I'm sorry if I didn't get the fine points of it. But that's one of the main concerns that I saw when I was reading through their comments.

DR. HILL: I'm pretty much in full agreement with the responses that were drafted out. What exactly you want to have sent to them, if that's what you're asking for commentary on, I'm not --

DR. MARKS: I think for our purpose, for Jinqiu, is do any of his responses now get edits for the next revision of the precedence paper? So, I assume that Jinqiu's responses were all quite appropriate. And then the question is -- and maybe this, Monice, addresses yours -- is, how much of this gets now in the next -- if we do a next revision, how many edits come from this? Should we pick and choose or, again, are we happy with the precedent document the way it stands now, and just respond to the Women's Voices?

DR. SHANK: I like the latter. I like the precedent document as you've written it. And I like your response to the Women's Voices for the Earth, as you've written it. There're separate.

DR. SLAGA: Yeah.

DR. SHANK: If anything, you've gone well beyond what was necessary to respond to their questions. It's very good.

DR. SLAGA: But to a degree that's necessary with that group, to go beyond.

DR. MARKS: Yeah. But that's okay. I get the sense then, Ron, you're happy with the precedent document, with the highlights and the changes, and there's no needed revisions?

DR. SHANK: Correct.

DR. MARKS: Only change the title.

DR. HILL: I haven't looked to see, is there anything in the letter responses that isn't in the precedence document? And actually, Jinqiu would be the best person to know that directly. But, if there's any conceptual information that's captured in there that ought to be -- I don't want to say precedence, because I think we've changed the title. A resource document.

DR. MARKS: No, a precedence document. We can still refer to it as that. Jinqiu, can you answer Ron Hill's question. Is there anything in your response to the Women's Voices for the Earth, which you think should be in the precedence document?

DR. HILL: That isn't already?

DR. MARKS: Yeah.

DR. HILL: Or that needs to be for some reason?

DR. ZHU: Actually, no. Everything is included.

DR. HILL: This is what I thought, too.

DR. MARKS: Okay. So, tomorrow I'm going to say we had a robust discussion. We considered the council's comments from the 12/3/18 memo. We considered the Wave 3, Women's Voices for the Earth letter. And Jinqiu's responses, we felt that no edits were necessary in this precedence document, and only request the change in title to Respiratory Exposure From Cosmetic Ingredients. And we'll see what the Belsito team feels.

DR. SLAGA: Sounds good.

DR. MARKS: Does that capture --

DR. SHANK: Yes, it does.

DR. MARKS: Robust discussion. Okay. Good. And I think -- is that the last order of business? Okay.

DR. ZHU: Sorry, I have some specific questions for the panel.

DR. MARKS: Sure. You were saving it to spring on us right at the end, that's fine.

DR. ZHU: So, the Women's Voices for the Earth suggested that the boilerplate language should include information for deodorant sprays; up to 50 percent of the particles are respirable. Because in our boilerplate language, we did not include that information. Do we need to clearly state that? We only discuss that in the background part of the document.

DR. HILL: Again, I would like to see the boilerplate language disappear from our publicly-available document. I realize I might not be the majority opinion yet, but I'm hoping to persuade everybody that that's the right way to go here.

Because then we get control over what goes in, document by document, based on the circumstances and the art of use for that set ingredients or that particular ingredient. And it can change and evolve over time as we get new science; because as we can tell, there are gaps in the science, and some of those are in the process of being filled. So, we have new papers this time and they seem to be very good papers. But there are still gaps.

DR. SHANK: That's a good solution to -- every time we have the boilerplate, somebody has an objection to this line or that word. Don't have a boilerplate for inhalation. Generate a new statement, tailormade to each ingredient report. Rather than having something that's generic.

DR. HILL: And I don't have any problem with having an internal document. And you can give, as far as I'm concerned, our SSC full interface and access; because they're helping us evolve this as we go, in terms of getting science done. But I just don't think that that needs to be part of the information that is shared, chronically, with outside groups.

DR. MARKS: I think we have to be transparent.

DR. SHANK: Yeah.

DR. MARKS: There can't be anything that is --

DR. HILL: But we are being transparent, because we're putting the language in the documents as they are pertinent. So, then we give them in context. Being transparent, with language that might or might not be in context or where there are gaps in science that it's really up to industry to supply, and if we proceed with them in any particular ingredient set, we can say, sorry we don't think this is sufficient until you supply us with information to tell us what's the exposure.

But when you put a boilerplate language there that says, this is what we're going to use, which might or might not be appropriate -- and as far as I'm concerned, 70 percent of the time isn't appropriate with what I've been seeing. And then I suggest clean up. And some of the writers are better than others, because they're more experienced or they're more knowledgeable and they get it right the first time quite nicely.

In many other cases, there's just this big disconnect because you're talking about things that are being delivered as liquids, and suddenly have this thing that's based on toxicology of respirable particle in the occupational workplace, which his totally irrelevant. And we're using that to dismiss something that might be a real concern, and it looks not credible. In my humble opinion.

DR. MARKS: Well, I think we'll see what the discussion is tomorrow. As I said, I don't think there should be anything that's only an internally utilized format. I think the idea of -- there can be, as we have here, what perhaps will be called the Respiratory Exposure From Cosmetics precedence. That document exist. We can refer to it. But each ingredient needs to be addressed individually if we feel that appropriate.

MS. FIUME: And then technically if each ingredient is addressed individually, then we don't have boilerplate; because each ingredient is being addressed individually.

DR. SHANK: Right.

DR. HILL: And then precedence is still relevant. You just might have 25 or 30 precedence, and then somebody has to figure out which circumstance applies to get the best starting point. Because you're really looking for a starting point for your writers, based on the circumstance, I think.

DR. MARKS: I, quite frankly, liked the precedence documents because it covers the breadth, and we don't end up, in three years, forgetting to cover something.

DR. HILL: Then at least make them a separate document, or connect them in some way. That's an appendix to the main document or something. But I just feel like precedence is different from, here's how we think about assessing inhalation toxicology. And again, that's the way I see it.

DR. MARKS: Okay. Well, we'll have this discussion tomorrow.

DR. SHANK: Tomorrow.

DR. MARKS: Yeah. Okay, any other comments?

MS. FIUME: Jinqiu, did you have more questions?

DR. ZHU: Oh, one more question. For those new type of sprays, that's indicated by the WAVE; so, do we need additional boilerplate language to address that issue? So we do not -- you know, we cannot characterize the inhalation exposure to those types of product that we do have data for.

DR. HILL: Page 3, of Wave 3, is really where this comes to a head. Because they say, there's no available data on these types of cosmetic sprays that could corroborate this assumption; is also true for these products and their potential exposures. I don't fully understand and grasp that statement, because these types of cosmetic sprays is just really aerosol, there's pumps, there's -- what else is there?

So, if you're trying to assert that somehow an aerosol propellant spray for a suntan is different than a hairspray, bologna. It depends on how the nozzle is designed, and it could not necessarily be the same for this ingredient in a hairspray from manufacture A, versus B, versus C, versus Q, right? It depends on what device they're using to do the delivery, not that it's a suntan product, or a hairspray, or deodorant.

And then, what's in that device? What's the propellant, what's the ingredient, because that will affect how big are those particles. It's not that it's a hairspray that it affects the size of the particles, it's what's in that spray can.

MS. FIUME: So, how does that affect when we say a deodorant has different distribution than a hairspray if they're both aerosols?

DR. HILL: Show me your evidence.

MS. FIUME: Well, we did have the data.

DR. HILL: Do we have it from every manufacturer of propellant hairsprays, and every manufacturer in every can? Because I don't think we do.

DR. SHANK: We don't have that for anything.

DR. HILL: We don't have that for anything.

MS. FIUME: Linda, you're probably familiar with the data, Linda?

DR. LORETZ: Yeah. I'd say there was a consistency to it. It did have -- yeah.

DR. HILL: All right. Well, then that's fine, that should go in the resource document.

MS. FIUME: And it is.

DR. HILL: Okay. I was going to say, it is, isn't it? Yeah.

MS. FIUME: But what they're questioning is, and this is comment number two, is that when they say cosmetic sprays, the data that were used to generate that information that was used in the boilerplate, the 95 to 99 percent respirable, is based on hairsprays. Deodorants have a different distribution. So, they're saying what about -- this one was tanning -- what about the face and neck sprays, the foot sprays, the different --

DR. ANSELL: And that's because they're anchored exclusively to particle size. And I think when you put it in overlay of spray duration, respiration room, then all of a sudden these tier 1 assumptions, we don't really care.

DR. HILL: Exactly. Exactly.

DR. ZHU: But the boilerplate language need to state that the particle size distribution data is still important; although it is not considered in the inhalation assessment, but it is still an important factor, needed to be

considered, right?

DR. ANSELL: Not at tier 1.

DR. ZHU: Not -- tier 3, right?

DR. ANSELL: At the higher tiers. But at the lower tiers, it based more in terms of duration and respiration; that you can only take a certain number of breaths in a 15-second period where the material still is in the breathing zone. And so, I think, what they do is they look at the particle size and say, you guys say it's 10 percent, we say it's 30 percent, so you're under estimating the exposure by 3 fold. And we say well, yeah, so it's going from essentially nothing to really nothing.

DR. HILL: You're right.

DR. ANSELL: And that's the part we try to capture in terms of the tiered exposure; that if we find that under those assumptions the exposure is concerning, then we need to go up to a higher tier and start looking at the exposure models. But the lower tiers are more based on duration, and concentration, than respirable percentages.

DR. LORETZ: But maybe the point -- the 95 to 99, you could make an argument that that shouldn't be such a default factor, since that really is a hairspray data; and the deodorant data is pulled away from that because it is a different number.

MS. FIUME: And I think what also came to light, though, is we don't have any of those numbers.

DR. LORETZ: Right.

MS. FIUME: So, you're making assumptions, but you don't have the information to plug in. So, that's part of the problem, is we don't have any of those numbers. And I think that's what was coming to light, is that we don't have that information.

DR. ANSELL: And there are circumstances where we would need to generate those, but not at the lower tiers.

DR. HILL: And in other cases, you just assume it's all respirable; but then how much do you actually get in, when you take a breath, if you walk through that cloud of stuff.

DR. LORETZ: That's the tier 1, right?

DR. HILL: And that's tier 1.

MS. FIUME: And so I think that's part of -- and, Jinqiu, if I'm paraphrasing wrong, please let me know. Is then do we develop a worst-case scenario, and do all of these other product types fall under that worst-case scenario?

DR. ZHU: Yeah.

MS. FIUME: So, can you state that?

DR. ZHU: Okay. We can state that, right?

MS. FIUME: Well, that's what we need to ask.

DR. ZHU: Okay, sure.

DR. MARKS: So team, what do you think?

DR. HILL: Yes.

DR. SLAGA: Yeah.

DR. HILL: So, we said no edits and now it sounds like make an edit with a worst-case scenario, respiratory exposure. Is that --

DR. HILL: Are we talking about for his letter of response, or are we talking about the resource document?

DR. MARKS: Okay, that's important. Which, still no edits?

DR. SHANK: This is the response.

DR. MARKS: Response. Okay. To the letter?

DR. SLAGA: Yeah.

DR. MARKS: Okay. Any other comments? If not, we'll adjourn for today. Thank you everyone.

DR. MARKS: It definitely is our team's opinion. I guess I would start by saying that we want to change the title to "Respiratory Exposure for Cosmetic Ingredients." That was probably the most substantial result of, actually, a very robust discussion, including the Council Science and Support Committees' comments from the memo we were given yesterday, the Wave 3, Women's Voices of the Earth letter, and Jinqiu's responses to that.

We felt that there weren't any edits necessary. I suspect that's not -- Don, your team may have some edits. But we didn't think there was any significant edits necessary, other than changing the title.

And then, I'll have Ron Shank address this more, but he really emphasized the point that the respiratory exposure, from cosmetic ingredients, is more than just particle size. It's interesting because as we talked earlier, about respiratory exposure, we kind of got back into particle size is the most important. But it should be an exposure and risk assessment focus, and we like the tiered approach that was presented.

DR. BERGFELD: Ron.

DR. MARKS: Ron Shank, do you want to say anything more than my summary?

DR. SHANK: You summarized it well. Changing the title takes the emphasis on particle size away. That's all I wanted to see. Particle size is, of course, important. But there are a whole slew of things, in addition, that should be considered if you're worried about respiration of a particle, a droplet, a gas, a dust, a mist, or whatever. So changing the title, I think, takes away this strong focus on particle size for the document.

DR. BERGFELD: Don.

DR. BELSITO: Well, I would agree with that, but I did have concern that we were sort of saying that particle size -- and we say it very strenuously several times throughout the document. "The panel noted that particle droplet size data, under simulated consumer uses, are generally not needed when conducting a risk safety assessment." I think that is way too strong of a language, because you do want some particle size.

I think it needs to be toned down to something like, particle size are not the only factors that need to be looked at, and one can consider a tiered approach. I agree with a tiered approach; I just don't agree with him saying that they're not needed. They are needed.

And so, if you just put in particle size are needed -- there are about three or four times, in this whole document, where that is put out. I think I'll let Paul talk, because I think he also had a lot of agreements to what you're saying, Ron.

DR. BERGFELD: Paul.

DR. SNYDER: Yes, I agree. I think it goes back to our earlier discussion. I prefer that we get data that tells us, that we have a certain level of confidence, that we don't have toxicity issues related to incidental exposures during cosmetic use. I think we should continue to ask for that data, whatever that is.

It's driven by lots of factors. Because if we have evidence of some systemic toxicity, and we use that data just to know what level it's at, and whether or not the exposure from aerosol is relevant, because you certainly can have -- and I was just thinking about this after the discussion that Dan brought up. We can certainly say, safe as used for an aerosol spray cosmetic, even though we know there's some minimal, to negligible, exposure to the respiratory system. It doesn't mean just because there's -- to say that it's non-respirable, I think is too high of a bar. I think that you can have some exposure that is not of any concern for health hazards.

As I thought about that more, I think we need to focus on this document and the type of data that we want, and the type of data we're going to use for our interpretation for safe as used; and the uses be driven by the concentrations in the products, the formulations, and all those other issues.

DR. BERGFELD: Paul, a question from myself; with the changes in deemphasizing the particle size, as Don Belsito has stated, do you think the document meets all the criteria you're asking for?

DR. SNYDER: I think it's headed that way.

DR. BERGFELD: Headed that way. Okay.

DR. SNYDER: Headed that way. I'm still a believer -- again, I'm not an inhalation toxicologist. But for respiratory exposure, for the lower levels of the lung, it's driven by physical properties. The toxicity may

be influenced by other properties of those particles that reach the lungs, but the reaching of the lungs is just purely a physical property. So, the larger particles are picked up by the mucociliary apparatus, and coughed up, and swallowed and eliminated.

So, I think there's some -- it's not an insignificant thing. I don't want to downplay it too much. I agree there are other factors. But I personally believe, in the way I understand inhalation toxicology, is that the exposure to the lower airways is largely a physical property. And, again, I agree with Ron, physical --

DR. SHANK: And chemical.

DR. SNYDER: Well, less chemical, but more physical.

DR. HILL: It's physical until --

DR. SNYDER: I mean, if it's electrostatic and things like -- certainly, there's some properties that could be different. But, again, there's another point that I wanted to make, really, to one of the comments Ron made. By nature, doing toxicology studies, you want to identify hazards. Okay? That's the goal. And so, the reason that the experimental conditions for inhalation toxicology are to ensure that whatever dose you're giving is reaching the level that you want it to reach. So, I agree that that's not representative of use conditions, but that's how you do toxicology.

So, you use that information to -- a weight of evidence to say that you're not concerned because, yes, this was an experimental condition, very high doses. They were able to induce toxicity in the lung. However, under conditions of use, depends upon the airflow of the room, the size of the room; there's all other kinds of factors that we bring into the context of whether or not we think that there's a risk to humans for exposure.

While I agree that the experimental conditions don't replicate use conditions, but it's how you do it. And I just don't want to lose that perspective.

DR. BERGFELD: Ron Hill.

DR. HILL: Yeah, I thought about this a bit last night in the specific example of something we couldn't have predicted; and we still don't know if it's related to the ingredient, which is this polyaminopropyl biguanide thing. Because it's toxicology that only seems to occur, and relevant, in the deep lung, based on that specific mechanism that occurs; and the very cumulative exposure that if you don't have that, it doesn't occur. We do have ways to defend our self. We have defense against a lot of reactive sorts of things, so there will be concentration responses. It's peristalsis, right? Tox 101, the dose makes the poison.

I thought about that in the context of saying, no testing on animals; and you know how I feel about that. I disagree with that general position on things, that there's sometimes no substitute for that.

It's important that we talk about when are we going to say, we don't need this information even though we see there are things that have incidental inhalation? That's the long, robust discussion including a consideration of, what are the specifics of the concern for that substance?

So, when I asked the question, what is this stuff, I mean, what is this stuff? There's some times you can't make the prediction, where there would be no substitute for inhalation toxicology, and animals is our best available model. Or incidental human exposures; if an accident has occurred, we use that data, right?

DR. BERGFELD: So, what we have here is that we're looking at this document; and what we've done is to reinstate the particle size and put the tiered approach into it. Is this document ready to be posted, or we have to continue to discuss it at our next meeting? And the third thing is that Don has suggested -- and I think that Alex has agreed -- to bring an expert regarding the propellants, and the differences in them and the particle sizes in these propellants.

DR. BELSITO: I think with this document there are more than just minor changes that need to come back. I think Paul also made the point that as opposed to the hair dye epidemiology, where we just put it in and say, okay, this is it, that yes, this will serve as an important document. But when we get into specific discussions of inhalation, we can't just say, here's the document and dismiss everything. It's really going to be a case by case basis, depending upon the material that we're evaluating. So, this document is not going to have the boilerplate effect of a hair dye epidemiology statement.

DR. BERGFELD: But it will be a guide.

DR. BELSITO: It'll tell people how we look at a respiratory tox endpoint. But in the actual

documents, we will need to put in a little bit more data sometimes. Sometimes it'll be sufficient, sometimes it may not be. But it will be a case by case basis, as opposed to hair dye epidemiology that we just throw in every hair dye.

DR. BERGFELD: So, what you've actually heard is that we're going to be very interested in the details of the inhalation studies; very interested and be demanding more in the future. I think that's what you've heard.

DR. HILL: Or details of the delivery systems, and better information about exposure.

DR. BERGFELD: The delivery system, all of that. Right, exactly. All of that.

DR. SNYDER: We live in a very enabling society these days, as a father of two teenagers. What I don't want to do is enable industry to not provide us data, by saying that we default to our boiler document. I think sometimes it's better off to clear it with data; always better off to clear it with data.

DR. BERGFELD: Well, we're going to be using it as a guide. And it sounds like we need to continue to discuss it. And so, it will appear on April's agenda or, at least, as a point for right now, yes?

DR. SNYDER: Certainly. So, does Jinqiu have all of the edits and everything that you're expecting to see, come April, or is there more that we need to discuss for him to change?

DR. BERGFELD: Dan?

DR. LIEBLER: I'm just thinking, downstream, to when we get to -- the next draft will be -- if this is like a penultimate, maybe, hopefully, we get to a pretty close to final draft. I'm wondering if we should consider enlisting a couple of bona fide card-carrying inhalation toxicologist to provide comments on the final draft.

DR. BERGFELD: I'm going to ask Alex, is there a committee within the PCPC that could first take a look at it?

MS. KOWCZ: Yeah. Let's take a first pass. There is.

DR. LIEBLER: Because several times a comment has been, on this panel, well, I'm not an inhalation toxicologist, but. And that --

DR. HILL: But you all have gained very substantial acumen over the years, and I'm getting a little bit, bit by bit. I actually proposed, yesterday, to separate out the resource document, that basically was guidance, and that we would post, that said, here's our approach to evaluating incidental inhalation substances.

Then anything that resembled either boilerplate or precedence would become an internal document, so that we didn't -- and then the question was raised, would that represent a loss of transparency? I didn't think so, because when you're looking at boilerplate language, that may or may not apply in a particular situation, it's completely out of context. I was still tossing that out there yesterday, if you have it constrained to a resource document, that you will make publicly available, that you will refer to when you write the reports and then whatever precedence you want to list in there, that would be okay.

But boilerplate language is to help the writers have a starting point. So, at least, they would have to have some sort of idea. Honestly, I think, for one of the younger writers, there's no substitute for having more experienced people's eyes on each particular ingredient. Because our first drafts go out there on the web page. And I think that it compromises the credibility, if we get something there that's way far off the mark by mistake. So anyway, just some thoughts.

DR. BERGFELD: Well, this is a working draft, so to speak. And we're going to look forward to hearing Jinqiu's final editorial responses that each team has made. We'll have another look at it, and we'll have some feedback from PCP, and the inhalation committee that they have.

DR. MARKS: One last brief comment just for both panels to consider. Do we want a conclusion portion of this document? Because it's a lot of information, and do we want to try and summarize it in a conclusion?

DR. BELSITO: I think the problem with a conclusion is, again, Paul's point that we can't just use this as a blanket statement like we used the hair dye epidemiology. It will be a case by case. So, if there was a conclusion at all, it would be, this is the panel's general approach, however, depending upon the ingredients in question, additional --

DR. MARKS: I think that may be a worthwhile statement. I don't know.

DR. BELSITO: Toxicologic considerations, however you want to phrase it, may be necessary.

DR. BERGFELD: Any comments?

MR. ZHU: So, one clarifying question. So, does the title need to be changed?

DR. BERGFELD: The title?

DR. BERGFELD: I had no problems with the change in the title that was suggested.

DR. BERGFELD: So the title's going to be changed. Anything else to be added to this discussion? Again, this is a working document. As you heard, it's going to serve as a guide, not an absolute. And it's dissimilar to the hair dye epidemiology statement and paper.

Well, we've come to the end of this very busy morning, and these 12 ingredients and some other add-on thoughts that we've had to make on various items. I want to wish you all a Merry Christmas and a happy new year. We look forward to seeing you in April at the Westin, again, for a big load of work. Happy holidays.

COSMETIC INGREDIENT REVIEW

CIR Precedents

Respiratory Exposure from Cosmetic Ingredients

09/2019

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. Prepared by Jinqiu Zhu, PhD, DABT, ERT, CIR Toxicologist.

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.[1,3,5]

Aerosols are broadly defined as multiphase systems of particulate solids or liquids dispersed in air or other gases, including mists, fumes, and dusts. 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. While particle/droplet size is an important parameter, the physicochemical properties of ingredients in a spray formulation, as well as the realistic exposure factors under in-use conditions, also play significant roles in evaluating inhalation safety of ingredients as spray formulation. It should also be noted that droplet/particle size data generated under experimental conditions may be different from droplet/particle size in actual consumer exposures. Other exposure factors are key in assessing inhalation safety, such as temperature, humidity, spray distance, spray time, container fullness, the amount of pressure on the actuator, etc.

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,[6] although the mechanism(s) of overload-induced tumor formation is not completely understood.[6-9] 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).[1,10]

Droplet/particle size is variable across individual products. Industry can ensure that inhalation exposures to cosmetic sprays and powders are minimized.[10] 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.[11] 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.

Regional Particle Deposition

The physical parameter most strongly associated with the deposition pattern of an aerosol in the respiratory tract is the aerodynamic equivalent diameter (d_{ae}).[12,13] The d_{ae} of a droplet/particle is defined as the diameter of a hypothetical, smooth sphere of unit density (e.g., 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.[5,14]

The droplets/particles of an aerosol can be divided into three mass fractions, based on the depth to which they will penetrate the respiratory tract. These fractions include the inhalable fraction (median

d_{ae} ~ 100 µm), which can enter the nasopharyngeal region through the nose or mouth, the bronchial fraction (median d_{ae} ~ 10 µm), which can pass through the larynx to enter the trachea, bronchi and bronchioles, and the respirable fraction (median d_{ae} ~ 4 µm), which can enter the alveolar region of the lungs.[1-3,15] 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 cleared via mucociliary action, sternutation, expectoration, or deglutition.[16] 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 µm into the pulmonary region is essentially zero.[1,5,17-21] Thus, only droplets/particles with $d_{ae} \leq$ 10 µm are considered to be respirable. This is a conservative assumption because a d_{ae} of 5 µm or less is often reported in the scientific literature as the threshold below which droplets/particles can reach the alveoli.[1,22] In addition, there is consensus that droplets/particles with d_{ae} > 15 µm 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 µm from these regions within 24 hours through mucociliary action.[1]

Inhalation Exposure Assessment

Particle size distributions are product-specific (i.e. the particle size of a raw material prior to formulation may have little to no impact on the particle size distribution resulting from consumer product use). 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, differential pressure through the nozzle for propellant sprays, and formulation and nozzle characteristics for pump sprays.[1,10] 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.[1,14,15,17,23,24] For example, all of the water and other volatile solvents and propellants in droplets with d_{ae} < 40 µm will evaporate within 1 second of release from a spray can, so that the remaining particles will contain non- or low-volatile constituents (e.g., polymers with little or no biological activity in hair sprays). Accordingly, a wide spectrum of particle size distributions can be released from cosmetic sprays.[1,23,25,26]

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. For example, the median d_{ae} of the airborne droplets/particles of pump hair sprays range from 60 µm to 80 µm.[1,10,23] Typically, < 1% of the airborne droplets/particles released from pump sprays are in the range considered to be respirable (i.e., d_{ae} < 10 µm). In comparison, the median d_{ae} of the airborne droplets/particles of propellant hair sprays range from 25 µm to 50 µm.[1,10,23] Usually, 1% to 2.5%, but no more than 5%, of the droplets/particles emitted from propellant hair sprays are within the respirable range.[10]

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 µm with a coefficient of variation of 0.3.[17,23] 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 µm with a coefficient of variation of 0.3, suggesting that half of these particles are within the range considered to be respirable.[17,23]

Measurement of Particle Size Distribution

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 incidentally respired during intended 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 systemic exposure resulting from 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.[1,10] 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.[5,10,14,23,24] 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.[10] The droplets/particles are likely to be undetectable in the breathing zone within 10 minutes after spraying.

Due to the compressed format and low usage amounts, inhalation exposure to compact powders is not expected at use conditions.[28] In contrast, loose powders, which lack the particle cohesion, have the potential to generate airborne particles, with which there is potential for inhalation exposure. Most of the mass (85% to 93%) of inhaled airborne particles released from cosmetic powders is deposited in the head airways.[29,30] The current weight-of-evidence suggests that particles from cosmetic powders are predominately large, and only small amounts of powder deposit in the lower regions of the respiratory system (pulmonary region). Further reduction of incidental inhalation exposures to respirable particles from cosmetic products can be accomplished, however, by utilizing use devices, ingredients, and formulations that enable minimized aerosol generation, and/or skew the size distributions, of the particles released from these products, outside of the respirable range.[29]

One industry survey provides volume weighted particle size distribution data, measured using laser diffraction, for propellant hair sprays and propellant deodorant/antiperspirant sprays.[27] Data are reported as volume diameter defined by 10%, 50% (volume median), and 90% of the cumulative volume undersize (Dv10, Dv50, and Dv90, respectively). The 90% particle sizes (Dv90) of droplets/particles released from propellant hair sprays are distributed within the size range of 23.5 – 409 µm, whereas the mean (SD) values of Dv50 and Dv10 are 70.5 (36.3) and 32.7(18.2) µm, respectively. Propellant deodorant/antiperspirant sprays have consistently smaller median particle/droplet size than propellant hair sprays. The mean (SD) values of Dv90, Dv50 and Dv10 of droplets/particles released from propellant deodorant/antiperspirant sprays are 4.1 (2.6), 23 (33.2), and 35.3 (7.6) µm, respectively. In addition, the percentage of respirable particles/droplets (% < 10 µm) is 3.24 ± 4.48 and 26.6 ± 13.4 (mean ± SD) for propellant hair sprays and deodorant/antiperspirant sprays, respectively. Hairsprays have consistently larger median droplet/particle size than deodorant/antiperspirant.

It should be noted that droplet/particle size data using laser diffraction measurements of a free spray may be generated for other purposes, such as qualifying packaging, or determining consumer product acceptability. These types of particle/droplet size data, while not equivalent to consumer exposure, can be leveraged in refined exposure assessments with a full understanding of the conservative nature of the exposure estimate.

Measurement of Exposure under In-use Conditions

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.[11] Thus, these measurements may not correlate well with the size distributions of the particles released from the product under consumer use conditions. Some photographic methods are being developed to characterize the actual sizes and shapes of the particles released from powder products during use, such as scanning mobility particle sizer (SMPS) and aerodynamic particle sizer (APS). These sampling devices provide airborne particle concentrations and size distributions in the range between 14.1 nm and 20 μm,[30,31] which does not cover the full spectrum of particle sizes typically released from cosmetic sprays (with the largest portion being in the 50 – 300 μm range). In addition, SMPS requires at least 3 minutes of application period to scan the entire particle size, which represents an exaggerated estimate of duration per aerosol spray application, compared to customary cosmetic use conditions.[28] Organic particles or a more complex mixture are hard to detect using electron microscopy.[29] It is not clear whether these methods are amenable to characterizing the aerodynamic equivalent diameters of the particles under real use conditions, because factors such as particle/droplet density and maturation are also important considerations.[32] Furthermore, the composition of chemical substances in the particle mixtures, along with their different physical properties (e.g. adhesive character, solubility, surface charge, etc.) and sizes, has a substantial impact on particle size distribution, and relies on different measurement methods.[29,33]

A conservative estimation indicates up to 50% of the particle size distribution released from propellant deodorant sprays consist of respirable particles.[17,23] However, it is important to note that particle/droplet size data generated under experimental conditions may be significantly different from particle/droplet size under realistic consumer use conditions, in which exposure to droplets/particles from propellant sprays is highly affected by numerous critical factors, including nozzle size, spray distance, spray time, spray direction, temperature, humidity, ventilation, room size, propellant gas and the solvent applied, as well as physiological factors, such as respiratory rate, tidal volume and clearance mechanisms.[28,29,32,34] Additionally, inhalation exposure to airborne droplets/particles released from cosmetic aerosol sprays can be refined to adjust for the amount of material that ends up on skin/hair and is therefore not available for inhalation.[35]

The CIR Expert Panel has previously noted that in practice, 95% to 99% of the droplets/particles released from cosmetic pump and propellant hair sprays have aerodynamic equivalent diameters greater than 10 μm. While a larger fraction of respirable particles would release from propellant deodorant sprays, the realistic consumer exposure is generally many times lower compared to the amount calculated with the in silico models.[28,29] 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. Unintentional exposure to an ingredient by inhalation during the application of cosmetic sprays will be very low to negligible.

Tiered Approach for Inhalation Safety Evaluation

The Panel noted that particle/droplet size data under simulated consumer use scenarios are generally not needed when conducting inhalation risk assessment due to the tiered approach to risk assessment, which provides an adequate margin of safety at the screening and modeling tiers. This is consistent with the very low product and ingredient exposures based on short exposure durations, ingredient content of product and total amount of product used.[36] An exposure assessment is based, in part, on detailed knowledge of the use conditions established from data on consumer use habits and practices. A preferred approach for the evaluation of inhalation safety includes three tiers:[32]

- Tier I is a screening approach that employs worst case default assumptions, assuming all product leaving the container is potentially inhalable and likely to become systemically available. This approach uses existing habits and practices data and assumes the total amount of sprayed product immediately enters the breathing zone (about 1 to 2 m^3 for cosmetics sprayed towards

the body). This simple, very conservative exposure assessment value is then compared to a systemic threshold and if the outcome is acceptable, no additional work is needed.

- Tier II refines the above estimate to arrive at a more realistic, though still conservative, exposure assessment. Additional refinements take into account factors such as room volume, room ventilation rate, discharge rates, spray times and particle/droplet size. Computational models of varying complexity have been developed, for example, one-box and two-box models, which vary in the number of assumed zones in which the emitted material is homogeneously dispersed. More sophisticated models may incorporate factors to determine how much of a spray/chemical is actually inhaled, exhaled, is reaching the deeper lung, or is deposited.

- Tier III requires actual measurements of exposure under simulated use conditions, and is used for applications where computational modeling might not give a sufficient level of confidence for risk characterization. For instance, particle/droplet size could be dynamic due to the evaporation of the solvent after releasing the spray container. Currently, no computational modelling is available to conduct a sufficiently reliable simulation of this particle/droplet maturation.

In practice, exposure to cosmetic spray products is very low, due to low use quantities and very short exposure times. As a result, Tier I assessments may be all that is needed, and there is rarely a need to go beyond a Tier II evaluation. However, in some cases, where the screening output is very conservative, further refinement may be needed. It is important to note that the final exposure is determined not only by the particle size, but also the distribution of particles/droplets in the exposure room under in-use conditions. The composition of the formulation and the spray characteristics are of significant impact.

Other considerations of Sprayed Product

While there may be some unique considerations in the evaluation of safety following exposure by the inhalation route, the basic framework for risk assessment – consisting of hazard assessment, exposure assessment, and risk characterization – is fully applicable. Both local (lung) effects and systemic effects are considered in the process. Data useful for the assessment, in addition to animal inhalation toxicity data (if available), include safety data generated using routes of exposure other than inhalation, physical/chemical properties, and data on mucosal membrane, skin, and eye irritation. The latter are relevant to the potential for causing local irritation to the respiratory tract. Mathematical models which take into consideration known data on lung irritants may also be useful. In vitro methodologies are under development and offer promising approaches for inhalation safety assessment as well.[37]

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.

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 μm and none < 90 μm. Thus, the formation of granulomas in the animals was not considered to be relevant for evaluating the inhalation safety of this ingredient as used in cosmetic products.

The Panel also noted data are currently insufficient to assess the inhalation exposure assessment of some types of cosmetic sprays (e.g., airbrush make and lotion sprays). 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.

Sample Exposure Calculations

Conservative estimates indicate that inhalation exposures for once-a-day application of a pump hair spray, propellant hair spray, or propellant deodorant spray containing 2% of an ingredient would be no more than 1.5, 4.7, or 6.8 μg/kg/day, respectively.[36,38] These estimates were based on the following conservative assumptions:

- All of the spray enters the breathing zone (i.e., 100% is available for inhalation)
- Two-box exposure model: the droplets/particles distribute in 1000 L in the first 2 minutes, and distribute 10,000 L in the next 18 minutes
- 25% of the inhaled droplets/particles are exhaled
- Breathing rate: 10 L/minute
- Body weight: 60 kg
- Amount of product used: 15.6, 9.89 and 1.43 g/day pump-hair, propellant-hair, and propellant-deodorant spray, respectively[39]
- Respirable fraction: 1%, 5%, and 50% for pump-hair, propellant-hair, and deodorant spray, respectively

The percentage of particles/droplets with d_{ae} < 10 µm, measured for deodorant/antiperspirant spray products, is 26.6 ± 13.4 (mean ± SD).[36] Repeating the calculation with such empirical data results in an inhalation exposure of no more than 5.4 µg/kg/day of an ingredient present at a concentration of 2% in a deodorant spray product.

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 µg/kg/day for infants or adults, based on the following assumptions:[33,40,41]

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

Literature reports of use amount for one-a-day application of a loose face powder range from 73.1 to 85 mg.[28,42,43] Assuming 1% of a loose face powder is respirable yields an estimated exposure no more than 0.9 µg/kg/day for a 60 kg person,[44] based on a conservative estimate use of face powder at 510 mg per application per day.[45]

When a tiered approach is applied for exposure assessment, considering realistic use conditions as well as different particle size-dependent depths of particle penetration into the respiratory system, the overall systemic exposure to aerosol sprays via inhalation would be dramatically reduced. In one study, exposure to aluminum from four antiperspirant sprays containing up to 1.5% aluminum is assessed using a two-box model, and the exposure of the upper respiratory tract and deep lung deposition are calculated using the Multiple Path Particle Deposition (MPPD) model.[46] The total systemic exposure to aluminum from antiperspirant sprays via inhalation is found to be less than 0.5 µg per application, or 0.0168 µg/kg/day for a 60 kg person, based on a conservative estimate of frequency of use at two applications per day.[47] Such inhalation exposure estimates were further examined when the cosmetic product was sprayed against a skin surrogate compared to spraying in the air ("free spraying"). Free spraying overestimated uptake by more than a factor of two. This study suggests that exposure estimates incorporating spray product use levels and ingredient concentrations and adjusted for distribution in two boxes result in highly conservative estimates of lung exposure.

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.[33,36,40] 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. ACGIH also defined the TLV-TWA for respirable, poorly soluble low toxicity particles at 5 mg/m^3 for an 8-hour workplace.[28] 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 2182 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 1091 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.

In contrast to the workplace scenario, the exposure duration and the typical quantities of airborne particles is less prominent during the consumer application of cosmetic sprays. Moreover, the toxic potential of the ingredients used is significantly lower compared to general industrial chemicals, as all of them have to be carefully reviewed for the use in such consumer products.[28] 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.

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 hair 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).[1,10,17,48] 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). [1,17] [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).[1] However, data are not sufficient to determine the extent of lung exposures that result from the use of deodorant sprays, compared to other cosmetic sprays. Particle/droplet size distribution as well as regional deposition data under consumer use conditions are generally considered but rarely needed when assessing the inhalation safety of an ingredient in a spray cosmetic product. A tiered approach to the exposure assessment of spray products requires actual exposure measurements and more refined modelling to determine the realistic estimates of respirable particle fractions released from aerosol sprays. (Steiling et al 2014, CIR SSC 2018) [IF PRODUCTS INCLUDE EMERGING SPRAY TYPES THAT DO NOT HAVE INHALATION EXPOSURE DATA, E.G., AIRBRUSH MAKEUP, ADD: particle size distribution for airbrush makeup is not currently available; it is uncertain what, if any, ingredient or combination of ingredients in this product might cause inhalation safety issues. [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, talcum 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).[33,40,41]]

Discussion Section

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 APPLICAPLE**: 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., ≤ 10 μm) or were not reported.]

[ALTERNATIVELY, ADD THE FOLLOWING, **IF APPROPRIATE**: There were no inhalation toxicity data available. The Panel would request additional information from Industry and further evaluate the sufficiency of other exposure data based on a tiered approach.]

[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 were reported to range from 0.05 – 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 pump and propellant hair sprays would not be respirable to any appreciable amount. While larger fraction of respirable particles would release from deodorant propellant sprays, particle size data are rarely needed when conducting inhalation risk assessment for cosmetic spray products. In practice, exposure to an ingredient during the application of cosmetic sprays will be very low, due to low use quantities and very short exposure times. A tiered approach to the exposure assessment of spray products requires actual exposure measurements and more refined modelling to determine the realistic estimates of respirable particle fractions released from aerosol sprays.

[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) The Panel 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) The Panel 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 "https://www.cir-safety.org/cir-findings."

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Acetyl Trialkyl Citrates

CONCLUSION: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) first published the Final Report on the Safety Assessment of Acetyl Trialkyl Citrates in 2002.[1] The Panel concluded that Acetyl Triethyl Citrate, Acetyl Tributyl Citrate, Acetyl Triethylhexyl Citrate (previously known as Acetyl Trioctyl Citrate), and Acetyl Trihexyl Citrate are safe as cosmetic ingredients in the present practices of use and concentration, as described in that report. Data identified in the published literature[2-16] that have become available since the Final Report was issued, support the conclusion that was reached by the Panel in the original review. The Panel also reviewed updated information regarding product types and ingredient use frequencies as reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database,[17] and the maximum use concentrations provided by the Personal Care Products Council (Council).[18] The Panel determined to not reopen this safety assessment and reaffirmed the original conclusion that Acetyl Triethyl Citrate, Acetyl Tributyl Citrate, Acetyl Triethylhexyl Citrate (previously known as Acetyl Trioctyl Citrate), and Acetyl Trihexyl Citrate are safe as cosmetic ingredients in the present practices of use and concentration, as given in Table 1.

DISCUSSION: The data indicate that only Acetyl Triethyl Citrate and Acetyl Tributyl Citrate are currently reported to be used in cosmetic products.[17,18] The frequency of use has increased for both of these ingredients since the initial assessment. According to VCRP data, Acetyl Triethyl Citrate and Acetyl Tributyl Citrate were reported to be used in 9 and 27 formulations, respectively, in 1998.[1] In 2019, VCRP data indicate that Acetyl Triethyl Citrate is used in 22 formulations, and Acetyl Tributyl Citrate is used in 438 formulations.[17] There were no reported uses of Acetyl Trihexyl Citrate or Acetyl Triethylhexyl Citrate (formerly Acetyl Trioctyl Citrate) in 1998 or in 2019. For Acetyl Triethyl Citrate, the maximum concentration of use was 7% in nail products in 1999;[1] however, according to a recent survey provided by the Council, current use concentration data on this ingredient were not submitted.[18] For Acetyl Tributyl Citrate, the maximum concentrations of use have increased slightly since the original report was issued. In 1999, Acetyl Tributyl Citrate was used at up to 7% in nail products and up to 3% in products that resulted in dermal contact (i.e., eyeliners);[1] data collected in 2018 indicate that the maximum concentrations of use are 8.9% in nail products and 7% in products that result in dermal contact.[18] Though increases in use concentrations are noted when the two years are compared, the higher use concentrations were not considered to be dissimilar to the values that were reported initially and do not warrant any safety concerns.

After reviewing *prima facie* positive results of in vitro cell reporter assays, the Panel noted that these results for Acetyl Tributyl Citrate and Acetyl Triethyl Citrate may be due to adaptive effects or trigger activation of reporter constructs. The Panel stated that toxicity cannot be concluded unless these effects are evaluated in vivo.

Table 1. Current and historical frequency and concentration of use of acetyl trialkyl citrates according to duration and exposure.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Acetyl Triethyl Citrate				**Acetyl Tributyl Citrate**			
	2019[17]	**1998[1]**	**2018[18]**	**1999[1]**	**2019[17]**	**1998[1]**	**2018[18]**	**1999[1]**
Totals*	**22**	**9**	**NR**	**4-7**	**438**	**27**	**0.0015-8.9**	**0.8-7**
Duration of Use								
Leave-On	*21*	*9*	*NR*	*4-7*	*437*	*26*	*5.8-8.9*	*0.8-7*
Rinse-Off	*1*	*NR*	*NR*	*NR*	*1*	*1*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	5	3	7.5	3
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	10	NR	NR	NR	1	NR	0.0015 - 0.09	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	5	3	0.0015 – 7.5	3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	11	1	NR	NR	3	1	0.09	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	11	8	NR	4-7	428	23	6-8.9	0.8-7
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	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.

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BHT

CONCLUSION: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) first published the Final Report on the Safety Assessment of BHT (butylated hydroxytoluene) in 2002.[1] The Panel concluded that this ingredient is "safe as used in cosmetic formulations." Data identified in the published literature[2-16] that have become available since the original review support the conclusion reached by the Panel in 2002 publication. The Panel also reviewed updated information regarding product types and ingredient use frequencies as reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database,[17] and the maximum use concentrations provided by the Personal Care Products Council (Council).[18] The Panel determined to not reopen this safety assessment and reaffirmed the original conclusion that BHT is safe as a cosmetic ingredient in the present practices of use and concentration, as given in Table 1.

DISCUSSION: The reported frequency of use for this ingredient has increased significantly since the initial review was considered. According to VCRP data, BHT was reported to be used in 1709 formulations in 1998.[1] In 2019, VCRP data indicate that BHT is used in 9485 formulations.[17] The current maximum concentration of use (0.5%) in leave-on products,[18] according to the results of the Council survey, is approximately the same as that reported in 1999 (0.5%).[1]

Although a substantial increase in frequency of use was reported, the lack of genotoxicity, systemic, and clinical effects continues to support the safety of this ingredient. According to the Panel, BHT did not pose a toxicological risk as used in cosmetics; and therefore, the original conclusion was reaffirmed.

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

	# of Uses		*Max Conc of Use (%)*	
	2019[17]	**1998[1]**	**2018[18]**	**1999[1]**
Totals*	**9485**	**1709**	**0.0000007 – 0.5**	**0.0002 – 0.5**
Duration of Use				
Leave-On	*7367*	*1460*	*0.0000007 – 0.5*	*0.002 – 0.5*
Rinse-Off	*2044*	*196*	*0.000001 – 0.5*	*0.01 – 0.5*
Diluted for (Bath) Use	*74*	*53*	*0.00024 – 0.15*	*0.05 – 0.1*
Exposure Type				
Eye Area	976	610	0.00009 – 0.3	0.0002 – 0.5
Incidental Ingestion	981	261	0.000001 – 0.29	0.03 – 0.5
Incidental Inhalation-Spray	1708; 847[a]; 1581[b]	146; 84[a]; 108[b]	0.0000035-0.21;0.0003-0.09[a]; 0.0000007-0.5[b]	0.02-0.5; 0.008-0.5[a]; 0.02-0.5[b]
Incidental Inhalation-Powder	226; 847[a]	42; 84[a]	0.0021-0.3; 0.0003-0.09[a]; 0.00005-0.5[c]	0.05-0.5; 0.008-0.5[a]
Dermal Contact	8071	1385	0.000001-0.5	0.008-0.5
Deodorant (underarm)	140[b]	10[b]	0.000001-0.4; 0.012-0.19[b]	NR
Hair - Non-Coloring	270	40	0.0000007 - 0.5	0.02 - 0.5
Hair-Coloring	13	6	0.0015 - 0.005	0.05
Nail	37	8	0.0005 - 0.25	0.02 - 0.5
Mucous Membrane	2654	404	0.000001 - 0.31	0.03 - 0.5
Baby Products	6	5	0.0013 – 0.031	0.1

* 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.
[a] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
[b] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.
[c] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

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EDTA & Salts

CONCLUSION: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) first published a final report on the Safety Assessment of EDTA & Salts in 1998.[1] The Panel concluded that EDTA, Calcium Disodium EDTA, Diammonium EDTA, Dipotassium EDTA, TEA-EDTA, Tetrasodium EDTA, Tripotassium EDTA, Trisodium EDTA, HEDTA, and Trisodium HEDTA are safe as used in cosmetic formulations as described in that report. Because it has been at least 15 years since the report was published, in accord with CIR Procedures, an updated search was performed, and the Panel considered whether the safety assessment of EDTA and the related salts should be re-opened. Data identified in the published literature[2-9] that have become available since the original report was issued, support the original conclusion. The Panel also considered updated information regarding product types and ingredient use frequencies as reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database,[10] and the maximum use concentrations provided by the Personal Care Products Council.[11] The Panel determined to not reopen this safety assessment and reaffirmed the original conclusion that EDTA and salts of EDTA are safe as cosmetic ingredients in the present practices of use and concentration, as given in Table 1.

DISCUSSION: According to VCRP data, Disodium and Tetrasodium EDTA are reported to be used in 12,509 and 7691 formulations, respectively, while in 1998 they were reported to be used in 1165 and 1285 formulations.[1,10] In addition, in 1998, Calcium Disodium EDTA and Tripotassium EDTA were not reported to be in use. According to 2019 VCRP data, these ingredients are reported to be used in 25 and 1 formulation, respectively. In 1998, the maximum concentrations of use were reported for EDTA (2% in hair products; rinse-off) and Trisodium EDTA (2% in bath soaps and detergents; rinse-off).[1] According to 2019 concentration of use data, the ingredient with the highest maximum concentration of use is Disodium EDTA, which is used at 3% in "other hair coloring preparations."[11] This ingredient was previously reported to be used at a maximum of 1% in bath products. Disodium EDTA is also reported to have the highest concentration of use in leave-on products (0.85%; hair color sprays) and in products which would come in contact with the skin (0.6%; skin cleansing). All other in-use ingredients are reported to be used at 2% or less.

Although a substantial increase in frequency of use was reported, the lack of genotoxicity and clinical effects continues to support the safety of this ingredient group. According to the Panel, EDTA and its salts did not pose a toxicological risk as used in cosmetics; and therefore, the original conclusion was reaffirmed.

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

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Calcium Disodium EDTA				**Dipotassium EDTA**			
	2019[10]	**1998[1]**	**2019[11]**	**1998, 1999[1]**	**2019[10]**	**1998[1]**	**2019[11]**	**1998, 1999[1]**
Totals*	**25**	**NR**	**0.000098 – 0.025**	**NR**	**17**	**21**	**0.054**	**0.05 – 0.09**
Duration of Use								
Leave-On	*1*	*NR*	*0.025*	*NR*	*7*	*16*	*NR*	*0.09*
Rinse-Off	*24*	*NR*	*0.000098-0.00059*	*NR*	*10*	*5*	*0.054*	*0.09*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	1	NR	NR	NR	8	1	NR	NR
Incidental Ingestion	22	NR	0.000098 – 0.00059	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	2[a]	NR	0.000098[a]	NR	5[c]	9[a]; 6[c]	NR	0.09
Incidental Inhalation-Powder	NR	NR	NR	NR	5[c]	NR	NR	NR
Dermal Contact	2	NR	0.025	NR	17	21	0.054	0.05 – 0.09
Deodorant (underarm)	NR	NR	0.025	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	1	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	22	NR	0.000098 – 0.00059	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Disodium EDTA				**EDTA**			
	2019[10]	**1998[1]**	**2019[11]**	**1998, 1999[1]**	**2019[10]**	**1998[1]**	**2019[11]**	**1998, 1999[1]**
Totals*	**12509**	**1165**	**0.00002 – 3**	**0.001 – 1**	**1011**	**923**	**0.000004 - 2**	**0.02 – 2**
Duration of Use								
Leave-On	*8455*	*590*	*0.000075 – 0.85*	*0.001 – 0.6*	*210*	*85*	*0.0000055 – 0.1*	*0.03 – 0.5*
Rinse-Off	*3931*	*498*	*0.00002 - 3*	*0.005 – 0.8*	*794*	*835*	*0.000004 - 2*	*0.02 – 2*
Diluted for (Bath) Use	*123*	*77*	*0.05*	*0.1 - 1*	*7*	*3*	*0.025*	*NR*
Exposure Type								
Eye Area	755	33	0.05 – 0.33	0.1 – 0.6	28	5	0.0001 – 0.05	0.03 – 0.05
Incidental Ingestion	39	NR	0.00033 – 0.1	0.05 – 0.1	25	NR	NR	NR
Incidental Inhalation-Spray	150; 3986[a]; 2292[c]	33; 271[a]; 125[c]	0.0001 – 0.85; 0.00075–0.12[a]; 0.1 – 0.2[c]	0.05 – 0.2; 0.02 – 0.5[a]; 0.05 – 0.6[c]	2; 58[a]; 52[c]	2; 38[a]; 15[c]	0.0000055 – 0.0005; 0.0033 – 0.1[a]	0.05 – 0.1[a]; 0.03 – 0.5[c]
Incidental Inhalation-Powder	50; 11[b]; 2292[c]	13; 1[b]; 125[c]	0.1; 0.00045 – 0.35[b]; 0.1 – 0.2[c]	0.02 – 0.05; 0.05 – 0.6[c]	3; 2[b]; 52[c]	2; 15[c]	0.00001 – 0.1[b]	0.1; 0.03 – 0.5[c]
Dermal Contact	9988	783	0.000075 – 0.6	0.01 - 1	284	122	0.000004 – 0.1	0.03 – 0.5
Deodorant (underarm)	57[a]	2[a]	NR	0.2[a]	26[a]	3[a]	NR	0.1 – 0.5[a]
Hair - Non-Coloring	1664	303	0.00002 – 0.95	0.005 – 0.8	175	72	0.0000055 – 0.22	0.05 – 0.3
Hair-Coloring	631	76	0.016 – 3	0.05 – 0.4	506	725	0.000055 – 2	0.02 – 2
Nail	20	1	NR	0.001 – 0.02	11	3	NR	NR
Mucous Membrane	1377	130	0.000075 – 0.25	0.05 - 1	111	19	0.02 - .052	0.05 – 0.3
Baby Products	45	5	0.2 – 0.35	NR	4	NR	NR	0.03
	HEDTA				**Tetrasodium EDTA**			
	2019[10]	**1998[1]**	**2019[11]**	**1998, 1999[1]**	**2019[10]**	**1998[1]**	**2019[11]**	**1998, 1999[1]**
Totals*	**1**	**1**	**NR**	**NR**	**7691**	**1285**	**0.000002 – 1.9**	**0.004 – 1.3**
Duration of Use								
Leave-On	*1*	*NR*	*NR*	*NR*	*3230*	*355*	*0.002 – 0.5*	*0.005 – 0.5*
Rinse-Off	*NR*	*1*	*NR*	*NR*	*4391*	*825*	*0.000002 – 1.9*	*0.004 – 1.3*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*70*	*105*	*NR*	*0.01 – 0.1*
Exposure Type								
Eye Area	NR	NR	NR	NR	571	24	0.002 – 0.1	0.004 – 0.5
Incidental Ingestion	NR	NR	NR	NR	6	1	0.08	0.009 – 0.02
Incidental Inhalation-Spray	NR	NR	NR	NR	54; 1327[a]; 665[c]	11; 106[a]; 87[c]	0.043 – 0.15; 0.02 – 0.26[a]; 0.078[c]	0.04 – 0.08; 0.04 – 0.2[a]; 0.04 – 0.3[c]
Incidental Inhalation-Powder	NR	NR	NR	NR	102; 9[b]; 665[c]	1; 1[a]; 87[c]	0.048; 0.02 – 0.26[b]; 0.078[c]	0.04; 0.1[a]; 0.04 – 0.3[c]
Dermal Contact	NR	NR	NR	NR	5630	634	0.004 – 0.56	0.004 – 0.5
Deodorant (underarm)	NR	NR	NR	NR	47[a]	9[a]	0.016 – 0.5	0.04 – 0.3[a]
Hair - Non-Coloring	1	1	NR	NR	1047	414	0.000002 – 0.75	0.02 – 1.3
Hair-Coloring	NR	NR	NR	NR	918	225	0.01 – 1.9	0.3 – 0.4
Nail	NR	NR	NR	NR	7	4	0.05	0.2
Mucous Membrane	NR	NR	NR	NR	2277	265	0.024 – 0.56	0.009 – 0.5

Baby Products	NR	NR	NR	NR	50	14	0.19 – 0.2	0.05 – 0.3
	Tripotassium EDTA				**Trisodium EDTA**			
	2019[10]	**1998[1]**	**2019[11]**	**1998, 1999[1]**	**2019[10]**	**1998[1]**	**2019[11]**	**1998, 1999[1]**
Totals*	**1**	**1**	**0.01**	**NR**	**507**	**616**	**0.000000045 – 0.35**	**0.00001 – 2**
Duration of Use								
Leave-On	*NR*	*NR*	*0.01*	*NR*	*368*	*479*	*0.0000045 – 0.24*	*0.00001 – 0.5*
Rinse-Off	*1*	*1*	*NR*	*NR*	*137*	*130*	*0.000000045 – 0.35*	*0.03 – 2*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*2*	*7*	*NR*	*0.01 – 0.4*
Exposure Type								
Eye Area	NR	1	NR	NR	137	128	0.0005 – 0.2	0.3
Incidental Ingestion	NR	NR	NR	NR	NR	4	0.2	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	5; 76[a]; 82[c]	11; 117[a]; 65[c]	0.05; 0.0000045[a]	0.00001 – 0.01; 0.01 – 0.5[a]; 0.02 – 0.2[c]
Incidental Inhalation-Powder	NR	NR	NR	NR	8; 82[c]	11; 65[c]	0.1; 0.002 – 0.24[c]	0.07 – 0.2; 0.021 – 0.2[c]
Dermal Contact	1	1	0.01	NR	415	531	0.0005 – 0.24	0.00001 – 2
Deodorant (underarm)	NR	NR	NR	NR	NR	1[a]	NR	0.2[a]
Hair - Non-Coloring	NR	NR	NR	NR	5	29	0.000000045 – 0.0000045	0.01 – 0.4
Hair-Coloring	NR	NR	NR	NR	28	18	0.35	0.1 – 0.5
Nail	NR	NR	NR	NR	2	10	NR	0.1 – 0.2
Mucous Membrane	NR	NR	NR	NR	52	27	0.2	0.01 – 2
Baby Products	NR	NR	NR	NR	1	1	NR	NR

	Trisodium HEDTA			
	2019[10]	**1998[1]**	**2019[11]**	**1998, 1999[1]**
Totals*	**124**	**159**	**0.000017 – 0.3**	**0.1 – 0.7**
Duration of Use				
Leave-On	*24*	*13*	*0.004 – 0.1*	*0.1 – 0.3*
Rinse-Off	*97*	*144*	*0.02 – 0.3*	*0.1 – 0.7*
Diluted for (Bath) Use	*3*	*2*	*0.000017*	*NR*
Exposure Type				
Eye Area	3	1	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	5[a]; 2[c]	3[a]	0.004[a]	0.1 – 0.3[a]; 0.1[c]
Incidental Inhalation-Powder	2[c]	NR	0.021 – 0.1[b]	0.1[c]
Dermal Contact	92	35	0.000017 – 0.1	0.1 – 0.5
Deodorant (underarm)	NR	6[a]	NR	0.1 – 0.3[a]
Hair - Non-Coloring	32	23	0.004 – 0.13	0.1 – 0.7
Hair-Coloring	NR	98	0.11 – 0.3	0.1
Nail	NR	2	NR	NR
Mucous Membrane	62	22	0.000017 – 0.084	0.2 – 0.5
Baby Products	NR	NR	NR	NR

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] It is possible these products are powders, but it is not specified whether the reported uses are powders.
[c] 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
NR – no reported use

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Imidazolidinyl Urea

CONCLUSION: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) first published the Final Report on the Safety Assessment of Imidazolidinyl Urea in 1980.[1] The Panel concluded that this ingredient was "safe when incorporated in cosmetic products in amounts similar to those presently marketed," as described in that report. In 2001, after considering new studies and updated use data on this ingredient, the Panel determined to not re-open the safety assessment.[2] Data identified in the published literature[3-31] that have become available since the 2001 re-review was issued support the conclusion reached by the Panel in the original review. The Panel also reviewed updated information regarding product types and ingredient use frequencies as reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database,[32] and the maximum use concentrations provided by the Personal Care Products Council (Council).[33] The Panel determined to not reopen this safety assessment and reaffirmed the original conclusion that Imidazolidinyl Urea is safe as a cosmetic ingredient in the present practices of use and concentration, as given in Table 1.

DISCUSSION: The reported frequency of use for this ingredient has decreased significantly since the initial re-review was considered. According to VCRP data, Imidazolidinyl Urea was reported to be used in 2025 formulations in 2001.[2] In 2019, VCRP data indicate that Imidazolidinyl Urea is used in 1558 formulations.[32] The current maximum concentration of use (0.6%) in leave-on products[33], according to the Council, is approximately the same as that reported in 2001 (0.7%).[2]

The Panel noted that Imidazolidinyl Urea is a formaldehyde-releasing preservative, and use of these types of ingredients as a whole has decreased. The Panel determined that there were no new relevant data that necessitated a new review of this ingredient.

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

	# of Uses		*Max Conc of Use (%)*	
	2019[32]	**2001[2]**	**2018[33]**	**2001[2]**
Totals*	**1558**	**2025**	**0.0000004-0.6**	**0.01-1**
Duration of Use				
Leave-On	*1217*	*1576*	*0.0002-0.6*	*0.01-0.7*
Rinse-Off	*335*	*363*	*0.0000004-0.5*	*0.1-1*
Diluted for (Bath) Use	*6*	*86*	*NR*	*0.2-0.5*
Exposure Type				
Eye Area	336	433	0.2-0.5	0.01-0.6
Incidental Ingestion	2	11	0.2	0.4
Incidental Inhalation-Spray	2; 367[a]; 269[b]	32; 369[a]; 202[b]	0.2-0.6[a]	0.4-0.5; 0.2-0.6[a,b]
Incidental Inhalation-Powder	82; 269[b]; 2[c]	88; 202[b]; 2[c]	0.2; 0.3-0.5[c]	0.2-0.4; 0.2-0.6[b]; 0.3-0.6[c]
Dermal Contact	1277	1814	0.000024-0.5	0.01-1
Deodorant (underarm)	3[a]	4[a]	0.3[a]	0.4[a]
Hair - Non-Coloring	152	125	0.0000004-0.6	0.2-0.5
Hair-Coloring	91	6	0.0006-0.3	0.2-0.4
Nail	6	10	0.0002-0.35	0.2-0.5
Mucous Membrane	42	138	0.00008-0.3	0.2-0.5
Baby Products	4	4	NR	0.3-0.6

*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.

[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 – not reported

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