

ADMIN

Memo

Agenda

Minutes

Triacetin (RR SUM)

Polyaminopropyl Biguanide (Strategy
Memo)

Resource Documents:

Hair Dye Epidemiology

Aerosols and Inhalation

**CIR EXPERT PANEL MEETING
DECEMBER 3-4, 2018**

MEMORANDM

To: CIR Expert Panel Members and Liaisons
From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review
Subject: 149th Meeting of the CIR Expert Panel — Monday and Tuesday, December 3-4, 2018
Date: November 9, 2018

Welcome to the December 2018 CIR Expert Panel Meeting. Enclosed are the agenda and accompanying materials for the 149th CIR Expert Panel Meeting to be held on December 3 - 4, 2018. The location is the same as the last meeting – the Darcy Hotel, 1515 Rhode Island Avenue, NW, Washington, District of Columbia, 20005-5595. Phone: (202) 232-7000.

The meeting agenda includes the consideration of 12 reports advancing in the review process, including 5 final reports, 2 tentative reports, and 5 draft reports. Also on the agenda are a re-review summary of Triacetin, a strategy memo regarding the data insufficiencies for Polyaminopropyl Biguanide, and 2 resource documents: Hair Dye Epidemiology and Aerosols.

Schedule and hotel accommodations

We have reserved rooms for the nights of Sunday, December 2nd and Monday, December 3rd at the Darcy Hotel. If you encounter travel problems, please contact Monice on her cell phone at 703-801-8156.

Team Meetings

Draft Reports - there are 5 draft reports for review.

1. Alkyl Lactyl Lactate Salts (agenda and flash drive name – Alkyl Lactyl Lactate Salts) – This is the first time that the Panel is seeing this report on 10 alkyl lactyl lactate salts. In August 2018, a Scientific Literature Review (SLR) was issued with an invitation for submission of data on these ingredients.

The following unpublished data were received from the Personal Care Products Council (Council) and incorporated into the report: maximum use concentration data, primary skin and acute eye irritation studies (rabbits) on undiluted Sodium Lauroyl Lactylate, guinea pig dermal sensitization study on a silicone antifoam emulsion with 2% Sodium Stearoyl Lactylate, human skin irritation data on a hair styling product containing 5% Calcium Stearoyl Lactylate, and data from four human skin irritation tests on a molding cream containing 7% Calcium Stearoyl Lactylate. Additionally, comments on the SLR have been addressed.

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. Fatty Acids and Fatty Acid Salts (agenda and flash drive name – Fatty Acids and Fatty Acid Salts). This is the first time that the Panel is seeing this report on Fatty Acids and Fatty Acid

Salts. On October 2, 2018, CIR issued the SLR for these ingredients. According to the *Dictionary*, these ingredients are reported to function mainly as anticaking agents, emulsion stabilizers, viscosity increasing agents, opacifying agents, and surfactants in cosmetics.

This safety assessment was initiated based on the high frequency of use of Linoleic Acid reported to the VCRP in 2016/2017, which led to its prioritization for review by the Panel. Several previously assessed ingredients, such as Oleic Acid, Myristic Acid, and Stearic Acid, have been included in the report, as they fit within this grouping of fatty acids and salts and can be appropriately re-reviewed here within. Each of the ingredients in this report comprises a carboxylic acid functional group and an aliphatic (fatty) chain. Relevant data from the previous reports have been summarized in italics in the appropriate sections of this safety assessment.

According to 2018 VCRP data, Linoleic Acid has 633 total uses in cosmetic products; the majority of these uses are in leave-on skin care products. Stearic Acid, a previously reviewed ingredient, has the most reported uses of the ingredients in this safety assessment, with a total of 5738; the majority of these uses are in leave-on eye makeup preparations and skin care products.

The Council provided maximum concentration of use data and comments on the SLR. These have been incorporated and addressed, respectively. The results of the concentration of use survey conducted in 2016 by the Council indicate that Linoleic Acid is used at up to 21.8% in rinse-off skin cleansing products and at up to 3.4% in face, neck, body, and hand skin care products. Sodium Laurate/Linoleate/Oleate/Palmitate is used at up to 84.7% in bath soaps and detergents and at up to 74.5% in leave-on baby products. Stearic Acid is reported to be used at up to 37.4% in rinse-off products (bath soaps and detergents) and at up to 21% in leave-on products (eyebrow pencil).

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

3. Silicates (agenda and flash drive name – Silica & Silicates). This is the first time the Panel is seeing this safety assessment of Silica and silicate ingredients as used in cosmetics. In 2003, the Panel published a safety assessment on 17 silicate and clay ingredients, with the conclusion that that these ingredients are safe as used in cosmetic products.

At the June 2018 meeting, the Panel considered a re-review of the above safety assessment, and decided to re-open this report to add an additional 23 ingredients. The add-on ingredients, listed below, include 9 silica and silicate ingredients that were previously reviewed by the Panel and 15 ingredients that have not been reviewed by the Panel.

According to 2018 VCRP data, Silica has the most reported uses in cosmetic products, with a total of 8024; the majority of the uses are in leave-on eye makeup preparations and makeup preparations. Kaolin has the second most reported uses in cosmetic products, with a total of 1794; the majority of the uses are also in leave-on eye makeup preparations and makeup preparations. The results of the concentration of use survey conducted in 2018 by the Council indicate Silica has the highest reported maximum concentration of use; it is used at up to 82% in face and neck products and 50% in mascaras. Kaolin is used at up to 53% in “other” manicuring products and up to 35% in rinse-off “other” skin care preparations.

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

4. Basic Red 76 - (agenda and flash drive name – Basic Red 76). This is the first time the Panel is seeing this safety assessment on this hair dye. On October 2, 2018, CIR issued the SLR for this ingredient.

In addition to the data found in a search of the publically available literature, data and comments on the SLR received from the Council are incorporated into this assessment and attached to the report. Of note, the Council suggested the addition of a study published in 2018 regarding an updated method of patch-testing. This study was introduced in a presentation given by Dr.

Maya Krasteva at the December 2017 Panel meeting. The presentation has been included in the packet. A summary regarding this study has been included in the Cosmetic Use section of the report, and is indicated by highlighting. Please review this addition, and address whether it is appropriately placed in the report.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should identify matters to be addressed in the Discussion, and then issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion. If, however, the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

5. Benzyl Salicylate (agenda and flash drive name – Benzyl Salicylate). On October 9, 2018, CIR issued the SLR for this ingredient. According to the *Dictionary*, Benzyl Salicylate is reported to function mainly as a fragrance ingredient and light stabilizer.

The Council provided concentration of use survey data for the light stabilizer function (only) of Benzyl Salicylate, as well as the IFRA Standards for Benzyl Salicylate in finished products. Comments on the SLR were received from the Council and addressed. No other unpublished data were provided.

According to 2018 VCRP data, Benzyl Salicylate is reported to be used in 2908 formulations, 2312 of which are leave-on products. Additionally, 906 of those uses are in fragrance-type formulations. However, the VCRP does not indicate the function of ingredients in cosmetic formulations, so it is not known what the intended function of Benzyl Salicylate is in any of the reported ingredient categories. The results of the concentration of use survey conducted in 2016 by the Council indicate that the greatest concentration of use of Benzyl Salicylate as a light stabilizer is up to 0.5% in skin cleansing preparations, and the greatest leave-on use concentration for this function is up to 0.15% Benzyl Salicylate in "other" makeup preparations.

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 2 draft tentative reports.

1. Brown Algae (agenda and flash drive name – Brown Algae). At the September 2018 meeting, the Panel issued an Insufficient Data Announcement for these 82 ingredients. The Panel's data needs were:
 - Composition and organic constituent data for each of these Brown Algae-derived cosmetic ingredients
 - 28-Day dermal toxicity data for those ingredients that are not GRAS
 - Sensitization data at relevant use concentrations for all ingredients (e.g., *Macrocystis Pyrifera* (Kelp) Extract at 36.4%)
 - Genotoxicity data for those ingredients that are not GRAS

Since the September Panel meeting, CIR has received a significant amount of data, which have been incorporated into the report and have been designated by highlighting. The data that were presented to the Panel in Wave 2 and Wave 3 for the September meeting have also been incorporated into the report.

Comments provided by the Council prior to the September meeting on the draft report have been addressed. A draft Discussion has been incorporated into the report, based on the proceedings and comments from the September meeting. The draft Discussion addresses irritation/sensitization data, impurities concerns, estrogenic effects, and the outstanding data needs. Please determine if these concerns are addressed properly, and identify any other issues that need to be discussed.

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

2. Alkoxylated Fatty Amides (agenda and flash drive name – Alkoxylated Fatty Amides). The Panel first reviewed this group of 40 ingredients at the September 2018 meeting. At that meeting, the report included 41 ingredients. However, the tertiary amide, PEG-5 Oleamide Dioleate was inadvertently retained in that grouping; this family of ingredients is intended to comprise secondary amides exclusively. Noting our error, we have deleted PEG-5 Oleamide Dioleate from the report.

During the review in September, the Panel found the data insufficient to determine safety for this group of ingredients and issued an IDA with the following data requests:

- Method of manufacture
- Impurities data
- Dermal absorption data on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide
 - If absorbed, then 28-day dermal toxicity data, as well as data on other toxicity endpoints, may be needed

Method of manufacture and impurities data for PEG-50 Hydrogenated Palmamide were the only data received in response to the IDA. Updated concentration of use data, and studies of acute dermal toxicity in the rat, skin irritation in rabbits, and skin sensitization in guinea pigs, for PPG-2 Hydroxyethyl Cocamide, were also received. The updated concentration of use data reported a lower concentration in one category (but the overall reported maximum use concentrations did not change), and the animal studies on PPG-2 Hydroxyethyl Cocamide had already been reported as summary data in a NICNAS report.

If the Panel finds that the data are still insufficient, then a Tentative Report with an insufficient data conclusion should be issued. However, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a conclusion of safe as used, safe with qualifications, or unsafe. Also, please review the draft Discussion and determine whether it accurately captures the Panels deliberations, and please identify any other issues that should be addressed.

Draft Final Reports - there are 5 draft final reports for consideration (including three 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. Hydroxyethyl Urea (agenda and flash drive name – Hydroxyethyl Urea). The Panel reviewed this document for the first time at the September 2018 meeting, and determined that the available genotoxicity, dermal, inhalation, reproductive/developmental toxicity, and irritation/sensitization data were sufficient to issue the conclusion that Hydroxyethyl Urea is safe in the present practices of use and concentration described in the report when formulated to be non-irritating. Carcinogenicity data are lacking; however, because the genotoxicity studies were negative and there are no structural alerts, the Panel was not concerned that Hydroxyethyl Urea had carcinogenic potential. Also, because the potential exists for dermal irritation with the use of products formulated using Hydroxyethyl Urea, the Panel specified that products containing Hydroxyethyl Urea must be formulated to be non-irritating.

Council comments regarding the Tentative Report were received and addressed. The Panel should carefully review the Abstract, Discussion, and Conclusion of this safety assessment. If these are satisfactory, the Panel should issue a Final Report.

2. Methylxanthines (agenda and flash drive name – Methylxanthines). The methylxanthines (previously titled Xanthine Alkaloids) reviewed in this report are Caffeine, Theophylline, and Theobromine. The Panel reviewed this document for the first time at the September 2018 Panel meeting, and issued a Tentative Report for public comment with the conclusion that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

The safety of these ingredients was supported by negative carcinogenicity studies and the historically safe use of these ingredients in food and beverage products. The Panel noted the false positive genotoxicity studies observed in vitro without metabolic activation. However, any concern over these false positives was mitigated by in vitro and in vivo studies performed with metabolic activation that yielded exclusively negative results. Positive developmental and reproductive studies were also noted, but were considered negligible considering these effects were only seen at concentrations much higher than what would be used in cosmetics.

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

3. Acrylates Copolymers (agenda and flash drive name – Acrylates Copolymers). At the September 2018 meeting, the Panel issued a Tentative Amended Report with the conclusion that the 126 ingredients named in this report are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

No new data have been received since the September Panel meeting. Comments provided by the Council prior to the September meeting, and on the Tentative Amended Report issued after that meeting, have mostly been addressed. One comment requires input from the Panel. In the comments received on the Tentative Amended Report, it is suggested that the paragraph regarding the risk assessment of Acrylates/C10-30 Alkyl Acrylates Crosspolymer in benzene should be deleted. ***Does the Panel agree with that comment, or, should this information remain in the report to support the statements in the Discussion regarding polymerization in benzene?***

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

4. Salicylic Acid & Salicylates (agenda and flash drive name – Salicylic Acid & Salicylates). A CIR Final Report on Salicylic Acid and 16 salicylates was published in 2003. The conclusion in that safety assessment states that these ingredients are safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection.

At the June 2018 meeting, the Panel determined it was appropriate to re-open the safety assessment to amend the conclusion and to include 3 additional related ingredients, Amyl Salicylate, Hexyl Salicylate, and Isotridecyl Salicylate. The Panel also determined that MEA-Salicylate would not be included in the amended report because it was recently reviewed by the CIR in the safety assessment of Ethanolamine and Ethanolamine Salts. The Panel then issued a Tentative Amended Report with a "safe when formulated to be non-irritating" conclusion on Salicylic Acid and 18 salicylate ingredients.

It should be noted that this report has been updated to include data from the following sources: Chemical registration dossiers submitted to the European Chemicals Agency (ECHA); a 2002 Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) opinion document on Salicylic Acid; and a September 2018 Scientific Committee on Consumer Safety (SCCS) preliminary opinion document on Salicylic Acid. These data are highlighted in the report text. The Draft Final Amended Report also references the various restrictions, relating to the use of Salicylic Acid and salicylates in cosmetics, that have been established by the European Union (EU). These restrictions are summarized in the report, and should be taken into consideration in light of the tentative amended conclusion that was previously issued by the Panel.

The Panel had requested that CIR calculate a margin of safety for Salicylic Acid exposure, taking into consideration the extent of dermal absorption during cosmetic product use (at highest maximum use concentration of 30% in leave-on products). This calculation is also highlighted in the report text.

Furthermore, it should be noted that updated 2018 use concentration data on Salicylic Acid and

salicylates were received from the Council, and these have been added to the Draft Final Amended Report. Also, the comments on the re-review document that were reviewed at the June 2018 Panel meeting and comments on the Tentative Final Amended Report that were received from the Council have been addressed.

The Panel should review the safety test data summarized in the Draft Final Amended Report to determine whether or not the report Discussion or Conclusion should be revised in any way based on the additional data that have been added. If these are satisfactory, a Final Amended Report should be issued.

5. Vinylpyrrolidone Polymers (agenda and flash drive name – Vinylpyrrolidone Polymers). At the September 2018 meeting, the Panel issued a Tentative Report on 30 vinylpyrrolidone copolymers (21 ingredients reviewed for the first time + 9 ingredients previously reviewed) with a split conclusion. The Panel determined that 27 of these vinylpyrrolidone polymers are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

For the 27 vinylpyrrolidone polymers deemed safe, concern over the lack of dermal absorption data was mitigated by large ingredient molecular weights, low residual monomer content, and similar chemical and physical properties, despite differences in monomer identities. However, for the following urethanes subgroup, the Panel concluded that the data are insufficient to determine safety:

Urethanes

VP/Dimethiconylacrylate/Polycarbamyl/Polyglycol Ester

VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester

VP/Polycarbamyl Polyglycol Ester

The Panel determined that the following data are needed to assess the safety of these 3 ingredients:

- Residual monomer concentration for at least a representative ingredient from this subgroup

To date, the data requested have not been received.

Most of the comments that were received from the Council prior to the September meeting and in response to the Tentative Report have been addressed. However, a few of the comments require further input. Regarding the comment on the Cytotoxicity section, it would be helpful if the Council would provide a reference confirming that the PVP modified with a hydrophobic group (such as octadecyl or di(dodecyl)) is not a cosmetic ingredient. The Panel's input is needed to address comments relating to changes in the Discussion and Conclusion.

After reviewing these documents, if the available data on the 3 urethane ingredients are still considered insufficient, the Panel should issue a Final Report with an insufficient data conclusion on these ingredients, specifying the data needs in the discussion section of the report. Furthermore, if the data are still deemed sufficient for issuing a safe conclusion on the 27 vinylpyrrolidone polymers, then this conclusion should also be issued. Thus, it is possible that a Final Report with a split conclusion on all 30 vinylpyrrolidone polymers will be issued at this meeting.

Re-Review Summary – there is 1 Re-Review Summary

1. Triacetin (agenda and flash drive name - Triacetin). The Panel published the Final Report on the Safety Assessment of Triacetin in 2003. Based on the available data, the Panel concluded that Triacetin is safe as used in cosmetics. Limited new data (a developmental/reproductive toxicity screening test and two genotoxicity studies) were identified in the published literature; the results of these newly available studies supported the conclusion reached by the Panel in the original review. The Panel reviewed updated information regarding product types and ingredient use frequencies provided by the US Food and Drug Administration (FDA), and the maximum use concentrations provided by the Council.

The Panel determined to not reopen this safety assessment and reaffirmed the original conclusion that Triacetin is safe as used in cosmetic products. The Panel should read this summary carefully and confirm that it is in agreement with their thinking.

Administrative Items - there is 1 strategy memo and there are 2 resource documents

1. Polyaminopropyl Biguanide (agenda and flash drive name – Polyaminopropyl Biguanide). At the December 2017 Panel meeting, the Draft Final Report was tabled in response to a commitment from the cosmetics industry to complete a 100-person human repeated insult patch test (HRIPT) of a product containing Polyaminopropyl Biguanide. On November 2, 2018 a communication from the Council was received stating that this HRIPT study began on October 31, 2018. It is scheduled to be completed on December 7, 2018 and the final report should be available during the first quarter of 2019. Accordingly, the Panel should expect to see this Draft Final Report on Polyaminopropyl Biguanide return thereafter.

In addition to the request for this HRIPT study, the Panel issued an insufficient conclusion with the following data also needed:

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

The most recent use data reported in the Council's survey indicated the maximum use concentration of Polyaminopropyl Biguanide in pump and propellant hair sprays is 0.053% and 0.0004%, respectively. Inhalation exposure concentrations of Polyaminopropyl Biguanide were estimated using the ConsExpo Web Spray Model (Consumer Exposure Model, Web version 1.0.1), and the margin of safety (MOS) calculation was based on a no observed adverse effect concentration (NOAEC) derived from a 28-day inhalation study in which rats were exposed, nose only, to Polyaminopropyl Biguanide in an aerosolized water solution, 6 h/day, 5 days/week. The MOS values were 200 for propellant hair sprays and 11 for pump hair sprays. In order to achieve an adequate MOS of 100 for hair pump sprays, the weight fraction of Polyaminopropyl Biguanide in hair pump sprays should be decreased from 0.053% to 0.0058%.

In reviewing this risk assessment, however, the Panel noted that the exposure scenario (e.g., sprayed over 6 h) in the principle animal study was not representative of pump and propellant hair spray product use. In addition, no default exposure parameters were available specifically for pump hair spray products in the ConsExpo Web Spray Model. Thus, the spray duration assumed for propellant hair sprays (14.4 sec) and default values for pump toilet-water sprays were used in the calculations for pump hair sprays. Furthermore, other conservative default values published by Rijksinstituut voor Volksgezondheid en Milieu (RIVM – the Dutch National Institute for Health and Environment) were applied in all of the calculations with the ConsExpo Web Spray Model. However, real consumer use data on pump and propellant hair sprays would help refine the estimates of inhalation exposure in such a risk assessment, and therefore redefine the safety margins. To date, CIR has not received such consumer use data. ***The Panel should determine a course of action regarding the absence of these data.***

The Draft Final Report (not included for Panel review; expected for the April 2019 meeting) will be updated to include the HRIPT study described above, a published case report (Jaque and DeKoven, 2017), and the following published data on Polyaminopropyl Biguanide (from Chowdhury et al. 2018): absorption, distribution and excretion; short-term oral toxicity; and carcinogenicity + mode of action for tumor formation.

No vote is required for this administrative item. We are merely seeking your expert input in advance of document preparation.

2. Hair Dye Epidemiology Resource Document (agenda and flash drive name – Hair Dye Epi). At the June meeting, the Panel suggested this Resource Document be reformatted. The Panel also requested Dr. Luigi Naldi, Director of the Department of Dermatology, San Bortolo Hospital in Vicenza, Italy, comment on the two newly discovered studies on the potential breast cancer-hair dye association. Furthermore, the Panel requested a clarifying statement on the types of further investigations that are necessary to examine the association between hair dye use and the incidence of breast cancer. Dr.

Naldi's comments, as well as the professional opinions on further investigations, were incorporated in this revised Resource Document accordingly (highlighted in the text).

The Panel should review this Resource Document, especially noting the additions and formatting. If this Document is in agreement with their thinking, it should be finalized and used to replace the version currently posted on the CIR Findings & Resources Documents page (<https://www.cir-safety.org/cir-findings>).

3. Aerosols & Inhalation (agenda and flash drive name – Aerosols). At the September 2017 meeting, the Panel requested additional information on spray product particle size for hair spray and deodorants. These data are included in this submission, and have been added to the document. In addition, the CIR Science and Support Committee (SSC) provided the following recommendations for the document revision:
 - Revise the CIR Aerosols Precedents document to clearly outline a tiered approach to assess inhalation exposure and risk assessment.
 - Reference the updated particle/droplet size data in the Precedents document. These data are generally consistent with earlier data. Importantly, particle/droplet size data are generally not needed when assessing the inhalation safety of an ingredient in a spray cosmetic product.
 - Revise the boilerplate language to reflect less reliance on particle size and more emphasis on exposure levels from spray cosmetic products by the inhalation route. These exposure levels are generally *de minimus*.

The enclosed document has been updated (highlighted in the text) to address the comments from the CIR SSC, as well as include the information from the presentations at the September 2017 meeting that covered the topics of exposure assessment of aerosols from cosmetic spray and powder products and considerations for inhalation safety assessments.

Furthermore, the Panel noted that the document should be corrected to replace the assumption that 5% of the particle-size distribution released from propellant deodorant sprays consist of respirable particles with the assumption that 50% of the particles are respirable. The document has been revised to address this issue. In addition, inhalation exposures to a pump/ propellant hair spray or propellant deodorant spray were recalculated with updated respirable particle size data by implementing the tiered approach.

The Panel should determine how, and to what extent, the draft resource document should be revised further, based on the information provided by the presentations and the papers and the comments from the CIR SSC. If this Document is in agreement with the Panel's thinking, it should be finalized and used to replace the version currently posted on the CIR Findings & Resources Documents page (<https://www.cir-safety.org/cir-findings>).

Full Panel Meeting

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

The Panel will consider the 5 reports to be issued as final safety assessments, followed by the remaining reports advancing in the process (including the tentative reports and draft reports); a re-review summary; a strategy memo; and 2 resource documents. It is likely that the full Panel session will conclude before lunch on day 2, so plan your travel accordingly.

Have a safe journey!

Agenda

149th Cosmetic Ingredient Review Expert Panel Meeting

December 3rd - 4th, 2018

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

Monday, December 3rd

8:00 am	CONTINENTAL BREAKFAST	
8:30 am	WELCOME TO THE 149th EXPERT PANEL TEAM MEETINGS	Drs. Bergfeld/Heldreth
8:45 am	TEAM MEETINGS	Drs. Marks/Belsito

Dr. Marks' Team*

FAR (WJ)	Salicylic Acid & Salicylates
FR (WJ)	Vinylpyrrolidone Polymers
DR (WJ)	Alkyl Lactyl Lactate Salts
SM (WJ)	Polyaminopropyl Biguanide
DR (CB)	Fatty Acids & Fatty Acid Salts
DAR (CB)	Silica & Silicates
DR (AA)	Benzyl Salicylate
FR (AA)	Hydroxyethyl Urea
FR (PC)	Methylxanthines
TR (PC)	Brown Algae
DR (PC)	Basic Red 76
RRsum (MF)	Triacetin
FAR (MF)	Acrylates Copolymers
TR (MF)	Alkoxylated Fatty Amides
Admin (JZ)	Hair Dye Epi
Admin (JZ)	Aerosols & Inhalation

Dr. Belsito's Team

TR (MF)	Alkoxylated Fatty Amides
FAR (MF)	Acrylates Copolymers
RRsum (MF)	Triacetin
DR (PC)	Basic Red 76
TR (PC)	Brown Algae
FR (PC)	Methylxanthines
Admin (JZ)	Hair Dye Epi
Admin (JZ)	Aerosols & Inhalation
FR (AA)	Hydroxyethyl Urea
DR (AA)	Benzyl Salicylate
FAR (WJ)	Salicylic Acid & Salicylates
FR (WJ)	Vinylpyrrolidone Polymers
DR (WJ)	Alkyl Lactyl Lactate Salts
SM (WJ)	Polyaminopropyl Biguanide
DR (CB)	Fatty Acids & Fatty Acid Salts
DAR (CB)	Silica & Silicates

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

(AA): Alice Akinsulie || (CB): Christina Burnett || (JZ): Jinqiu Zhu || (MF): Monice Fiume || (PC): Priya Cherian || (WJ): Wilbur Johnson

*Team moves to breakout room.

Tuesday, December 4th

8:00 am	CONTINENTAL BREAKFAST	
8:30 am	WELCOME TO THE 149 th FULL CIR EXPERT PANEL MEETING	Dr. Bergfeld
8:45 am	Admin MINUTES OF THE SEPTEMBER 2018 EXPERT PANEL MEETING	Dr. Bergfeld
9:00 am	DIRECTOR'S REPORT	Dr. Heldreth
9:10 am	FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, OTHER ITEMS	

Final Reports

FR (AA)	Hydroxyethyl Urea – <i>Dr. Belsito Reports</i>
FR (PC)	Methylxanthines – <i>Dr. Marks Reports</i>
FAR (MF)	Acrylates Copolymers – <i>Dr. Belsito Reports</i>
FR (WJ)	Vinylpyrrolidone Polymers – <i>Dr. Marks Reports</i>
FAR (WJ)	Salicylic Acid & Salicylates – <i>Dr. Belsito Reports</i>

Reports Advancing

DR (WJ)	Alkyl Lactyl Lactate Salts – <i>Dr. Marks Reports</i>
DR (CB)	Fatty Acids & Fatty Acid Salts – <i>Dr. Belsito Reports</i>
DAR (CB)	Silica & Silicates – <i>Dr. Marks Reports</i>
TR (PC)	Brown Algae – <i>Dr. Belsito Reports</i>
DR (PC)	Basic Red 76 – <i>Dr. Marks Reports</i>
DR (AA)	Benzyl Salicylate – <i>Dr. Belsito Reports</i>
TR (MF)	Alkoxylated Fatty Amides – <i>Dr. Marks Reports</i>

Other Items

RRsum (MF)	Triacetin – <i>Dr. Belsito Reports</i>
SM (WJ)	Polyaminopropyl Biguanide – <i>Dr. Marks Reports</i>
Admin (JZ)	Hair Dye Epi – <i>Dr. Belsito Reports</i>
Admin (JZ)	Aerosols & Inhalation – <i>Dr. Marks Reports</i>

ADJOURN - Next meeting Monday and Tuesday, April 8-9, 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

(AA): Alice Akinsulie || (CB): Christina Burnett || (JZ): Jinqiu Zhu || (MF): Monice Fiume || (PC): Priya Cherian || (WJ): Wilbur Johnson

ONE HUNDRED FORTY-EIGHTH MEETING

OF THE

EXPERT PANEL

September 24-25, 2018

Darcy 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.

Others Present at the Meeting

Alice Akinsulie	CIR
Jay Ansell	PCPC
Don Bjerke	P & G
Lucretia Burgess	CIR
Christina Burnett	CIR
Priya Cherian	CIR
Carol Eisenmann	PCPC
Monice Fiume	CIR
Kevin Fries	CIR
Bart Heldreth	CIR
Wilbur Johnson, Jr.	CIR
Linda Katz	FDA
Alexandra Kowcz	PCPC
Jon Lalko	Estee Lauder
Julia Linthicum	CIR
Linda Loretz	PCPC
Wang Zemin	FDA
Jinqiu Zhu	CIR
Merle Zimmermann	AHPA

MINUTES FROM THE 148th CIR EXPERT PANEL MEETING

CHAIR'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 148th meeting of the Cosmetic Ingredient Review (CIR) Expert Panel (Panel). She then stated that 14 ingredient reports were reviewed in Teams on the preceding day, and noted that deliberations on the safety of Brown Algae and the Parabens, in particular, were rather challenging. Dr. Bergfeld thanked the CIR staff and the CIR SSC for their input, and also noted that the safety assessments reviewed are very well done.

APPROVAL OF MINUTES

The minutes of the June 4-5, 2018 CIR Expert Panel meeting were approved.

DIRECTOR'S REPORT

Dr. Heldreth expressed gratitude for the Panel's and other stakeholders' continued support of the CIR program. He noted that the CIR Steering Committee will be considering a nominee to fill the seat of an independent representative of the Society of Toxicology. The Committee is tentatively scheduled to convene in October to vote on this nominee.

Dr. Heldreth also noted the statuses of 9 ingredients are set to change this year. Sunflower Extract, Sunflower Leaf/Stem Extract, and Sunflower Sprout Extract received an insufficient data conclusion (needs: method of manufacture; composition, especially protein content (including 2S albumins); and impurities) in September of 2016 (part of the *Helianthus annuus* (Sunflower)-Derived Ingredients report). Sunflower Extract was reported to be in use at the time of that report and will thus move to the "use not supported" category, while Sunflower Leaf/Stem Extract and Sunflower Sprout Extract had no uses according to VCRP data and thus will move to the "zero use" category.

Also at the September 2016 meeting, Adipic Acid/CHDM/MA/Neopentyl Glycol/Trimellitic Anhydride Copolymer, Isostearoyl Trimellitic Anhydride/Trimethylolpropane Copolymer, Propylene Glycol/Sebacic Acid/Trimellitic Anhydride Copolymer, and Trimethylpentanediol/Isophthalic Acid/Trimellitic Anhydride Copolymer received an insufficient data conclusion (needs: method of manufacture and composition; Trimellitic Anhydride Copolymers report). These 4 ingredients had no reported use and will thus move to the zero use category. Two other ingredients from that report have partial status changes. Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer and Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer were concluded to be safe in nail product formulations in the present practices of use and concentration described in the safety assessment; however, the data were deemed insufficient to make a determination of safety on the use of these ingredients in all other types of cosmetic formulations. These 2 ingredients, combined, had 3 reported uses in the "dermal contact" category. Accordingly, the conclusion of safe in nail product formulation is unchanged, but the conclusion for all other types of cosmetic formulations is thus changed to "use not supported."

Finally, Dr. Heldreth noted that CIR was invited to present at a special forum arranged in part by the US Department of Commerce to inform other parts of the world, specifically Brazil in this case, about the great work of this Panel. Scheduled for late October, Dr. Heldreth will provide representatives from the Brazilian Health Regulatory Agency and the Brazilian Ministry of Industry, Foreign Trade and Services with an overview of the CIR process and the significant utility of this Panel's reports.

Final Safety Assessments

***Ginkgo biloba*-Derived Ingredients**

The Panel issued a final report with the conclusion that the following 5 ingredients are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Ginkgo Biloba Leaf Extract
Ginkgo Biloba Leaf*

Ginkgo Biloba Leaf Cell Extract*
Ginkgo Biloba Leaf Powder

Ginkgo Biloba Leaf Water*

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

The Panel also determined that the data are insufficient to determine the safety of the following 5 ingredients:

Ginkgo Biflavones**

Ginkgo Biloba Nut Extract

Ginkgo Leaf Terpenoids**

Ginkgo Biloba Meristem Cell**

Ginkgo Biloba Root Extract**

***Not reported to be in current use.*

The data needed to determine safety for these cosmetic ingredients are:

- Method of manufacturing, composition, and impurities data for each of these ingredients, except Ginkgo Biloba Meristem Cell
- 28-Day dermal toxicity data for each of these ingredients
 - Dependent on the results of these studies, additional data on other toxicological endpoints, such as developmental and reproductive toxicity and carcinogenicity, may be needed
- Dermal irritation and sensitization data at leave-on use concentrations
- Ocular irritation data, if available

The Panel determined that the data on Ginkgo Biloba Leaf Extract are sufficient, and reasonable inferences to four other leaf-derived ingredients can be made. The Panel noted the positive carcinogenic findings of the rodent studies performed by the National Toxicology Program (NTP), but determined that the *Ginkgo biloba* leaf extract used therein contained unusually high concentrations of certain constituents that are markedly different from those found in the leaf extracts used in dietary supplements, which are similar to those extracts used in cosmetics. Furthermore, the NTP study administered this specific leaf extract at high doses by gavage, allowing for concentrations in the blood that would not be achieved through cosmetic use. The leaf extract that is similar to that used in dietary supplements did not produce increased incidences of cancer in a dietary study. This, combined with a long history of use of *Ginkgo biloba* leaf extracts in folk medicine, indicated that the findings of the NTP study are not relevant to cosmetic use.

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

Hydrogen Peroxide

The Panel issued a final report with the conclusion that Hydrogen Peroxide is safe in cosmetics in the present practices of use and concentration described in the safety assessment. The Panel noted the positive genotoxicity studies and determined concerns about these results were mitigated by the quick reaction of Hydrogen Peroxide with the surface of the skin. The Panel considered the available data on carcinogenicity, reproduction/development, irritation, and sensitization, and concluded that these data are sufficient to support the safety of Hydrogen Peroxide in cosmetics.

Hydrogen Peroxide is reported to be used in hair dyes at, up to 15% in a professional product (that is then diluted for use) and at up to 12.4% in consumer hair dyes and colors formulations; Hydrogen Peroxide is reported to be used in a total of 390 cosmetic formulations, 250 of which are hair-coloring formulations. Other categories of use include formulations that result in dermal leave-on exposure at up to 3%, and there are reported to be 93 formulations that come in contact with mucous membranes and may result in incidental ingestion, including at up to 4.6% in dentifrices.

Dialkyl Dimer Dilinoleates

The Panel issued a final amended report with a conclusion that the following dialkyl dimer dilinoleates are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Diisopropyl Dimer Dilinoleate

Diethylhexyl Dimer Dilinoleate*

Dicetearyl Dimer Dilinoleate*

Di-C16-18 Alkyl Dimer Dilinoleate*

Diisostearyl Dimer Dilinoleate

Di-C20-40 Alkyl Dimer Dilinoleate*

Diethylhexyl [previously “Diocetyl”] Dimer Dilinoleate*

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

The Panel considered that the available data on systemic toxicity, genotoxicity, irritation, sensitization, and phototoxicity were adequate to assess the safety of these ingredients as used in cosmetics. The potential skin penetration of these ingredients was estimated, in part, using an octanol/water partition coefficient ($\log P_{ow} > 17$) of Diisopropyl Dimer Dilinoleate. The Panel did not believe there would be significant skin penetration resulting from cosmetic use, and therefore concluded that the risk of systemic toxicity was mitigated.

According to US FDA Voluntary Cosmetic Registration Program (VCRP) 2018 data, only 2 dialkyl dimer dilinoleates are currently in use. Diisopropyl Dimer Dilinoleate is reported to be used in 145 formulations, with a maximum concentration of 29% in lipsticks; Diisostearyl Dimer Dilinoleate has a maximum concentration of 16% in lipsticks, and is reported to be used in 20 formulations.

Polyol Phosphates

The Panel issued a final report, concluding that Sodium Phytate, Phytic Acid, Phytin*, and Trisodium Inositol Triphosphate* are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

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

However, the Panel also concluded that the data are insufficient to determine the safety of the following 6 ingredients: Disodium Glucose Phosphate, Manganese Fructose Diphosphate, Sodium Mannose Phosphate, Trisodium Fructose Diphosphate, Xylityl Phosphate, and Zinc Fructose Diphosphate. Of these, only Sodium Mannose Phosphate is reported to be in use. The Panel determined that the following data are needed to assess the safety of these 6 ingredients:

- Method of manufacture
- Impurities
- Absorption, distribution, metabolism, and excretion (ADME) data

While method of manufacture and impurities data on Sodium Mannose Phosphate were received, no ADME data were submitted. The Panel agreed dermal absorption data on this ingredient were needed to conclude on safety. The Panel previously requested skin sensitization data on Phytic Acid at the highest maximum use concentration; these data were received, and the Panel agreed that the results of submitted studies indicate that these ingredients do not have discernible skin sensitization potential at cosmetic use concentrations.

Polyfluorinated Polymers

The Panel issued a final report with the conclusion that PTFE and Hexafluoropropylene/Tetrafluoroethylene Copolymer* are safe in cosmetics in the present practices of use and concentration described in the safety assessment. (**Not reported to be in current use. If this ingredient is to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to PTFE.*) However, the Panel determined that the data are insufficient to determine the safety of the following ten ingredients, none of which are reported to be in current use:

Acrylates/Perfluorohexylethyl Methacrylate Copolymer
 Behenyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer
 C6-14 Perfluoroalkylethyl Acrylate/HEMA Copolymer
 Stearyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer
 Acrylates/Methoxy PEG-23 Methacrylate/Perfluorooctyl Ethyl Acrylate Copolymer
 PEG-10 Acrylate/Perfluorohexylethyl Acrylate Copolymer
 Polyperfluoroethoxymethoxy Difluoroethyl PEG Diisostearate
 Polyperfluoroethoxymethoxy Difluoroethyl PEG Ether
 Polyfluoroethoxymethoxy Difluorohydroxyethyl Ether
 Polyperfluoroethoxymethoxy Difluoromethyl Ether

The Panel determined that the following data are needed to determine the safety of these ingredients:

- Method of manufacture
- Impurities
- Skin sensitization data at the maximum use concentration

Method of manufacture, impurities, and skin sensitization data were received and considered sufficient for determining that Hexafluoropropylene/Tetrafluoroethylene Copolymer and PTFE would be safe at maximum reported cosmetic use concentrations up to 13%. The available impurities data indicated that the tetrafluoroethylene monomer is undetectable (75 ppb detection limit), that perfluorooctanoic acid (PFOA) is present at concentrations of < 25 ppb, and that the incidental content of perfluorooctyl sulfonate (PFOS) is detectable in the ppb range. In light of the Environmental Protection Agency (EPA)'s 70 ppt limit (a 100-fold safety factor is inherent in this limit) on PFOA and PFOS combined in drinking water and the developmental toxicity/carcinogenicity that is associated with these impurities, the Panel previously determined that a value for the greatest possible amount of incidentally ingested PFOA and PFOS that would result from the use of oral hygiene products at the maximum use concentration of PTFE should be calculated and included in this safety assessment. Although the available use information now indicates that PTFE is not being used in cosmetic oral hygiene products, 2018 FDA VCRP data indicate that it is being used in lipsticks (maximum use concentration data unavailable). Thus, the use of PTFE in products that are applied to the lips at the highest maximum use concentration of PTFE (13%) in cosmetic products (including those for which incidental ingestion is extremely unlikely) were used in this calculation. It was determined that an overly conservative estimation of ingredient exposure from lipstick use results in a total dose of PFOA exposure that is 755-fold lower than the EPA's advisory level for drinking water (in addition to the 100-fold safety factor inherent in EPA's limit).

The Panel also discussed the issue of incidental inhalation exposure from powders, having taken into consideration that PTFE is reported as being used in [fragrance] powders (dusting and talcum, excluding aftershave talcum) and in face powders, which may result in incidental inhalation exposure. Data received from the Council indicate that PTFE is being used in face powders at maximum use concentrations ranging from 0.5% to 3%. The Panel noted that 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. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <http://www.cir-safety.org/cir-findings>.

Tentative Safety Assessments

Titanium Complexes

The Panel issued a tentative report for public comment with a split conclusion:

Isopropyl Titanium Triisostearate is safe in cosmetics in the present practices of use and concentration described in the safety assessment, when used as a surface modifier. The data are insufficient to determine the safety of the following 4 ingredients: Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, and Titanium Salicylate.

The Panel determined that the following data are needed to assess the safety of these 4 ingredients:

- Maximum use concentrations
- Methods of manufacture
- Impurities
- 28-day dermal toxicity data
 - Depending on the results of these studies, various systemic toxicity data may also be needed
- Genotoxicity data
- Skin irritation and sensitization data at maximum cosmetic use concentrations, except for Titanium Citrate

Skin irritation and sensitization data on Titanium Citrate previously requested are no longer needed because the Panel determined that results of a study on 37 patients (all suspected of having titanium allergy) patch tested with 0.16% and 0.32% Titanium Citrate were sufficient for evaluating these endpoints.

Only one of the titanium complexes is reported to be in use. According to 2018 VCRP data, Isopropyl Titanium Triisostearate is reported to be used in 580 cosmetic products (573 leave-on and 7 rinse-off products). The results of a concentration of use survey conducted by the Council in 2017 indicate that Isopropyl Titanium Triisostearate is used at concentrations up to 1.5% in leave-on products (eye shadows) and at concentrations up to 0.3% in rinse-off products (eye make-up removers).

These titanium complexes are reported to have the following functions in cosmetics: Isopropyl Titanium Triisostearate (surface modifiers), Titanium Citrate (colorants; humectants), Titanium Ethoxide (binders), Titanium Isostearates (film formers; opacifying agents), and Titanium Salicylate (preservatives). Submitted method of manufacture data demonstrate that as a surface modifier in cosmetic products, Isopropyl Titanium Triisostearate is covalently bound to a pigment (e.g., black iron oxide) via reaction (Figure 1).

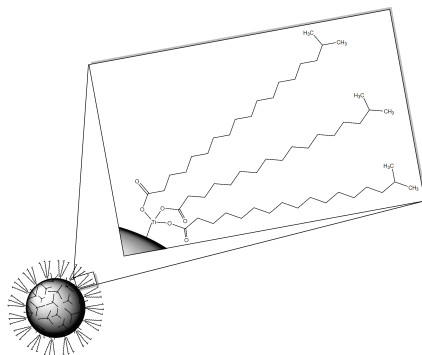


Figure 1. Pigment, surface modified by reaction with Isopropyl Titanium Triisostearate (depicted isostearyl chains are one example of an “iso”)

Thus, the presence of any residual or unreacted Isopropyl Titanium Triisostearate in the product formulation would be considered an impurity. The Panel noted that if data indicating the presence of significant levels of residual Isopropyl Titanium Triisostearate resulting from use as a surface modifier are provided, 28-day dermal toxicity data and genotoxicity data would then be needed to evaluate the safety of this ingredient. The same would apply to any other identified use(s) of this ingredient that would yield free Isopropyl Titanium Triisostearate in the product formulation. The Panel requested clarification of the following: (1) Isopropyl Titanium Triisostearate is only being used as a surface modifier, (2) the other titanium complex ingredients are not being used as surface modifiers, and (3) surface modification does not result in any appreciable residual Isopropyl Titanium Triisostearate in the final product. No data have been submitted to suggest that Titanium Citrate, Titanium Ethoxide, Titanium Isostearates, or Titanium Salicylate are used in cosmetic formulations to modify pigment surfaces in this way. Thus, the available information suggests that these four ingredients are discrete, unreacted complexes (e.g., Titanium Ethoxide in Figure 2).

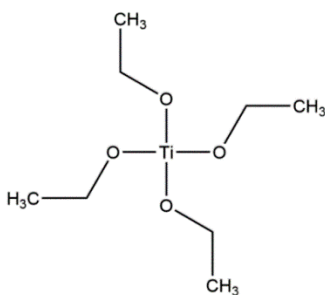


Figure 2. Titanium Ethoxide

The Panel requested that in addition to addressing their concerns relating to surface modifier chemistry, that industry determine the form of Isopropyl Titanium Triisostearate (bound to pigment or not) that is associated with the use concentration data that were provided and determine the form (and resultant concentrations) of Isopropyl Titanium Triisostearate in the unpublished product formulation safety test data that were provided.

Vinylpyrrolidone Polymers

The Panel issued a tentative report for public comment with a split conclusion. The Panel determined that the following 27 vinylpyrrolidone polymers are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

VP Copolymers

Acrylic Acid/VP Crosspolymer
Maltodextrin/VP Copolymer
PVP/Decene Copolymer
PVP/VA/Itaconic Acid Copolymer
PVP/VA/Vinyl Propionate Copolymer
Styrene/VP Copolymer
Triacontene/VP Copolymer
VP/Eicosene Copolymer
VP/Hexadecene Copolymer
VP/VA Copolymer
VP/Vinyl Alcohol Copolymer

VP Acrylate Copolymers

Acrylates/Stearyl Methacrylate/VP Copolymer
Acrylates/VP Copolymer
Ammonium Acryloyldimethyltaurate/VP Copolymer
Ethylhexyl Acrylate/VP/Dimethicone Methacrylate Copolymer
Ethylhexyl Methacrylate/Methyl Methacrylate/VP Copolymer
Methacrylic Acid/Styrene/VP Copolymer
Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer
VP/Acrylates/Lauryl Methacrylate Copolymer
VP/Dimethylaminoethylmethacrylate Copolymer
VP/DMAPA Acrylates Copolymer
VP/Vinyl Caprolactam/DMAPA Acrylates Copolymer

Polyvinylpyrrolidone (PVP) and Modified PVP Polymers

Butylated PVP
PVP
Triacontanyl PVP

VP Crosspolymers

Hydrolyzed Wheat Protein/PVP Crosspolymer
Sodium Acryloyldimethyltaurate/VP Crosspolymer

For these 27 vinylpyrrolidone polymers deemed safe, concern over the lack of dermal absorption data was mitigated by large ingredient molecular weights, low residual monomer content, and similar chemical and physical properties, despite differences in monomer identities. However, for the following urethanes subgroup, the Panel concluded that the data are insufficient to determine safety:

Urethanes

VP/Dimethiconylacrylate/Polycarbamyl/Polyglycol Ester
VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester
VP/Polycarbamyl Polyglycol Ester

The Panel determined that the following data are needed to assess the safety of these 3 ingredients:

- Residual monomer concentration for at least a representative ingredient from this subgroup

Parabens

The Panel issued a tentative amended report for public comment with the conclusion that the following 20 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

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

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

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

The Panel discussed concerns about the bioaccumulation potential of parabens. The Panel noted that, as lipid-soluble chemicals, parabens may distribute to tissues despite metabolism. Recent studies with sensitive analytical methods have demonstrated the presence of parabens in various human tissues. However, the data are equivocal regarding cumulative storage in such tissues; and importantly, the available evidence suggests no significant association of parabens exposure with diseases or other adverse health conditions. The Panel noted that paraben exposures are attributed to cosmetic products, foods, medicines and other sources; and refined aggregate exposure models suggest that cosmetic product use is a major source of parabens exposure, topically. However, the vast quantity of biomonitoring data indicate that systemic exposure to these ingredients is very low.

The Panel also discussed the safety of parabens as used in vaginally-applied cosmetic products. One published reference was submitted to the Panel along with the assertion that these ingredients cause irreparable damage to sperm and may preclude fertilization in users. However, of the multiple endpoints asserted in the reference, each was either constructed around an improperly chosen/assayed assay to make such assertions unequivocally, and/or resulted in no significant effects. Another published reference was submitted, this one along with an assertion these ingredients may increase the chances of developing a vaginal yeast infection. However, the cell culture studies performed therein were dosed with extremely high concentrations compared to cosmetic use (i.e. 15 - 25% preservative in these studies vs a maximum use concentration of parabens in cosmetics of 0.5%). The Panel requested that these studies be included in the CIR report. However, the Panel's discussion thereof classified these studies as illustrations of potential, general hazards, which fail to demonstrate risks relevant to cosmetic safety in the context of concentration of use.

The main emphasis of the Panel's deliberations on the draft assessment report comprised extensive revisions to better identify, and explain the rationale for, the values utilized in conducting the risk assessment therein. The Panel also requested that the margin of safety (MOS) should be re-calculated, weighing the different use concentrations and exposures of Butylparaben in various cosmetic products categories.

Methylxanthines (previously referred to as Xanthine Alkaloids)

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

Caffeine
Theobromine
Theophylline

Each of these ingredients is reported to be in use. According to 2018 VCRP data, Caffeine is used in 1033 formulations at a maximum concentration of 6%. Theobromine and Theophylline were reported to be used in 5 formulations, each.

The Panel found that the systemic toxicity, development/reproductive toxicity, genotoxicity, carcinogenicity, and irritation data in this report were sufficient. The Panel recognized the positive genotoxicity studies therein, but considered those to

be potentially misleading. Indeed, positive results were only observed in in vitro studies without metabolic activation (those in vitro studies with metabolic activation were negative); and, the positive results of studies performed with mammalian cell cultures were in sharp contrast to the in vivo mammalian studies which yielded negative results (suggesting that those positive results were actually false-positives). Furthermore, the Panel noted the negative results of the carcinogenicity studies performed by the NTP, further eliminating the need for concern of the positive genotoxicity studies. Positive results for development and reproductive studies were also noted, but were considered negligible considering these effects were only seen at concentrations much higher than what would be used in cosmetics.

Acrylates Copolymers

The Panel issued a tentative amended report for public comment with the conclusion that the 126 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.

Acrylates Copolymer
 Acrylates Crosspolymer
 Acrylates Crosspolymer-3
 Acrylates Crosspolymer-4
 Acrylates Crosspolymer-5*
 Acrylates/Ammonium Methacrylate Copolymer
 Acrylates/Beheneth-25 Methacrylate Copolymer
 Acrylates/Beheneth-25 Methacrylate/Steareth-30 Methacrylate Copolymer*
 Acrylates/C10-30 Alkyl Methacrylate Copolymer
 Acrylates/C10-30 Alkyl Acrylate Crosspolymer
 Acrylates/C12-13 Alkyl Methacrylates/Methoxyethyl Acrylate Crosspolymer*
 Acrylates/C12-22 Alkyl Methacrylate Copolymer
 Acrylates/C26-28 Olefin Copolymer*
 Acrylates/C5-8 Alkyl Acrylate Copolymer*
 Acrylates/Ceteareth-20 Methacrylate Crosspolymer*
 Acrylates/Ceteareth-20 Methacrylate Crosspolymer-2*
 Acrylates/Ceteth-20 Methacrylate Copolymer*
 Acrylates/Ethylhexyl Acrylate Copolymer
 Acrylates/Ethylhexyl Acrylate Crosspolymer
 Acrylates/Ethylhexyl Acrylate/Glycidyl Methacrylate Crosspolymer*
 Acrylates/Hydroxyesters Acrylates Copolymer
 Acrylates/Hydroxyethyl Acrylate/Lauryl Acrylate Copolymer*
 Acrylates/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer*
 Acrylates/Laureth-25 Methacrylate Copolymer*
 Acrylates/Lauryl Methacrylate Copolymer*
 Acrylates/Lauryl Methacrylate/Tridecyl Methacrylate Crosspolymer*
 Acrylates/Methoxy PEG-4 Methacrylate Copolymer*
 Acrylates/Methoxy PEG-15 Methacrylate Copolymer*
 Acrylates/Methoxy PEG-23 Methacrylate Copolymer
 Acrylates/Methoxy PEG-90 Methacrylate Crosspolymer*
 Acrylates/Palmeth-25 Acrylate Copolymer
 Acrylates/PEG-4 Dimethacrylate Crosspolymer*
 Acrylates/Steareth-20 Methacrylate Copolymer
 Acrylates/Steareth-20 Methacrylate Crosspolymer
 Acrylates/Steareth-30 Methacrylate Copolymer
 Acrylates/Steareth-50 Acrylate Copolymer*
 Acrylates/Stearyl Methacrylate Copolymer
 Acrylates/VA Copolymer

Acrylates/VA Crosspolymer
 Acrylates/Vinyl Isodecanoate Crosspolymer
 Acrylates/Vinyl Neodecanoate Crosspolymer
 Acrylic Acid/C12-22 Alkyl Acrylate Copolymer*
 Acrylic Acid/Stearyl Acrylate Copolymer
 Allyl Methacrylate/Glycol Dimethacrylate Crosspolymer*
 Allyl Methacrylates Crosspolymer
 Ammonium Acrylates Copolymer
 Ammonium Acrylates/Ethylhexyl Acrylate Copolymer*
 Ammonium Acrylates/Methyl Styrene/Styrene Copolymer
 Ammonium Polyacrylate
 Ammonium Styrene/Acrylates Copolymer
 Ammonium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer*
 Ammonium VA/Acrylates Copolymer*
 AMP-Acrylates Copolymer
 Behenyl Methacrylate/t-Butyl Methacrylate Copolymer
 Butyl Acrylate/Cyclohexyl Methacrylate Copolymer*
 Butyl Acrylate/Ethylhexyl Methacrylate Copolymer*
 Butyl Acrylate/Glycol Dimethacrylate Crosspolymer
 Butyl Acrylate/Hydroxyethyl Methacrylate Copolymer*
 Butyl Methacrylate/Acryloyloxy PG Methacrylate Copolymer*
 C12-22 Alkyl Acrylate/Hydroxyethylacrylate Copolymer
 C8-22 Alkyl Acrylates/Methacrylic Acid Crosspolymer*
 Calcium Potassium Carbomer*
 Carbomer
 Cyclohexyl Methacrylate/Ethylhexyl Methacrylate Copolymer*
 Ethylene/Acrylic Acid Copolymer
 Ethylene/Acrylic Acid/VA Copolymer*
 Ethylene/Calcium Acrylate Copolymer*
 Ethylene/Magnesium Acrylate Copolymer*
 Ethylene/Methacrylate Copolymer
 Ethylene/Sodium Acrylate Copolymer
 Ethylene/Zinc Acrylate Copolymer*
 Ethylhexyl Acrylate/Methoxy PEG-23 Methacrylate/Vinyl Acetate Copolymer*
 Ethylhexyl Acrylate/Methyl Methacrylate Copolymer
 Glycol Dimethacrylate Crosspolymer*

Glycol Dimethacrylate/Vinyl Alcohol Crosspolymer*
 Hydroxyethyl Acrylate/Methoxyethyl Acrylate
 Copolymer*
 Lauryl Acrylate Crosspolymer
 Lauryl Acrylate/VA Copolymer*
 Lauryl Acrylate/VA Crosspolymer*
 Lauryl Methacrylate/Glycol Dimethacrylate
 Crosspolymer
 Lauryl Methacrylate/Sodium Methacrylate
 Crosspolymer
 Methacrylic Acid/PEG-6 Methacrylate/PEG-6
 Dimethacrylate Crosspolymer*
 Methacryloyl Ethyl Betaine/Acrylates Copolymer
 Methoxy PEG-23 Methacrylate/Glyceryl Diisostearate
 Methacrylate Copolymer
 Methyl Methacrylate Crosspolymer
 Methyl Methacrylate/Glycol Dimethacrylate
 Crosspolymer
 Methyl Methacrylate/PEG/PPG-4/3 Methacrylate
 Crosspolymer
 PEG/PPG-5/2 Methacrylate/Methacrylic Acid
 Crosspolymer*
 Poly C10-30 Alkyl Acrylate
 Poly(Methoxy PEG-9 Methacrylate)*
 Polyacrylate-14
 Polyacrylate-29*
 Polyacrylate-34*
 Polyacrylate-1 Crosspolymer
 Polyacrylic Acid
 Polybutyl Acrylate*
 Polybutyl Methacrylate*

Polyethylacrylate
 Polyhydroxyethylmethacrylate*
 Polyisobutyl Methacrylate*
 Polymethyl Acrylate
 Polymethyl Methacrylate
 Polypropyl Methacrylate*
 Polystearyl Methacrylate*
 Potassium Acrylate Crosspolymer*
 Potassium Acrylates Copolymer
 Potassium Acrylates/C10-30 Alkyl Acrylate
 Crosspolymer
 Potassium Acrylates/Ethylhexyl Acrylate Copolymer*
 Potassium Aluminum Polyacrylate*
 Potassium Carbomer
 Potassium Polyacrylate*
 Sodium Acrylate/Acrolein Copolymer*
 Sodium Acrylate/Vinyl Alcohol Copolymer
 Sodium Acrylates Copolymer
 Sodium Acrylates Crosspolymer-2
 Sodium Acrylates/Beheneth-25 Methacrylate
 Crosspolymer*
 Sodium Acrylates/C10-30 Alkyl Acrylate Crosspolymer
 Sodium Acrylates/Ethylhexyl Acrylate Copolymer*
 Sodium Acrylates/Vinyl Isodecanoate Crosspolymer
 Sodium Carbomer
 Sodium Polyacrylate
 Sodium Polymethacrylate
 Steareth-10 Allyl Ether/Acrylates Copolymer
 Stearyl/Lauryl Methacrylate Crosspolymer*
 Styrene/Acrylates/Ammonium Methacrylate Copolymer
 VA/Butyl Maleate/Isobornyl Acrylate Copolymer

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

This ingredient family was created because the Panel found it appropriate to consolidate all related copolymers and crosspolymers prepared from monomers that comprise, in part, acrylic acid or methacrylic acid (as well as appropriate salts and esters of these acids) into one safety assessment. The Panel noted these polymers are generally large molecules, and significant dermal absorption is not expected. Therefore, topically applied cosmetics are not expected to result in systemic toxicity from these ingredients. Additionally, the existing data support a lack of sensitization potential.

The Panel addressed the concern for residual monomer that might be present in the copolymers; manufacturers should continue to use good manufacturing processes to ensure the amount of residual monomer is kept to a minimum. The Panel also discussed the issue of residual solvent that might be present. Again, the amount of residual solvent should be minimized; however, the Panel was particularly concerned with polymerization in benzene. It cannot be predicted with certainty what quantity of benzene would be volatilized/leached from a polymer during manufacture, formulation, or use; while some benzene is inevitably volatilized during manufacture, some benzene may be trapped in the polymer matrix and may leach out during formulation and use. Because of this uncertainty, the Panel stipulated that these ingredients should not be polymerized in benzene.

The Panel was concerned that the potential exists for dermal irritation with the use of products formulated using the ingredients named in this assessment. Therefore, the Panel specified that products containing the ingredients listed above must be formulated to be non-irritating. The Panel requested information on molecular weight ranges of these copolymers, as well as on residual monomer levels of each ingredient, which would help to inform this safety assessment.

Hydroxyethyl Urea

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

Panel suggested that an emphasis should be added that there is a difference between hydroxyurea (not an ingredient, but a commonly used chemical in laboratories for cell cycle synchronization or generating replication) and this ingredient, Hydroxyethyl Urea. The Panel found that the data on chemical and physical properties, systemic toxicity, development/reproductive toxicity, and dermal sensitization in this report were sufficient. The Panel also found that the irritation data given in this report were sufficient to proceed with a tentative conclusion. However, the Panel discussed the potential of dermal irritation with the use of products formulated using Hydroxyethyl Urea, and specified that such products should be formulated to be non-irritating.

Re-Review Action

Triacetin

The Panel reaffirmed its original conclusion of safe as used in cosmetics for Triacetin. This conclusion was originally published in 2003.

In accord with CIR's Procedures to reassess previously-reviewed conclusions after a period of 15 years, the Panel was asked to determine whether a rereview of Triacetin was warranted. No new ingredients were proposed for inclusion in this re-review. The results of an oral development and reproductive toxicity study in rats and a mouse lymphoma L5178Y assay were the only new data found in the published literature; both had negative results. Because these studies did not cause any concern, and because the frequency of use of Triacetin in cosmetics increased only slightly (while the maximum use concentrations decreased from 4% to 0.95%), the Panel determined to not reopen this assessment.

Insufficient Data Announcements

Alkoxyated Fatty Amides

The Panel reviewed the available data for the following 41 alkoxyated fatty amides and found these data to be insufficient to determine safety:

PEG-2 Cocamide	PEG-2 Lauramide	PEG-15 Stearamide
PEG-3 Cocamide	PEG-3 Lauramide	PEG-50 Stearamide
PEG-4 Cocamide	PEG-5 Lauramide	PEG-5 Tallow Amide
PEG-5 Cocamide	PEG-6 Lauramide	PEG-8 Tallow Amide
PEG-6 Cocamide	PEG-11 Lauramide	PEG-50 Tallow Amide
PEG-7 Cocamide	PEG-3 Oleamide	PEG-2 Tallowamide DEA
PEG-11 Cocamide	PEG-4 Oleamide	Polyglyceryl-4-PEG-2 Cocamide
PEG-20 Cocamide	PEG-5 Oleamide	PPG-2 Cocamide
PEG-3 Cocamide DEA	PEG-6 Oleamide	PPG-1 Hydroxyethyl Caprylamide
PEG-20 Cocamide MEA	PEG-7 Oleamide	PPG-2 Hydroxyethyl Cocamide
PEG-6 Hydrogenated Palmamide	PEG-9 Oleamide	PPG-2 Hydroxyethyl
PEG-50 Hydrogenated Palmamide	PEG-5 Oleamide Dioleate	Coco/Isostearamide
PEG-13 Hydrogenated Tallow	PEG-4 Rapeseedamide	PPG-3 Hydroxyethyl Soyamide
Amide	PEG-4 Stearamide	
PEG-5 Lanolinamide	PEG-10 Stearamide	

Therefore, the Panel issued an insufficient data announcement (IDA) with the following data requests:

- Method of manufacture
- Impurities data
- Dermal absorption data on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide
 - If absorbed, then 28-day dermal toxicity data, as well as data on other toxicity endpoints, may be needed

The Panel noted that PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide have the highest reported frequency of use, which is the reason dermal absorption data were specifically requested on these two ingredients. The Panel did remark on the lack of carcinogenicity data; however, because there were sufficient negative genotoxicity studies and there are no structural alerts for carcinogenicity, the Panel's concerns were mitigated.

Additionally, the Panel responded to a comment from industry that questioned whether the two di-*N,N*-alkoxyl-substituted amides should be included in the report. It was the opinion of the Panel that the information on the mono-*N*-alkoxyl-

substituted ingredients informs the safety of the di-*N,N*-alkoxyl-substituted ingredients; therefore those ingredients should remain in this assessment.

Brown Algae

The Panel reviewed the available data for the following 82 brown algae and found these data to be insufficient to determine safety:

Agarum Cribrosum Extract	Laminaria Cloustoni Extract
Alaria Esculenta Extract	Laminaria Diabolica Extract
Ascophyllum Nodosum	Laminaria Digitata Extract
Ascophyllum Nodosum Extract	Laminaria Digitata Powder
Ascophyllum Nodosum Powder	Laminaria Hyperborea Extract
Cladosiphon Novae-Caledoniae Extract	Laminaria Japonica Extract
Cladosiphon Okamuranus Extract	Laminaria Japonica Powder
Cystoseira Amentacea/Caespitosa/ Branchycarpa Extract	Laminaria Longissima Extract
Cystoseira Baccata Extract	Laminaria Ochroleuca Extract
Cystoseira Balearica Extract	Laminaria Saccharina Extract
Cystoseira Caespitosa Extract	Lessonia Nigrescens Extract
Cystoseira Compressa Extract	Lessonia Nigrescens Powder
Cystoseira Compressa Powder	Macrocystis Pyrifera (Kelp)
Cystoseira Tamariscifolia Extract	Macrocystis Pyrifera (Kelp)
Dictyopteris Polypodioides Extract	Blade/Pneumatocyst/Stipe Juice Extract
Dictyota Coriacea Extract	Macrocystis Pyrifera (Kelp) Extract
Durvillaea Antarctica Extract	Macrocystis Pyrifera (Kelp) Juice
Ecklonia Cava Extract	Macrocystis Pyrifera (Kelp) Protein
Ecklonia Cava Water	Nereocystis Luetkeana Extract
Ecklonia Kurome Extract	Pelvetia Canaliculata Extract
Ecklonia Kurome Powder	Pelvetia Siliquosa Extract
Ecklonia/Laminaria Extract	Phyllacantha Fibrosa Extract
Ecklonia Maxima Extract	Saccharina Angustata Extract
Ecklonia Maxima Powder	Saccharina Japonica Extract
Ecklonia Radiata Extract	Saccharina Longicuris Extract
Eisenia Arborea Extract	Sargassum Filipendula Extract
Fucus Serratus Extract	Sargassum Fulvellum Extract
Fucus Spiralis Extract	Sargassum Fusiforme Extract
Fucus Vesiculosus	Sargassum Glaucescens Extract
Fucus Vesiculosus Extract	Sargassum Horneri Extract
Fucus Vesiculosus Powder	Sargassum Muticum Extract
Halidrys Siliquosa Extract	Sargassum Pallidum Extract
Halopteris Scoparia Extract	Sargassum Siliquastrum Extract
Himanthalia Elongata Extract	Sargassum Thunbergii Extract
Himanthalia Elongata Powder	Sargassum Vulgare Extract
Hizikia Fusiforme Extract	Sphacelaria Scoparia Extract
Hizikia Fusiformis Water	Undaria Peterseniana Extract
Hizikia Fusiformis Callus Culture Extract	Undaria Pinnatifida Extract
Hydrolyzed Ecklonia Cava Extract	Undaria Pinnatifida Cell Culture Extract
Hydrolyzed Fucus Vesiculosus Extract	Undaria Pinnatifida Leaf/Stem Extract
Hydrolyzed Fucus Vesiculosus Protein	Undaria Pinnatifida Powder
	Undaria Pinnatifida Root Powder

The Panel issued an IDA for this ingredient group. The Panel noted that several ingredients included in the report are generally recognized as safe when used in foods (GRAS-foods). Since exposure via ingestion would likely result in far greater systemic exposure than could result from cosmetic use, the need for systemic toxicity data for these GRAS-foods ingredients is mitigated. However, for these ingredients, the Panel issued the following data requests:

- Composition
- Dermal sensitization data at or above maximum use concentrations

For all other brown algae ingredients, without a GRAS-foods designation, the Panel issued the following data requests:

- Composition
- If absorbed, 28-day dermal toxicity and genotoxicity
- Dermal sensitization data at or above maximum use concentrations

According to 2018 VCRP data, the greatest frequency of use is reported for Fucus Vesiculosus Extract, which is reported to be used in 287 formulations, 201 of which are leave-on products. Laminaria Digitata Extract had the second highest reported frequency of use (235 formulations). The results of a concentration of use survey conducted by the Council indicate Laminaria Digitata Powder and Macrocystis Pyrifera (Kelp) Extract are used in leave-on products at a maximum concentrations of 40% and 36.4%, respectively, which are the greatest use concentrations reported for the brown algae ingredients reviewed in this safety assessment.

Other Items:

Re-Review Summary - Aluminum Starch Octenylsuccinate

The Panel approved the re-review summary of Aluminum Starch Octenylsuccinate with the conclusion that it is safe as used in cosmetics provided that established limitations imposed on heavy metal concentrations are not exceeded. This conclusion was originally published in 2002. The Panel reviewed updated information regarding product types and ingredient use frequencies provided by the FDA, and maximum use concentrations provided by the Council.

Strategy Document – MI/MCI

More than 15 years have passed since the CIR “Final Report on the Safety Assessment of Methylisothiazolinone and Methylchlorisothiazolinone” was published. According to the CIR Procedures, it is thus time to consider a reassessment of the safety of this ingredient combination use. At the time of the original report, there were 381 uses of this preservative combination. Current data, obtained from the FDA VCRP in 2018, indicate this preservative combination is now used in 4595 formulations in the US. Accordingly, a maximum concentration of use survey will be requested and a re-review document will be prepared for the Panel’s consideration to re-open (likely for the April 2019 meeting).

However, a strategy memo was issued in advance to obtain Panel input and direct the CIR staff towards information sought in that re-review document. The Panel considered changes in report conclusion procedures and evaluated the relevance of a recent risk assessment. The Panel also commented that it may be helpful, after choosing a no expected sensitization induction level (NESIL), for industry stakeholders to provide a second generation quantitative risk assessment (QRA 2.0) calculation. Comments and any data or risk assessments, from the Panel and other stakeholders, will be incorporated into the re-review draft.

TRIACETIN

CONCLUSION: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published the Final Report on the Safety Assessment of Triacetin in 2003.¹ Based on the available data, the Panel concluded that Triacetin is safe as used in cosmetics. Limited new data (a developmental/reproductive toxicity screening test and two genotoxicity studies) were identified in the published literature;² the results of these newly available studies supported the conclusion reached by the Panel in the original review. The Panel reviewed updated information regarding product types and ingredient use frequencies provided by the US Food and Drug Administration (FDA),³ and the maximum use concentrations provided by the Personal Care Products Council.⁴ The Panel determined to not reopen this safety assessment and reaffirmed the original conclusion that Triacetin is safe as used in cosmetic products as given in [Table 1](#).

DISCUSSION: The reported frequency of use of Triacetin in cosmetics has increased slightly since safety was originally reviewed; 13 uses were reported 1998, and 59 uses are reported in 2018. However, the maximum use concentrations have decreased, from 2% in leave-on and 4% in rinse-off formulations to 0.95% in leave-on and 0.08% in rinse-off formulations.

Developmental and reproductive toxicity data were absent in the original assessment. However, the Panel found that because Triacetin is thought to be hydrolyzed to glycerol and acetic acid, neither of which is a developmental toxin, Triacetin did not present a risk of developmental or reproductive toxicity. The developmental/reproductive toxicity screening test that is now available, confirmed the Panel's conclusion. In a study in which 12 rats/sex received doses of 0 (vehicle; distilled water), 40, 200, and 1000 mg/kg bw/day Triacetin by gavage (males for 44 days from 2 weeks prior to mating and females for 41-48 days from 14 days before mating to day 3 postpartum), no maternal toxicity was observed, and there were no fetotoxic or developmental effects. Both the maternal and developmental no-observable-adverse-effect-level (NOAEL) was established as 1000 mg/kg bw/day.

Also, during its original review, the Panel recognized the US FDA affirmation of glycerides, including Triacetin, as a GRAS human food ingredient. This GRAS status was supportive of the overall safety of this ingredient.

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

	# of Uses		Max Conc of Use (%)	
	2018 ³	1998 ¹	2018 ⁴	1999 ¹
Totals*	59	13	0.0000013 – 0.95	0.8 - 4
<i>Leave-On</i>	57	13	0.0000013 – 0.95	0.8 – 2
<i>Rinse-Off</i>	2	NR	0.00012 – 0.08	4
<i>Diluted for (Bath) Use</i>	NR	NR	NR	NR
Eye Area	4	4	0.000025 – 0.008	1-2
Incidental Ingestion	NR	NR	0.00047 – 0.054	NR
Incidental Inhalation-Spray	1; 21 ^a ; 7 ^b	NR	0.0000013 – 0.95; 0.00047 – 0.021 ^a	0.8
Incidental Inhalation-Powder	7 ^b	NR	0.008 – 0.015 ^c	NR
Dermal Contact	34	11	0.000025 – 0.14	1
Deodorant (underarm)	NR	NR	0.13 (not spray) 0.14 (spray)	NR
Hair - Non-Coloring	4	NR	0.0000013 – 0.95	0.8
Hair-Coloring	NR	NR	NR	NR
Nail	20	NR	0.2	1-4
Mucous Membrane	NR	NR	0.00047 – 0.08	NR
Baby Products	NR	NR	NR	NR

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

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

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

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

NR – no reported use

REFERENCES

1. Andersen FA (ed). Final Report on the Safety Assessment of Triacetin. *Int J Toxicol*. 2003;22(Suppl 2):1-10.
2. European Chemicals Agency (ECHA). REACH registration dossier: Triacetin (CAS number: 102-76-1). <https://echa.europa.eu/en/registration-dossier/-/registered-dossier/15139>. Last Updated 2018. Date Accessed 8-28-2018.
3. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program (VCRP) - Frequency of Use of Cosmetic Ingredients. College Park, MD: 2018. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 3 2018; received February 5 2018).
4. Personal Care Products Council. 2018. Concentration of Use by FDA Product Category: Triacetin. Unpublished data submitted by Personal Care Products Council on June 1, 2018.



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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Date: November 9, 2018

Subject: Tabled - Draft Final Report on Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

At the December 4-5, 2017 Panel meeting, the Draft Final Report was tabled in response to a commitment from the cosmetics industry to complete a 100-person human repeated insult patch test (HRIPT) of a product containing Polyaminopropyl Biguanide. The Panel was informed that a task force that will be overseeing this project was being formed, and that the Panel will receive ongoing updates relating to this project. Subsequently, the tabled report was on the agenda of the June 4-5, 2018 Panel meeting, where an oral commitment from the Council to provide the data requested was received. On November 2, 2018 a communication from the Council was received stating that this HRIPT study began on October 31, 2018. It is scheduled to be completed on December 7, 2018 and the final report should be available during the first quarter of 2019. Accordingly, the Panel should expect to see this Draft Final Report on Polyaminopropyl Biguanide return thereafter.

In addition to the request for this HRIPT study, the Panel, at the September 11-12, 2017 meeting, issued an insufficient conclusion with the following data also needed:

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

The most recent use data reported in the Council's survey indicated the maximum use concentration of Polyaminopropyl Biguanide in pump and propellant hair sprays is 0.053% and 0.0004%, respectively. Inhalation exposure concentrations of Polyaminopropyl Biguanide were estimated using the ConsExpo Web Spray Model (Consumer Exposure Model, Web version 1.0.1), and the margin of safety (MOS) calculation was based on a no observed adverse effect concentration (NOAEC) derived from a 28-day inhalation study in which rats were exposed, nose only, to Polyaminopropyl Biguanide in an aerosolized water solution, 6 h/day, 5 days/week. The MOS values were 200 for propellant hair sprays and 11 for pump hair sprays. In order to achieve an adequate MOS of 100 for hair pump sprays, the weight fraction of Polyaminopropyl Biguanide in hair pump sprays should be decreased from 0.053% to 0.0058%.

In reviewing this risk assessment, however, the Panel noted that the exposure scenario (e.g., sprayed over 6 h) in the principle animal study was not representative of pump and propellant hair spray product use. In addition, no default exposure parameters were available specifically for pump hair spray products in the ConsExpo Web Spray Model. Thus, the spray duration assumed for propellant hair sprays (14.4 sec) and default values for pump toilet-water sprays were used in the calculations for pump hair sprays. Furthermore, other conservative default values published by Rijksinstituut voor Volksgezondheid en Milieu (RIVM – the Dutch National Institute for Health and Environment) were applied in all of the calculations with the ConsExpo Web Spray Model. However, real consumer use data on pump and propellant hair sprays would help refine the estimates of inhalation exposure in such a risk assessment, and therefore redefine the safety margins. To date, CIR has not received such consumer use data. ***The Panel should determine a course of action regarding the absence of these data.***

The Draft Final Report (*not included for Panel review; expected for the April 2019 meeting*) will be updated to include the HRIPT study described above, a published case report (Jaque and DeKoven, 2017), and the following published data on Polyaminopropyl Biguanide (from Chowdhury et al. 2018): absorption, distribution and excretion; short-term oral toxicity; and carcinogenicity + mode of action for tumor formation.



Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Polyaminopropyl Biguanide Interested Party Task Force of the Personal Care Products Council

DATE: November 2, 2018

SUBJECT: Polyaminopropyl Biguanide Repeated Insult Patch Test

The repeated insult patch test study of Polyaminopropyl Biguanide began on October 31, 2018. It is scheduled to be completed on December 7, 2018. The final report should be available during the first quarter of 2019.



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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, CIR Toxicologist
Date: November 9, 2018
Subject: Revised Draft Hair Dye Epidemiology Document for Panel Review

Enclosed is the updated draft of the CIR Resource Document – Hair Dye Epidemiology (*hdepi122018rep*), as well as the transcripts of the discussion of the Resource Document at the previous CIR Expert Panel meeting (*hdepi122018min*). The previous draft was reviewed by the Panel at the June 2018 meeting.

At the June meeting, the Panel suggested the Resource Document be reformatted. The Panel also requested Dr. Luigi Naldi, Director of the Department of Dermatology, San Bortolo Hospital in Vicenza, Italy, comment on the two newly discovered studies on the potential breast cancer-hair dye association. Furthermore, the Panel requested a clarifying statement on the types of further investigations that are necessary to examine the association between hair dye use and the incidence of breast cancer. Dr. Naldi's comments, as well as the professional opinions on further investigations warranted, were incorporated in this revised Resource Document accordingly (**highlighted** in the text).

The Panel should review this Resource Document, especially noting the additions and formatting. If this Document is in agreement with their thinking, it should be finalized and used to replace the version currently posted on the CIR Findings & Resources Documents page (<https://www.cir-safety.org/cir-findings>).

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

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

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

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

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

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

DR. SLAGA: I completely agree.

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

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

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

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

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

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

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

DR. HILL: Yeah

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

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

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

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

DR. BOYER: Okay

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

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

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

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

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

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

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

DR. BERGFELD: Okay

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

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

DR. HILL: Point well taken.

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

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

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

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

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

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

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

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

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

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

DR. MARKS: Okay.

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

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

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

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

DR. SHANK: The change is insignificant.

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

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

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

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

DR. LIEBLER: 36.

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

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

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

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

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

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

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

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

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

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

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

DR. BELSITO: Right, four plusses.

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

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

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

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

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

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

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

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

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

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

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

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

DR. BELSITO: Okay.

DR. MARKS: (inaudible)

DR. BELSITO: So, just off the top of my head, before I get to page 35. The one issue I had is, you know, yeah, the data is inconsistent. We say how we're looking at the data, yada yada yada. But, you know, there are some data coming out that are showing some linkages. So, for instance, in terms of, I believe it was bladder cancer in women in New Hampshire and Vermont, if they were college grads, that incidence was positive, if they weren't it wasn't. And just, you know, looking back at my own childhood in the 1950's and my parents. You know, my impression was that women who went to college smoked a lot more than women who didn't go to college in the 1950's. And I was just wondering how well these studies are controlled for other confounders that could influence the cancer's in question? And in our boilerplate, we never mention that. So, I mean, they are epi studies. They are very hard to control. But did they look at other confounding factors that might contribute to these cancers? And so I'm fine with the document. I don't think that, in consumers, there's any strong evidence to suggest carcinogenicity of these hair dyes. I would just like, as we're going through the documents, a simple statement as to how well they looked at potential confounders in these studies that might contribute to the specific cancer endpoints in question. You know, like, for instance, even the relationship between cosmetologists and bladder cancer, you know, there are studies that show that cosmetologists smoke more than the general population. And then we know smoking is a risk for bladder cancer. So is it the hair dyes? Is it the other chemicals they use? Is it the smoking? Is it the combination of all of these? So, just a mention as to how well these studies were controlled for other confounders.

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

DR. BELSITO: I understand.

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

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

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

DR. BELSITO: -- at least a comment.

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

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

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

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

DR. SLAGA: Yeah.

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

DR. SLAGA: Yeah.

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

DR. SLAGA: Right.

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

DR. SLAGA: Right.

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

Day 1 of the June 4-5, 2018 CIR Expert Panel Meeting – Dr. Belsito's Team

DR. BELSITO: Hair dye epidemiology, I guess that's the next one. That's also in admin, correct?

DR. HELDRETH: That's a separate book.

DR. BELSITO: Okay. Yes. I thought it looked fine. I had a couple of comments on PDF Page 3. The second line, third line -- so, let me see. It says, an odds ratio of 1 means that an exposure does not affect the odds of an outcome. RR of 1 means that there is no difference. I presume it's an odds ratio of less than 1. There is a less than sign missing there? Third line from the bottom, PDF Page 3.

DR. LIEBLER: I think odds ratio don't have a sign.

DR. BELSITO: Well, he's defining what it means. And odds ratio of less than 1, I believe, means an exposure does not affect; and of 1 means there's no difference; greater than 1 means the exposure may increase. He's defining what odds ratios mean. Read the sentence. So, I think it's an odds ratio of less than one means that an exposure does not. The 1 means there's no difference; and greater than 1 means it increases the risk. So, that needs to be changed.

And then on PDF, Page 9, the first paragraph. The sentence of the first paragraph, the one, two, three, four, five, starting with, "Using a random effect model and the Duval and Tweedie's trim and fill procedure to adjust for publication bias in the presence of between studies heterogeneity." What does that mean?

DR. HELDRETH: I'm sorry, I was looking at another page. Where is that?

DR. BELSITO: PDF Page 9. The one, two, three, four, five, six -- six lines from the top, starting with using a random effects model. Are you with me?

DR. HELDRETH: Yes.

DR. BELSITO: Okay. Show procedure to adjust for publication bias in the presence of between studies heterogeneity. For publication bias for study heterogeneity? I don't understand what you're saying there.

DR. ZHU: That's the method they used in this paper, by this author, to do the meta-analysis.

DR. BELSITO: I understand the method, but the sentence makes zero sense to me. "For publication bias in the presence of between." Publication bias between studies? Publication bias because of heterogeneity of studies?

DR. ZHU: Okay. I think this method is used to evaluate the study's heterogeneity for different studies, epidemiology studies.

DR. HELDRETH: Right. But he's asking you -- the verbiage that's there isn't quite clear. Could you give us a better sentence?

DR. BELSITO: I guess my question is, what does the Duval and Tweedie's trim and fill procedure adjust publication bias for? For study heterogeneity? And then it says, "such meta-analysis showed." What is the bias that it adjusts for? I don't understand that.

DR. HELDRETH: When they did the review of multiple studies, they excluded some studies. They had a bias, a rationale for why they excluded those studies, and possibly maybe that their rationale was questionable. But that's to be assessed by the experts here.

DR. BELSITO: Right. I got the understanding that the trim and fill means they cut out

some studies. I understand that. But for publication bias. I mean, what is in the presence of between studies heterogeneity? Publication bias because there was a lot of heterogeneity between the studies they put in the meta-analysis?

I don't understand what they're electing to trim. That sentence makes no sense to me and doesn't explain to me what that model is.

DR. ZHU: Sure. This is a model used by the author to do the meta-analysis.

DR. BELSITO: I understand. What I'm saying is, please look at what the model does and put it into a better sentence that makes it understandable as to what it's doing.

DR. ZHU: Sure.

DR. BELSITO: I had no other comments.

DR. LIEBLER: I just wanted to return to the odds ratio sentence because I think it was correct as originally written. So, this is again the bottom of Page 3 on the PDF. If we're talking about the same sentence, Don, I want to make sure; an odds ratio of one means that exposure does not affect the odds?

And if it's 1, that's exactly correct. If there's a lower risk of the outcome as a function of exposure, then that's when the odds ratio is less than 1, like .8 or .6 or .5. But as written, it was correct, so, it doesn't need to be "less than" added to that sentence.

DR. KLAASSEN: Well, the other aspect of these odds ratio is that they always give a confidence -- or a range. So, you can have an odds ratio of 1.5, but if the confidence interval is 0.9 to 2.3, it's not significantly different. It's kind of an over simplification because it's the odds ratio with the 95 percent confidence interval. For it to be significant, you not only have to have the odds ratio, but the 95 percent confidence limits greater than 1.0.

And there's a lot of them that are 1.4 that are not significantly different because you have the 1.4, and then your confidence interval goes from 0.8 to 2.3. So, then that's not significantly increased. Just so everybody realizes that.

DR. HELDRETH: Okay. Should we then add a small section about confidence intervals?

DR. KLAASSEN: I think for people that aren't familiar with that, and some people that are reading this probably aren't.

DR. LIEBLER: I think as written, it does at least introduce what the odds ratio and relative risks are -- defines them clearly enough.

DR. KLAASSEN: Yes.

DR. LIEBLER: But then I agree with Curt's suggestion that perhaps we add a sentence or two at the end of the paragraph to explain that typically odds ratios are presented with calculated ranges based on the application of the appropriate statistical test.

DR. ZHU: Okay. Will do.

DR. BERGFELD: I was confused with just the tabulation of all these different studies. And the takeaway message is what? Is it presented here in the first couple of paragraphs, conclusion? I think it's in the first paragraph, in the beginning of the document. Because you end this document with the DNA repair enzyme genes and no summary, no discussion, no nothing.

DR. LIEBLER: You think we ought to move the conclusion paragraph to the end of the document?

DR. BERGFELD: I think like all of our documents -- this is a lot of information. Somewhere there has to be a summary in a few paragraphs, maybe, and a conclusion. I don't mind keeping the conclusion up front, but when I was reading this, I said, is this this conclusion, or is this the past

conclusion? Because we've concluded the same thing in the past.

And then when it ends so abruptly. What is the information that we're passing on, risk, no risk? Maybe a risk?

DR. BELSITO: I agree with the conclusion part. I think the information is summarized under each of the cancer endpoints, prostate, bladder, breast, et cetera. And then at the end, you know, come to a little bit of a discussion that there have been reports of these various cancers associated with hair dyes. However, in reviewing all of the reports, there is no definite link between personal use and any of these cancers. And then our conclusion.

DR. BERGFELD: You agree that it should be added?

DR. BELSITO: Yeah. I mean, I see your point. I didn't see that when I was reading it because the conclusions were said, all at the end, for specific endpoints; but you're right. It could be taken that the conclusion up front was our prior conclusion and then at the end, we reviewed all of this and we haven't been able to make a conclusion. It's not the usual place that a conclusion is placed, at the beginning of a document.

DR. HELDRETH: For that conclusion that we're going to put at the end, is it the same verbiage that's already in the front? Or is there something different that the panel would like to say at the end?

DR. BELSITO: I think that the introduction should be what we had previously look at and what our prior conclusion was; and that since that time there had been a number of other reports, as outlined below, that have looked at these issues. And this is an update in our prior report, and a reconsideration of our conclusion.

DR. BERGFELD: With a date.

DR. BELSITO: With a date. And then go through all of this and then come back. And the conclusion can be the same; but it just points out that since 2014, or whenever it was that we last looked at this, we've now looked at all of the studies and still do not see a reason to change our initial conclusion.

DR. BERGFELD: Do you think there's a reason to put somewhere in the discussion that Dr. Naldi was asked to review these, that an expert reviewed it?

DR. BELSITO: I thought it was sort of clear there, but yeah, I mean, that's important.

DR. BERGFELD: I mean, it isn't just us looking at it, we've had an expert look at it.

DR. SNYDER: I agree with the Council's comment that we should change this to a guidance document.

DR. BERGFELD: Resource.

DR. SNYDER: Not from -- a guidance -- resource document from a guidance document. I think that the opening paragraph, which has been discussed here largely, should just be like one of our reports. It should be very succinct, like almost abstract form, and that language is exactly what we incorporate into the report.

And before that, we say this document was last updated, and give the date; just like we do in our regular reports with a thorough literature search and consideration. Any new publications relevant to the epidemiology of the association between hair dye use and various cancers.

But I think that the opening thing should be exactly what we take, and that should go straight into our reports for hair dyes. And under that we can give the methodologies that we use to generate this resource document. And then followed by all of the brief summaries of all the individual studies.

DR. BERGFELD: And then a discussion/conclusion; it's the same format?

DR. SNYDER: Yeah. I think almost like one of our reports. I think that would be the most succinct way to handle it.

DR. HELDRETH: Okay. So, then the suggestion is that we expand this from the type of document -- the hair dye epidemiology document that it was -- and make it also have a boilerplate functionality to it?

DR. SNYDER: That's the recommendation. Then you can clearly see where the language comes that we take from our resource document; and then it's updated, and then it goes into our reports as they're published, subsequent to the most recent update.

MR. GREMILLION: I have a clarifying question. So, the expert is only between hair dye and breast cancer; is this doctor Naldi a dermatologist?

DR. BELSITO: Dr. Naldi is an epidemiologist in Bergamo Italy. I know him through his work in dermatology. He's considered a real expert epidemiologist. He consults for the Research Institute for Fragrance Materials, and a large epidemiologic study that they're sponsoring in Europe called the EDEN Group. So, he may be associated with the Department of Dermatology, I don't know, but his background is as an epidemiologist.

MR. GREMILLION: I also wanted to call attention to kind of an inconsistency I saw in his report. At the end of this document he says, "The available evidence linking hair dye use and breast cancer is limited but warrants further investigations." And earlier in the document, just half of that sentence, "The available evidence linking hair dye use and breast cancer is limited" period, is stated. I just felt like that was maybe a little bit of a mischaracterization of what he concluded.

DR. HELDRETH: I think the intent of -- and you know, I'm just trying to understand it from reading it myself. But I think the intent there was to lay out, well there may be some epidemiology studies here that maybe there's some sort of association or maybe there's not. But either way, epidemiology studies never give you cause and effect. Even if it came out with a strong odds ratio, that still would not mean that there's cause and effect. And there would need to be further study done to see if it's an actual causality.

DR. BELSITO: I actually took that as being, okay, here's the opening remark. It's limited, here's the data. And after looking at this limited data, here's my conclusion. It starts, the available evidence linking hair dye use and breast cancer is limited. It is limited. That evidence is limited. He's reviewed the evidence and his conclusion is that further studies are warranted.

MR. GREMILLION: Yeah. And the conclusion that further studies are warranted is a reason that -- implicit in that is that there is some evidence out there that would make you want to look for more evidence.

DR. BELSITO: Usually, when you say further studies are warranted, in science, it's because there's no definite data. It's that the studies that exist are limited, they don't conclude one way or the other, and therefore, more information is needed.

DR. SNYDER: Because the effect could be a compounding effect and have nothing to do with hair dyes. And so, I think that's what he's alluding to.

MR. GREMILLION: Sure, but to say the available evidence is limited, but warrants further study, versus just, the available evidence is limited. I mean, the first says something about the body of evidence is out there but warrants further study; then there's some reason to believe that the further study may illuminate some relationship.

DR. BELSITO: Or just the opposite and show that there's no relationship.

DR. SADRIEH: I think maybe it would be a good idea to kind of suggest what kinds of

studies would be needed. Because, you know, the types of studies that have been looked at is case-control studies, which basically come with recall bias. So, I think that there's going to be inherently -- you're never going to find an association, even if you find a good relative risk or odds ratio, or whatever.

The question is, what would be enough? I guess, from my perspective, the way that this is being evaluated and by not really doing a systematic review, I don't know really what this kind of analysis is going to end up reporting; because there is no way of being able to get any information that is going to be useful in anyway.

I would maybe suggest that we look into the possibility of the types of studies that would be useful. And if they are prospective study that has to be done, then how would they have to be done? And if it's a systematic review of the existing literature, then how would that have to be done, to then weight the studies such that we actually can draw conclusions that are useful?

Because right now it's just kind of look at the information, you know, the previous data that wasn't conclusive. This data is not conclusive, I doubt that any data is ever going to be conclusive if we keep looking at the information in this manner. Thank you.

DR. BELSITO: Bart, maybe we can get back to Luigi and ask him what kind of studies he would, as an epidemiologist, believe would answer this type of question. And then further studies, further prospective studies, further da-da-da kind of studies, would be needed.

DR. HELDRETH: We can certainly pose that question to him.

DR. BERGFELD: Is that in the purview of this panel?

DR. BELSITO: I think it's in the purview of the panel to try and determine the safety of hair dyes. Normally, we don't conduct studies, but we're having an epidemiologist look at this and saying that the studies that exist aren't adequate.

And we will oftentimes, in the purview of the panel, say we wanted 28-day dermal toxicity and if it absorbs in other toxicological endpoints. So, we're not specifying the study in detail, but getting a comment as to what kinds of studies might help address this situation.

DR. BERGFELD: Most of the data, though, I believe said in 1980 there's a change in the epidemiology looking at breast cancer. The earlier dyes may have been carcinogenic. The newer dyes --

DR. BELSITO: The big issue is the new data that suggests African American woman have a higher risk of breast cancer with hair dyes; which sort of raised, for a lot of people I think, the question, are darker colored hair dyes of greater risk in terms of breast cancer? And that's always been a question in regard to other types of cancers as well. I do think that needs to be addressed in some fashion.

DR. BERGFELD: And also, they have to define what hair dyes they're actually using. Some of them are old types.

DR. LIEBLER: We talked about the conclusion and how the report just sort of stopped at the end of the narrative of the data review. Sometimes, when you have a document like this, it helps the reader to have not just a conclusion, which is usually very brief and probably maybe overly general, to have maybe a couple of paragraph discussion that summarizes the outstanding issues and what are the issues that probably won't be resolved by further studies of the types that have already been done and the meta-analyses that have been done.

So, in other words, what are the -- anyways, Don just pointed out, the association with breast cancer risk in African American women with hair dyes. That seems like a significant, interesting issue that could be resolved by another focus study, possibly. But the broader question of hair dye association, we've got actually a lot of data. And it's basically very modest affects and the data are

consistently inconsistent. In other words, there's a consistent marginal affect a little bit. Plus, a little bit, you know, higher than 1, a little bit less than 1.

But I think perhaps a paragraph that summarizes kind of what are the main outstanding questions that remain, and what issues are probably not going to be resolved any better than they're currently resolved, followed by a conclusion.

DR. SADRIEH: That may be true, but at some point, one has to address how one would resolve these questions. I think, you know, there has to be a way to be able to move sort of the answer a little bit forward, other than to say that, you know, there's no way that a link can be established because --

DR. LIEBLER: No, I wasn't saying that. I wasn't saying that. I think sometimes it's good to just step back and say, okay, what have we learned? What are the questions that we could resolve, and how could we resolve them? And what are the questions that we're unlikely to be able to resolve with these types of studies?

DR. SADRIEH: Right. But then we also have to say what kinds of studies would we have to do in order to -- so, identifying the deficiencies is one thing. But we have to also say, how are we going to address the deficiencies.

DR. HELDRETH: Isn't part of the answer to what kinds of studies would be done, it would be studies other than epidemiological studies, typical carcinogenicity endpoints that we would study where we were looking at a chemical and we're seeing an endpoint effect?

DR. EISENMANN: Hair dyes are very carefully studied for genotoxicity. And they've been coming up negative, the current hair dyes that are used.

DR. SADRIEH: Yeah, but you can't answer sort of the human risk aspect with the genotox or an animal carcinogenicity study. You have to look at human data. And I don't think you could do a human cancer study. So, you're going to have to look at epidemiology data and, you know, the studies have to be either prospectively designed -- I mean, I think a lot of the studies here are sort of other studies that were being done and they kind of asked an extra question about hair dye use, without knowing which hair dye, how often, what was the formulation, anything. So, you know, I think it's very difficult to draw conclusions from doing such a superficial review and then coming up with a conclusion that, you know, there's no evidence. Because I think that can be even more misleading than anything. Because you really haven't done the effort of trying to answer the question or identify what needs to get done to answer the question. And then the response is somewhat minimal and probably not helpful to the public.

DR. EISENMANN: One other comment that we have on our comments is back in 2006, Dr. Rollison did that paper and suggested the scoring of exposure for every epidemiology study. And that's been taken out of the table of this report. We'd like to see it put back in and, for the new studies, for that scoring to be added. So, it would be rated as to -- was the exposure just yes or no or was it more in detail about --

DR. BELSITO: So, you're talking about what is a Gemlish (phonetic) score? Is that what you're asking about?

DR. EISENMANN: No, it was Dr. Rollison score. It's in the text of some of it, and it used to be in the table, but it has been taken out. If they need the paper again, we can provide it. But she explained how to score exposure.

DR. ZHU: We have the paper, so I can add it back into the table.

DR. SADRIEH: Thank you.

DR. BELSITO: Any other comments on hair dye? Okay.

DR. BERGFELD: I have a comment. It would seem to me that this hair dye document

needs to come back again for review comment.

MR. GREMILLION: Just kind of random observation. On Page 18 of the PDF, he says, "Taking skin cancer aside, breast cancer is the most common cancer diagnosed in women worldwide." And that's at odds with the World Cancer Research Fund International. They said lung cancer was the most common cancer; and skin cancer is down there, pretty far. There's just some odd --

DR. BERGFELD: Usually melanoma ranks about third or fourth.

DR. BELSITO: Yeah, but skin cancer is not just melanoma; it's basal cell and squamous, which aren't reported. So, he's correct. And this is speaking about women, not population in general. And I think it's men who skew lung cancer ahead of breast cancer. Any other comments? Okay. Polyaminopropyl Biguanide.

Day 1 of the June 4-5, 2018 CIR Expert Panel Meeting – Dr. Mark's Team

DR. MARKS: Oh, now we're into the hair dye epidemiology. That's going to be significant. Here we go, let's see. Where do I have that? Here it is. And I am not fluent; and I assume -- is this Chinese?

DR. ZHU: It's Jinqiu.

DR. MARKS: Jin --

DR. ZHU: Jinqiu.

DR. MARKS: Jinqiu.

DR. ANSELL: A new CIR writer.

DR. MARKS: Oh, I know that. I was getting the pronunciation of Jinqiu's first name. And the last name is Zhu?

DR. ZHU: Zhu.

DR. MARKS: Zhu. So, I could say Dr. Zhu. That actually is easier in some way. But at any rate, thanks for your memo dated May 23RD. We had the latest draft. Particularly, regarding breast cancer incidences and the evaluations from Dr. Naldi.

And one of my comments, I guess, I would make, right off the bat; and then I'll ask Ron, Ron and Tom, is Dr. Naldi -- if I recall correctly, he's the head of dermatology at Vicenza. Is that correct? University of Vicenza?

DR. ZHU: He's also an epidemiologist.

DR. MARKS: Yeah, okay. I figured that. Well, not figured, I assumed, that had to be, that he was being used as an expert in epidemiology. But probably some way that should be captured. Obviously, now it's captured in the minutes.

I expected that would be the case, but I was a little bit interested. A dermatologist, also an expert in epidemiology. Not exclusive, obviously, but it's not very common in my experience.

DR. HELDRETH: Yeah. Dr. Belsito had recommended him because with his work in epidemiology, he's also helped the RIFM panel as well.

DR. MARKS: RIFM, okay. That makes sense. I didn't know that history. But at least now it's in the minutes. Comments on this? And then there was some -- was it this morning that we had -- yes, this morning we got a memo from Alexandra Kowcz. How do you pronounce her last name?

DR. HELDRETH: Kowcz. Yeah, Kowcz.

DR. MARKS: Codish. Huh?

DR. HELDRETH: Kowcz.

DR. MARKS: Kowcz.

DR. ANSELL: Like the company.

DR. MARKS: Okay.

DR. HILL: Put me in coach.

DR. MARKS: At any rate, there was some comments there dated June the 4TH, so we should note those. Key issues, additional considerations. First, do you want to make any comments, particularly, about -- Dr. Zhu, in reference to the comments from the industry liaison to Bart?

DR. ZHU: You mean my comment on the --

DR. MARKS: Yeah. Do you want to preface anything either --

DR. ZHU: Yeah, I agree.

DR. MARKS: Dr. Naldi and this memo here? You've had a little bit longer time to see it, not much, than we had.

DR. ZHU: Okay. I have the comment.

DR. MARKS: While you're looking at that --

DR. SHANK: Nothing to add.

DR. MARKS: Ron Shank, nothing to add, okay. You like it.

DR. SHANK: Yes.

DR. MARKS: Okay.

DR. SHANK: Very clear.

DR. MARKS: Tom?

DR. SLAGA: Same here. I didn't have no problem with it. Very clear.

DR. MARKS: Good. Okay. Did you look at the memo?

DR. SLAGA: I left mine in the other room, I think.

DR. MARKS: We'll take a minute and let -- Tom, for you to look at the memo. And I see that both Rons are reading over the memo also.

DR. WYATT: Is there an extra copy of the memo from Alexandra?

DR. MARKS: Pardon?

DR. WYATT: Is there an extra copy of the memo from Alexandra?

DR. MARKS: I just gave mine. A minute ago, I would have said, yes. But -- do you have an extra copy of the memo?

DR. ZHU: Yes. I have it.

DR. MARKS: Could you give me a copy or give this gentleman a copy.

DR. ZHU: A copy? I just have it on the computer.

DR. WYATT: My name is Mr. Wyatt, I'm with the FDA.

DR. MARKS: Okay.

DR. HILL: Should I go check out with Carla and see if there's one out there? An extra? There usually --

DR. MARKS: Well, if you've read it, maybe you could loan it.

DR. HILL: He's got an electronic, doesn't he? I thought that's what he was saying.

DR. HELDRETH: We don't have any extras. We got these this morning too.

DR. MARKS: Oh, you got it this morning too. Okay, so that is real time.

DR. WYATT: Understood, thank you.

DR. MARKS: Would Carla have it? Carla wouldn't have extras. I gave mine to Tom.

DR. ANSELL: Okay, we have one.

DR. MARKS: Do you want to look through it? Did you get to skim it or not?

DR. WYATT: I can just --

MS. FIUME: I know it. Yeah.

DR. MARKS: You know it.

DR. WYATT: I could just do the cursory look.

DR. HILL: Because it's not on the website yet, right? You got a phone, you could take a picture of it.

DR. MARKS: Again, Dr. Zhu was -- did you get to read the memo?

DR. ZHU: Yes.

DR. MARKS: Is there any comments the way you're going to change the boilerplate? I guess it's -- I'm not sure. I guess the boilerplate or at least an epidemiology update. Was there anything in the memo that you specifically --

DR. ZHU: The comment on the paper 2017, Dianatinasab paper; so, this comment indicated that the word, you know, risk should not be used. Instead use the association. Actually, the risk word, this word, risk, is used by the author in the paper. So, I just quote that.

But actually, I agree that we can use the word association instead of risk. Because, you know, in this paper there are multiple disparate factors has been compared. I think the -- because some of them shows a positive result; some of them shows a negative result. In our document, I agree that we use association instead of risk.

And I agree, you know, in the Table 1, we should correct that -- that should be prostate cancer instead of breast cancer. And also, I agree that in Dr. Naldi's write-up of the 2015 paper, because this here it indicated that when the odds ratio for more than 19 hair dye episodes used, that information has not been included in our Table 1. We should include that into our Table 1. Yeah.

And also, the comment on Dr. Naldi's write-up of the Mendelsohn 2019 paper; yes, I think Dr. Naldi just did not say clearly here, that -- but that should be corrected in our revised version about the three years use of the hair dye survey; that information can be updated. And several other things, you know --

DR. MARKS: Okay. Tom, any comments? You still like any -- and these changes suggested in the memo, they're fine?

DR. SHANK: Yeah. The editorial changes.

DR. SLAGA: Minor, yeah.

DR. MARKS: Yeah, they're fine. I think the bottom line is when I read -- and that's not yellow, but I want to be sure, Tom, Ron and Ron, you're fine with this. The conclusion is, the CIR expert panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer, based on the lack of strength of the associations and inconsistencies of the findings.

In addition, the panel noted there was no consistent pattern of genotype/phenotype influences on hair dye, epidemiology findings. These new studies all support, still, that conclusion.

DR. SLAGA: Yeah.

DR. MARKS: Okay. Because that's the bottom line for this. Okay, any other comments?

DR. SHANK: I don't see how they'll ever show an association between something like

hair dye use and adverse health effect.

DR. SLAGA: Yeah, even if it's a specific --

DR. SHANK: You have to do individual -- they're not all the same.

DR. MARKS: Right.

DR. SHANK: And until you do a quantitative study, on particular dyes, you really have a very slim chance of coming up with a significant association. Not that there is or isn't one, it's just there's no power to the analysis.

DR. HELDRETH: I think that's probably what the casual reader wouldn't conclude. They would wonder, okay here's all these studies and we don't think it's a problem. But I think the explanation you just gave would be a great addition, I think, to the document. I think that would make it clearer.

But it's up to you whether or not we should make that kind of addition. Because I think there's a couple instances, throughout the document, where it says further study may be warranted. But as you mentioned, the study's probably not possible.

DR. SHANK: Right.

DR. SLAGA: You'd never have enough with one specific hair dye.

DR. SHANK: Would you be willing to put that kind of statement in the hair dye epidemiology -- what do we call this -- paper? It's up to us?

DR. HELDRETH: It's up to you.

DR. MARKS: Document. That's what the -- Jinqiu? Am I saying that correct?

DR. ZHU: Yes.

DR. MARKS: Jinqiu, that's what he has. Hair dye epidemiology document. So, it's a document.

DR. SHANK: Document.

DR. MARKS: So, it's already now in the minutes for public consumption. It's not a matter of -- the question is, do you think it should be explicitly put in this document? That's very interesting. And would that help guide future epidemiologists in terms of trying to really determine.

DR. SHANK: Well, doing more studies like this, even with genetic markers -- there's one that had interesting genetic markers -- is not going to give you the scientific power to identify which dye.

It's not hair dye use that's going to cause cancer; it's particular hair dye that could. And if you lump them all together, with no quantitation or very little quantitation --

DR. SLAGA: Well, you have the delusion effect of bringing them all together, too.

DR. ANSELL: I don't think we are directing research. I think -- and Linda's clearly the expert here, but I think our process has been to continue to monitor the research and to make it available to you guys. I think your point's well taken, but none of us are actually running a research program.

I don't know how we would even -- what we would do, just send it into the ether, saying we think this would be type of study --

DR. SHANK: We can dictate studies. Every time I read further studies are recommended, I kind of cringe. Because these are extremely expensive studies. Epidemiology is not cheap.

And if you start off, really, with a very poor chance of coming up with a meaningful association, it's money not well spent. But I don't think we can say that in our document.

DR. SLAGA: We can't dictate that.

DR. ANSELL: Nor would you suggest that we stop our monitoring and reporting?

DR. SLAGA: No. No.

DR. SHANK: We should continue to monitor; I did not mean that. But I don't like recommending more studies.

DR. ANSELL: Okay.

DR. MARKS: And I think that's an important point. Because if we recommend more studies, then we should give what we think the studies may be. If I understood what you said, Ron Shank, correctly. If we're going to identify any cancer potential, it needs to be for specific dyes, not in a general --

DR. ANSELL: But we don't say that, do we, in our summaries; that we recommend additional studies?

MS. LORETZ: Oh, no. No.

DR. ANSELL: Our roll, or what we've taken on as our responsibility, is to continually monitor the research as it's being done with all of its bumps and bruises. And just make the panel aware that -- I think there was a specific study, which Don wanted to have an expect look at, and he's provided his comments.

DR. SLAGA: Yeah. I mean, no and that's important in itself.

MS. LORETZ: So, this gets revised then? I mean, and then what happens next? Or is there another comment period? Or how does that work?

DR. HELDRETH: If there's going to be substantive changes to it. If it's something as simple as changing the verbiage or put the relevant study back in the table, where it was before, and nothing's really changing and the conclusion's not changing, the panel can say go ahead with those changes and it's fine. But if you want to add some verbiage that's a substantive change, then, sure, we would want to put it out there for public comment again.

DR. MARKS: I think, addressing Ron, we do say if we use this document as such. If you look on page 9, just as Ron said, it's in the yellow highlighting right above genetic polymorphism.

The last sentence. "While these findings do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted." And that's exactly what Ron is talking about.

I think, Ron, the question is, do we want to keep that sentence or eliminate that one. Because that's exactly what you were talking about.

DR. SHANK: It's almost the standard statement, more research is needed. Every scientist says that because --

DR. MARKS: That's how they keep busy.

DR. SLAGA: That's how you get money.

DR. SHANK: I had to stop midsentence on that.

DR. MARKS: Yeah, I know. But I'll finish it.

DR. SLAGA: I don't want Ron on my review committee if I submit an epidemiological study on hair dyes.

DR. HILL: Well, but it is a policy question, and this is something off -- it's on the record, but it's off the record. Is do you spend a lot of money on an epidemiology study; or is it better to go at it from the other direction. Okay, we have this mechanism, is there any connection to a dye that's being used, potentially.

You know, and to me, you spend the money on the biology, in general, keep the

epidemiology cooking maybe; but the only one that I ever saw even a whiff was for about 10,000 professional hair dressers in China. And there wasn't still not statistical power, but a whiff of something that makes some sense. And that was the best I've seen in all of it.

DR. MARKS: So again, just to continue beating this horse, on Page 5, right above lymphoma and leukemia, again, while Tai et al. findings are limited and do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted.

We're back with ending a lot of these by saying, well it didn't show anything, but do more investigations. I shouldn't say it didn't show anything, it didn't support a causal relationship. Do we want to just eliminate those parts of this document that says further investigation? We know they're going to be further investigation.

DR. SLAGA: It's followed by maybe, so it's okay.

DR. MARKS: Yeah, maybe.

DR. SHANK: It doesn't say epidemiological investigations. But keep looking for --

DR. MARKS: Further investigations. Yeah, that's true.

DR. SHANK: Keep looking for any risk.

DR. MARKS: Okay. No, I think --

DR. ANSELL: I also think there's a difference between reporting that the author has concluded versus the panel recommends.

DR. MARKS: Right.

DR. ANSELL: And so, this is, well his finding are limited, so who is saying additional data here?

DR. HELDRETH: We are. That was the verbiage -- we were following up with what Dr. Naldi was saying. And so, we characterized it in the way that he had. And he makes those kinds of statements throughout, further should be done.

DR. ANSELL: So, I think we could change that.

DR. MARKS: Well, I don't know that we need to change it, because I think Ron's comment that when you say further investigation, that leave it wide open, not necessarily epidemiologic investigation.

DR. SHANK: That's right.

DR. MARKS: I think I like the way you interpret that. I think leaving it in, from my mind is fine. If that's okay with Ron, Tom and Ron.

DR. SHANK: It is with me.

DR. HILL: It is me, too; because I think investigation means if there really is -- I mean, you make the hypothesis there really is something and then try to figure out if there's mechanism. And of all the things society spends money on, to me, science should be more and other things less. There's never enough science.

DR. MARKS: Okay. We're going to be seconding, probably, I would think, a proposal to post this revised draft hair dye epidemiology document on the website. And we like the way it is, and our minutes will capture the nuances about doing epidemiologic studies on specific dyes, not general dye exposure. And that further investigations covers the waterfront.

DR. HILL: We did see something interesting from a presenter -- not the last meeting, but I think the meeting before -- that looked at differences between light colored hair dyes, certain exposures, versus dark ones. I thought that was an example of, that's interesting now let's see what that means.

DR. MARKS: Okay. Any further comments? Thank you Jinqiu. The J is like a Z?

Jinqiu.

DR. ZHU: Yes.

DR. MARKS: Good. You're going to educate me. I apologize for my ignorance.

DR. HELDRETH: He's also told us in house that we can call him James. So, if that's easier.

DR. MARKS: James.

DR. SLAGA: What was that? I didn't hear.

DR. HELDRETH: Oh, he also told us in house, instead, we can just call him James if we want to.

DR. SLAGA: James?

DR. HELDRETH: Yes.

DR. MARKS: I may revert to that in the next meeting if I can't remember. I mean it's just knowing how to -- the J is a Z. Jinqiu.

DR. ZHU: Jinqiu.

DR. MARKS: Jinqiu. Okay. Thank you for tolerating us. Okay, we've got a little less than 15 minutes to go to lunch. We can do the next one. This is straight forward, right?

DR. SHANK: Sure.

DR. MARKS: Yeah, sure is right. Well, it's only one ingredient, correct?

DR. SHANK: Yeah.

Day 2 of the June 4-5, 2018 CIR Expert Panel Meeting – Full Panel

DR. BELSITO: First of all, we liked the council's suggestion that these boilerplates be referred to as resource documents, going into the future; we like that terminology. In terms of the hair dye resources document, Dr. Naldi did some analysis, particularly on the new information that had come in regarding associations between hair dye use and breast cancer, particularly in African American women, and we appreciate that very much.

There were two additional studies that were available, subsequent to his analysis, that we would request that he relook at. And there was also concern, particularly from the Consumer Federation of America, with his last sentence that says, "While these findings do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted." And, therefore, I think a request should go back to Dr. Naldi as to clarifying that statement and what kind of investigations would be needed to try and resolve this question.

DR. BERGFELD: I'm sorry to interject, but being in your team meeting yesterday, was there also a suggestion of reformatting this document?

DR. BELSITO: Yes, that has to do with reformatting; the fact that the conclusion is stated up front rather than at the end and having -- we agreed that there can be discussion at each endpoint in terms of the cancers looked at, as to our assessment of the data that has been presented in terms of whether there is risk or not. But then at the end of the document there should be a final conclusion rendered, rather than the conclusion up front.

DR. BERGFELD: Thank you. Any comments. Dr. Marks?

DR. MARKS: Yeah, Ron Shank, I think had a pithy comment yesterday. Rather than me try and paraphrase it, Ron was referring to the epidemiologic studies as I understand. And as long as

they're done with multiple dye exposures, it's hard to come to a conclusion. That really needs to be with a specific dye.

And that, actually, we thought that further investigations was not a bad -- maybe clarify it -- but how we interpreted that is it covers all science and all toxicity. So, as we get more mechanistically driven, those would be the studies that probably would help us move forward. But Ron, please clarify what I think I heard you say.

DR. SHANK: You said it right. I think when you do epidemiological studies, such as been done in the past, where you're having a very broad sweep of the cost of agent, hair dyes, that's way to general to give any power to the epidemiological study, to come up with an association. And future studies should focus on particular hair dye. And there're many of them so this is probably going to be very difficult to achieve. So, when we say more studies should be done, I think what we mean, more studies but not just epidemiological studies.

Basically, that was it; that I thought the CIR panel should continue to monitor new information that comes out. But I don't think we should say there should more epidemiological studies, in particular, more investigations.

DR. SNYDER: Can we use language along the effect that these are largely observations, and that the cause and effect remains to be determined? Something along that line, rather than specify studies. We just say that the cause and effect remains to be determined.

DR. SHANK: Yes. Thank you.

DR. BERGFELD: There was some suggestion yesterday that we -- in the formatting of this particular resource document and perhaps the innovation one as well, in some other white hat kinds of statements that we've made -- that we put them together similar to how we put our ingredients reports together. With an abstract, what's been considered, and then the fill-in parts, as well as then a discussion and a conclusion. And I think that would be a better reading document.

Because this one left me particularly cold; what else is new kind of thing. All right. Well I think that we'll move forward with that. We don't need to have any vote on that, do we?

DR. HELDRETH: I don't believe so.

DR. BERGFELD: No, I don't think so.

DR. HELDRETH: Going forward Jinqiu will go through and make these sorts of edits, and reformat the document, and then it will come back to the panel again for finalization.

DR. BERGFELD: I think that you were going to also contact Dr. Naldi, and request what from him?

DR. HELDRETH: From Dr. Naldi we'll be requesting his outlook on what is meant by further investigations; and to have him look at the two studies that were discovered after he did his analysis.

COSMETIC INGREDIENT REVIEW

CIR Resource Document

Hair Dye Epidemiology
-Review Draft-

12/2018

BACKGROUND

Hair dyes may be broadly grouped into oxidative (permanent) and direct (semi-permanent) dyes. The oxidative dyes consist of precursors mixed with developers to produce color, while direct dyes consist of preformed colors. Epidemiology studies that seek to determine links, if any, between hair dye use and disease provide broad information and have been considered by the Cosmetic Ingredient Review (CIR) Expert Panel (Panel), although these studies do not specifically address the safety of individual hair dye ingredients.

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

The Panel considers that epidemiological studies, based on better information about exposure, can provide more useful findings than other such studies. According to one study, exposure assessments in hair dye epidemiology studies ranged from minimal information (e.g., ever/never use) to subject-recalled information on type, color, duration and frequency of use.² A scale from + to ++++ has been developed to rate the quality of hair dye exposure assessments in hair dye epidemiology studies, as shown below. This scale was used to score the studies that are summarized in Table 1.

+: Assessed ever/never use;

++: Assessed the type of hair dye, *or* dye type plus dye color or duration, *or* with information on two or three other factors (color, frequency, duration), but no information on type;

+++: Assessed dye type, color, *and* frequency *or* duration of use;

++++: Assessed all four critical aspects: hair dye type, color, duration, and frequency of use

An International Agency for Research on Cancer (IARC) working group summarized the relevant epidemiology studies and observations on breast, bladder and hematological cancers.^{1,3} The working group concluded that the animal studies provided limited evidence for the carcinogenicity of hair colorants, and the data are of insufficient quality, consistency, or statistical power to establish the presence or absence of a causal link between personal use of hair dyes and cancer. In addition, occupational exposure during work as a hairdresser, barber, or beautician was assessed. The working group found that exposures from these occupations are probably carcinogenic, based on limited evidence of increased risk for bladder cancer in hair dressers and barbers. However, occupational safety is outside the scope of the work of the Panel.

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

The following provides a brief summary of many relevant epidemiological studies that have been published since about 2010, as well as older epidemiological studies that were included in comprehensive reviews, such as that published by the IARC in 2010¹.

STUDY SUMMARY

Bladder Cancer

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

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

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

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

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

Prostate Cancer

A hospital-based case-control study was conducted among prostate cancer cases in Taiwan, involving 296 cases with newly diagnosed prostate cancer and 296 age-, ethnicity-, and hospital-matched controls. Information on hair dye use was obtained through a standardized questionnaire.¹⁰ The evaluation of hair dye exposure was ++ on the Rollison et al. (2006) scale. The prevalence of hair dye use was higher in the cases than the controls (95/296 = 32.1% vs. 64/296 = 21.6%, $p < 0.05$), and the hair dye users had increased odds of prostate cancer when compared with the non-users (adjusted OR 2.15; 95% CI 1.32–3.57). The study found personal hair dye use increased risk of prostate cancer with a dose-response effect. Meanwhile, to determine the rate of prostate cancer survival, another 608 incident prostate cancer cases were investigated. Of the 608 cases, 26.4% (161/608) reported having used hair dyes. The use of hair dye did not affect cumulative incidence estimates of prostate cancer-specific deaths ($p=0.753$).

This report was the first to show a positive association between personal hair dye use and risk of prostate cancer, revealing a dose-response relationship assessed by duration and frequency; however, cumulative exposure dose, a critical indicator to estimate a dose-response effect, was not assessed. The external validity of this study has been questioned.¹¹ Other studies targeted on hairdressers observed no increased risk of prostate cancer.¹² While Tai et al.'s findings are limited and do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted.

Lymphoma and Leukemia

A meta-analysis of 20 case-control studies of leukemia has been performed in 2017.¹³ The RRs for the associated risk of leukemia were: with permanent hair dye use RR = 1.19 (95% CI 1.07–1.33), with dark hair dye use RR = 1.29 (95% CI 1.11–1.50), with hair dye use among males RR = 1.42 (95% CI: 1.01–2.00), with hair dye use pre-1980 RR = 1.49 (95% CI: 1.21–1.83), and with hair dye use for longer than 15 years RR = 1.35 (95% CI: 1.13–1.62). Overall, findings suggest that ever use of hair dye is not a significant risk factor for leukemia.

A population-based case-control study was conducted to evaluate whether the hair dye use influenced the risk of leukemia and non-Hodgkin's lymphoma (NHL) in Italy.¹⁴ The analysis was restricted to women in the population studies because too few of the men reported any hair dye use. There were 161 cases (120 lymphoid and 41 myeloid) and 84 controls among the women. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale, because only duration of hair dye use < 15 years vs. ≥ 15 years was evaluated. In a multivariate analysis, the OR was 2.3 (95% CI 1.0-4.9), with $p = 0.036$ for a trend, for NHL in women using hair dye for at least 15 years. No association was found between lymphoid malignancies and tobacco smoking or the consumption of alcoholic beverages in this study.

A meta-analysis of 19 case-control studies of NHL subtypes was conducted, focusing on follicular lymphoma (FL).¹⁵ No associations between FL and hair dye use type, duration, or frequency were found in this study, except for a modest increase in women who used hair dyes before 1980 (OR = 1.4; 95% CI 1.10-1.78). Many oxidative hair dye products were reformulated in the early 1980s in the US to eliminate ingredients that produced tumors in animal bioassays.¹⁶ In comparison, the risk of FL in women was associated with current cigarette smoking, trending higher with increasing duration of smoking.

Another meta-analysis of 19 case-control studies of NHL subtypes was performed, focusing on diffuse large B-cell lymphoma (DLBCL).¹⁷ There were no overall and sex- or age-specific associations between DLBCL and hair dye use, based on the basic adjusted model results of this study. The OR for mediastinal DLBCL was 4.97 (95% CI 1.63-15.15) for use of hair dyes for at least 20 years, compared with never used hair dyes. Using hair dyes for at least 20 years was not associated with DLBCL at other anatomical sites, including the central nervous system (CNS), testis, gastrointestinal tract, and skin. Use of hair dyes for less than 20 years was not associated with DLBCL at any site. In comparison, smoking was associated with CNS, testicular and cutaneous DLBCLs in this study.

A hospital-based case-control study was conducted to investigate the hair dye use in the etiology of leukemia and lymphoma in Egypt.¹⁸ There were 130 cases, including 23 cases of chronic lymphocytic leukemia (CLL) and 107 cases of NHL, and 130 age- and sex-matched controls. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale. In a univariate analysis, no statistically significant association was found between these lymphoproliferative disorders and history of using hair dyes, family history of cancer, exposure to X-rays, or smoking (χ^2 , $p > 0.05$).

A hospital-based case-control study of myelodysplastic syndromes (MDSs) was performed in China.¹⁹ There were 403 cases and 806 controls, and the evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. In a univariate analysis, the OR for hair dye use (≥ 2 times per year) and all MDSs was 1.46 (95% CI 1.03-2.07). In a multivariate analysis performed to adjust for potential confounding factors, the OR was not statistically significant (OR 1.31; 95% CI 0.88-1.93). In comparison, smoking was associated with the development of MDSs in the univariate analysis and with refractory anemia with excess blasts (RAEB) in both the univariate and multivariate analyses.

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

Tissue samples from a NHL case-control study in males from Iowa and Minnesota were subjected to re-evaluation using FISH (fluorescence in situ hybridization) cytogenetic technique to examine both $t(14;18)$ -positive and $t(14;18)$ -negative NHL subtypes and IHC (immunohistochemistry) assays to evaluate expression of the anti-apoptotic protein bcl-2.²¹ There were 8 $t(14;18)$ -positive, 12 $t(14;18)$ -negative, 20 bcl-2 positive, and 4 bcl-2 negative NHL cases and 58 control subjects in the subpopulation tested (i.e., men having used hair dye at least once a month for at least one year, or occupational exposure to hair dyes on any job held for at least a year). The evaluation of hair dye exposure scored + on the Rollison et al. (2006) scale. Adjusting for age, state and proxy status (i.e., whether or not next-of-kin proxies were interviewed), a statistically-significant association between ever/never use of hair dyes and $t(14;18)$ -negative NHL (OR 2.9; 95% CI 1.6-5.0) and bcl-2 positive NHL (OR 2.2; 95% CI 1.4-3.4), but not with $t(14;18)$ -positive NHL (OR 1.3; 95% CI 0.6-2.6) or bcl-2 negative NHL (OR 1.4; 95% CI 0.5-3.8). Similarly, smoking was associated with $t(14;18)$ -negative NHL, but not clearly associated with $t(14;18)$ -positive NHL, bcl-2 negative NHL, or bcl-2 positive NHL in this study.

A hospital-based case-control study of acute myeloid leukemia (AML) was conducted in Shanghai.²² The investigation consisted of 722 newly diagnosed AML cases and 1444 individually gender-age-matched patient controls at 29 hospitals in Shanghai. The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. There was no increase in the risk of AML and personal use of hair dyes; The OR was 0.98 (95% CI 0.8-1.2). In contrast, there was an

association between AML and smoking, particularly among the male subjects, as well as alcohol consumption and a low level of education in this study.

Glioma

A meta-analysis including 4 case-control and 2 cohort studies of personal was conducted to investigate the hair dye use and the incidence of gliomas.²³ Matching or adjustment for age and sex was performed in all 6 studies included in this meta-analysis, and for smoking in 2 of the 6 studies. The most adjusted risk estimates were included, and the raw data were used when adjusted estimates were not available. Summary RRs for ever use of any hair dyes were 1.132 (95% CI 0.887-1.446) for all studies, 1.291 (95% CI 0.937-1.777) for case-control studies, and 0.903 (95% CI 0.774-1.054) for cohort studies. Similar results were obtained when the subjects were stratified by geographic regions and sex. No significant associations were found among the studies that evaluated permanent hair dye use and duration of any hair dye use.

Breast Cancer

In a case-control study conducted in the metropolitan New York City area and in ten counties in New Jersey (NJ), involving both African Americans and White women, breast cancer cases were identified by multiple sources, including hospital charts and NJ cancer registry.²⁴ The subjects were 1508 African American and 772 European American cases (52.0±10.7 and 52.0±10.0 years old, respectively) and 1290 African American and 715 European American age- and county-matched control subjects (50.9±10.3 and 49.8±8.7 years old, respectively). The evaluation of hair dye exposure was ++++ on the Rollison et al. (2006) scale. Final OR estimates were adjusted by age, education, body mass index, family history of breast cancer, and oral contraceptive use. In the control group, about 30% of African Americans and 58% of Whites reported regular use of hair dyes. Overall, ever use of hair dyes and duration of use were not significantly associated with increased cancer risk in both African Americans and Whites. Among African Americans, an increased risk of breast cancer was documented for the use of dark hair dye shades, and for salon application of dyes, adjusted OR being 1.51 (95% CI, 1.20-1.9) and 1.26 (95% CI, 1.00-1.58), respectively. In Whites, an increased risk was documented for dual use of relaxers and hair dyes with OR 2.40 (95% CI 1.35-4.27), the wide CI reflecting the limited number of exposed women. When considering the estrogen receptor status of cancer, the risk of estrogen positive breast cancer was increased in African Americans with a higher frequency of hair dye use (OR 1.36, 95% CI 1.01-1.84) and in Whites with the use of dark hair dye shades (OR 1.54, 95% CI, 1.01-2.33). These differences in risk profile between African Americans and Whites are not easy to reconcile. They may reflect different patterns of use, or represent chance effects due to multiple testing. In this study, women who started using hair dyes before 1980 were not distinguished from women who started in 1980 or thereafter. Replication of results by an independent study is needed. Ideally, such a study should be able to ascertain the type of hair dye product used and its timing of use.

A population based case-control study in Finland recruited a total of 6,567 breast cancer patients diagnosed between 2000 and 2007 and 21,598 age-matched controls.²⁵ The evaluation of hair dye exposure was a +++ on the Rollison et al. (2006) scale. The recruitment of patients was based on a nation-wide cancer registry covering almost 100% of solid tumors. The exposure of primary interest was the use of hair dyes with detailed information on the cumulative lifetime number of hair dye episodes, age at first use, and the types of dyes used. When calculating ORs, potential confounding factors, namely parity, age at first birth, family history of breast cancer, menarche age, use of hormonal contraceptives, physical activity, alcohol use, body mass index and education, were included in a stepwise regression model. Bias-adjusted ORs were calculated as well. A large proportion of women reported ever use of hair dye products, with rates increasing from 84% in women born before 1950 up to 92% in women born in or after 1960. The odds of breast cancer were significantly increased when comparing ever vs never users of hair dyes (OR 1.23, 95% CI: 1.11–1.36).

Early age at first dye (20 - 29 years) was associated with higher odds of breast cancer when compared to late age at first dye (40 years or later) (OR 1.14, 95% CI: 1.05–1.25). When considering ever use vs. non-use, the ORs were increased with all the different types of hair dyes, the highest estimates being obtained for women who reported to have used temporary and/or semi-permanent dyes, ORs being 1.32 (95% CI: 1.16 - 1.52) and 1.31 (95% CI: 1.17 - 1.46), respectively. Latency of effect was suggested by the fact that the OR for cumulative hair dye use was the highest among women born between 1950 and 1959. When considering the cumulative number of hair dye episodes, the OR ranged from 1.07 (1 - 2 dye episodes) to 1.28 (10 - 34 dye episodes) and 1.31 (35 - 89 dye episodes), and then decreased to 1.25 (≥ 90 dye episodes). The ORs did not change when smoking was included in the multivariate analysis.

One meta-analysis summarized results of studies conducted from 1966 up to 2005,¹² and included 12 case-control studies, which involved a total of 5019 cases and 8486 controls, and 2 cohort studies which recruited a total of 1135 incident cases of breast cancer. The pooled RR of breast cancer was 1.06 (95% CI 0.95-1.18) and nonsignificant when comparing ever use vs. never use of hair dyes. No significant increased risk was documented when considering intensive exposure or

restricting analyses to the use of permanent dyes only. It is noted that, giving the largely prevalent use of hair dyes in the population, frequency of use rather than simple distinction between users and nonusers, would be relevant to consider.

In a cohort study conducted in the framework of the Shanghai Women's Health Study, a total of 75221 women completed a baseline survey between 1996 and 2000 and were followed up to 2005.²⁶ A total of 358 incident cases of breast cancer were identified. In the sample, 29076 women (39.6%) reported ever using hair dye and a total of 358 incident cases of breast cancer were identified. The average number of person years was 7.31. The RR for breast cancer in hair dye users vs non-users, adjusted by age, education and smoking, was 0.93 (95% CI 0.78-1.09). No relation was documented between duration of hair dye use and risk of cancer. Stratification by menopausal status indicated no association between breast cancer and hair dye use in either pre- or post-menopausal women. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale.

A case-control study was conducted, including 191 breast cancer patients interviewed in a hospital in 1975 - 1976 in Oxford, UK, with 561 aged matched controls without cancer (within three years), marital status, and social class.²⁷ The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. Seventy-three cases and 213 controls had used permanent or semi-permanent hair dyes, giving an RR of 1.01. There was no evidence of an increasing risk for breast cancer with increasing duration of use of hair dyes or with use beginning more than four or more than nine years before diagnosis.

A case-control study consists of 50 breast cancer patients at a cancer treatment center with 100 hospitalized controls in London, Ontario, and 35 breast cancer cases with 70 neighborhood controls in Toronto, Ontario.²⁸ The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. The RRs for breast cancer from use of permanent hair dyes (at any time) were 1.3 (95% CI 0.6-2.5) in London and 1.1 (0.5-2.4) in Toronto. Further statistical analyses, allowing for smoking habits, family history of cancer and age at first birth, showed no significant relationship between hair-dye use and breast cancer incidence.

A case control study was performed among 398 breast cancer patients at a screening center between 1977 and 1981 in New York City, with 90 randomly selected, age matched controls.²⁹ The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. The OR for breast cancer from use of permanent hair dyes (at any time) was 0.8 (95% CI 0.6-1.1). There was also no evidence of a trend in risk with increasing number of hair dye uses (38% of the subjects had used hair dye at least 100 times, while 77% had used hair dyes at least once). An analysis of breast cancer risk from 5 or more years of work as a beautician was also compared. Although personal hair dye use was unrelated to breast cancer risk, the OR for beauticians was 3.0 (95% CI 1.1-7.8).

A hospital-based case-control study of breast cancer was conducted on 1052 women in Iran.⁴⁴ The evaluation of hair dye exposure was + on the Rollison et al. (2006) scale. There were 526 newly diagnosed breast cancer cases, with 526 age-matched controls randomly selected in Namazi Hospital between November 2014 and March 2016. The study showed that multiple factors were associated with the risk of breast cancer, such as hair coloring, age at first delivery, stress, and smoking. The OR of breast cancer from hair dye use on a regular basis compared to no use was 1.93 (95% CI, 1.41-2.62). However, the design the design of the study was not able to confirm a causal association between any investigated variables and breast cancer.

A meta-analysis was performed to investigate the association between hair dye use and breast cancer, including 8 case-control studies published between 1980 and 2017 with a total of 38037 participants.⁴³ In comparison, 5 perspective studies were excluded for various reasons: hazard ratio (HR) instead of an OR/RR was used, the death rate instead of cancer incidence was recorded, no information on the number of controls was provided, and the study had a high focus on other types of cancer. In addition, there was no significant correlation between the use of hair dye and incidence of/death from breast cancer in all five prospective studies. Using a random effects model the pooled RR for women using hair dyes was 1.18 (95% CI 1.03-1.37), which indicates an 18.8% increased risk of future development of breast cancer among hair dye users. However, the authors also stated that the reliability of this systematic analysis had decreased due to the large number of excluded prospective studies.

Genetic Polymorphisms

NAT1, NAT2, GSTM1, and GSTT1 Genotype/Phenotype

Altered genotype and phenotype of liver enzymes may activate or inactivate potential carcinogens.⁸ NAT1 and NAT2 genes encode arylamine *N*-acetyltransferases that can deactivate (or, less commonly, potentially activate) arylamine and hydrazine chemicals. Polymorphisms in these genes determine, in part, the liver-function phenotypes. Human populations segregate into rapid, intermediate, and slow acetylator phenotypes. *N*-acetylation is a major route of biotransformation of aromatic amine compounds, including those found in hair dyes. The GSTM1 gene encodes a

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

In one study, the association between hair dye use and effect modification by NAT1, NAT2, GSTM1, and GSTT1 genotypes was evaluated among patients with bladder cancer. The hair dye models were adjusted for age, race, sex, and smoking status. An increased risk of bladder cancer was reported primarily among exclusive users of permanent dyes who had NAT2 slow-acetylation phenotypes, compared to never users of dye with NAT2 rapid/intermediate-acetylation phenotypes. This increase was observed in females with a college degree, but the difference was not statistically significant. The authors concluded that NAT1, GSTM1, and GSTT1 genotypes did not appear to be important modifiers of the association between ever, permanent, or exclusive permanent hair dye use and bladder cancer.

One study reported that individuals with the NAT2 slow-acetylator phenotype who exclusively used permanent hair dyes had an increased risk of bladder cancer (OR 2.9; 95% CI 1.3-7.5) after adjustment for cigarette smoking, compared to individuals with the NAT2 rapid-acetylator phenotypes (OR 1.3; 95% CI 0.6-2.8).⁴⁵ The NAT*10 allele contains an altered polyadenylation signal that has been associated with elevated DNA adduct levels and greater risk of bladder cancer in other studies. Individuals with a NAT1*10 genotype who were non-smokers and used permanent hair dyes exclusively had an OR of 1.0 (95% CI 0.2-4.3), and those with a non-NAT1*10 genotype had an OR of 6.8 (95% CI 1.7-27.4) in this study.

A case-control study that evaluated the association of hair dye use with bladder cancer among females also examined the effect of hair-dye use among genetic subgroups.⁴⁶ ORs were estimated after adjustment for age, region, and smoking. No statistically significant differences in bladder cancer incidence were noted as a function of any of the genotypes examined, including those with slow- or intermediate/rapid-NAT2 acetylator phenotypes. For NAT2 slow-acetylator phenotypes, the OR was 0.6 (95% CI 0.3-1.4), and for NAT2 rapid/intermediate phenotypes, the OR was 0.9 (95% CI 0.3-2.6). Individuals with a NAT1*10 genotype had an OR of 2.9 (95% CI 0.7-11.6), and those with non-NAT1*10 had an OR of 0.6 (95% CI 0.2-1.6). These findings were directionally opposite to those of Gago-Dominguez et al. (2003).⁴⁵

A population-based case-control study was conducted to explore the relationship between hair dye use and the incidence of NHL.⁴⁷ The evaluation of hair dye exposure was ++ on the Rollison et al. (2006) scale. Subjects were identified among residents of 4 Surveillance Epidemiology and End Results (SEER) registries (Iowa, Los Angeles County, and metropolitan Detroit and Seattle). There were 101 cases and 98 control subjects reporting no use of hair coloring products and 509 cases and 413 control subjects among the women reporting use of such products, in the population studied. There were 317 cases and 269 control subjects reporting the use of hair dyes before 1980 and 192 cases and 148 controls reporting hair dye use in 1980 or thereafter. The risk estimates were adjusted for age, sex, race and SEER area; education, smoking status, history of farming, having a first-degree relative with a history of NHL or lymphoproliferative malignancy were excluded from the final models because these factors did not materially alter (> 10%) the parameter estimates.

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

One study re-evaluated data from a case-control study of NHL in Connecticut to consider NAT1 and NAT2 genotype/phenotype and 17 other single nucleotide polymorphisms (SNPs).^{48,49} The subjects, including 461 cases and 535 control subjects, were identified from the Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource (RCASR). Potentially confounding variables included in the final model were age and race. Adjustment for cigarette smoking, alcohol consumption, and farming history were not included in the final models because these factors did not materially alter the parameter estimates. The evaluation of hair dye exposure was ++ on the Rollison et al. (2006) scale.

With the exception of FL, none of the different individual genes examined was associated with a statistically-significant change in the risk of NHL for any of the NHL subtypes considered. The exception was a statistically-significant increase in the risk of FL in women with rapid/intermediate NAT2 phenotypes who started to use hair dye before 1980, compared with women who never used hair dye (OR 2.8; 95% CI 1.1-7.2; 24 rapid/intermediate acetylator cases vs. 79 control subjects). In women who carried the CYP2C9 allele (TT or CT genotypes) and started to use hair dyes before 1980, there was an increased risk of NHL in general (OR 2.9; 95% CI 1.4-6.1; 58 cases, 43 control subjects) and the follicular lymphoma subtype specifically (OR 6.3; 95% CI 1.6-24.7; 20 cases, 43 control subjects), compared with women who never

used hair dyes and women who started using hair dyes in 1980 or thereafter. No association evident in women who carried the CYP2C9 allele (TT or CT genotypes) and started using hair dyes in 1980 or thereafter (23 cases, 46 control subjects), compared with women who carried this allele and never used hair dyes (OR 1.0; 95% CI 0.4-2.3; 23 cases, 46 control subjects).

DNA Repair-Enzyme Genes

One study investigated the interaction between polymorphisms in DNA repair genes and hair dye use with NHL in a population-based case-control study in Connecticut.⁵⁰ The study population from which the subjects were drawn was the same as that of Zhang et al. (2009)⁴⁹ study summarized above, including 461 cases and 535 control subjects identified from the Yale Comprehensive Cancer Center's RCASR. The subjects included 518 NHL cases and 597 age-matched controls. All subjects were genotyped for 24 single nucleotide polymorphisms (SNPs) in 16 DNA repair-enzyme gene polymorphisms. The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale. All of the models were adjusted for age, race, and smoking status. The risk of FL, but not DLBCL, was statistically-significantly elevated in women with any one of 10 of the 24 SNPs and who used hair dye before 1980, compared to those who never used hair dyes; the ORs ranged from 1.93 (95% CI 1.00-3.72; 15 cases and 70 control subjects with EEC1rs3212961 CC) to 3.28 (95% CI 1.27-8.50; 7 cases and 110 control subjects with BRCA2rs144848 AC+CC). In addition, there was a statistically-significant interaction between hair dye use before 1980 and NHL in women with one of these 10 SNPs (1.88 (95% CI 1.26-2.80; 146 cases and 100 control subjects with WRNrs1346044 TT). There was no association between NHL, FL, or DLBCL in women who began using hair dyes after 1980.

DISCUSSION

The available evidence linking hair dye use and breast cancer is limited, but warrants further investigation. Two systematic reviews,^{12,43} three case-control studies,^{24,31,44} and one cohort study,²⁶ all published since 2004, were evaluated for relevance and validity by an external expert in the epidemiology field.³⁰ Strengths of the epidemiological studies include evaluation of a variety of populations, including those with exposure to dark hair colors. Limitations of some of the studies include lack of specificity for type of hair dyes used (oxidative versus non-oxidative) and details on color, type, or duration of use. In addition, it is worthy to note that formulations have changed over time, and they differ based on the region of the world in which they are produced and sold. Hence the specific product used and the timing of use should be better considered.

Based on the available human evidence, personal use of hair dyes is unlikely to be an important risk factor for breast cancer.³⁰ Given the limitations of the existing meta-analyses and the concerns on recent studies that pointed to an increased risk in different ethnic groups and populations, a further well-conducted meta-analysis is preferred to include the whole range of available studies (singly considered and weighted), and to use sensitivity analysis to assess the impact of the inclusion/exclusion of specific studies. In addition, further perspective investigations are warranted to determine whether a cause-effect relationship between hair dye use and breast cancer risk exists.

The ideal epidemiological study to investigate this risk would be a prospectively designed cohort study, requiring a large sample size of women who are undergoing breast screening procedures, with accurate background demographics data regarding important risk factors for breast cancer, such as previous breast biopsy, mammographic density, parity and age at puberty, hormone therapy history and the use of contraceptive pill, etc. At the outset of the study, use concentrations of all hair dye components that are considered potentially carcinogenic and mutagenic must be accurately recorded. Detailed information on exposure to hair dye must be collected following the "++++" scale aforementioned (i.e., assess all four critical aspects of hair dye use: hair dye type, color, duration, and frequency). The recruited subjects should not have previous history of cancer or have a high risk of breast cancer (e.g., BRCA1/2 mutation), and they must not be undergoing any radiotherapy or chemotherapy prior to enrollment. Furthermore, the required sample size should be at least 356,590 women, based on the assumptions of 1) an annual incidence rate of 200 per 100,000 female participants (aged 40 years or older), 2) a 35% exposure rate, and 3) a robust statistical analysis to detect a RR of 1.2 or 0.8 (80% statistical power and a 2-sided 5% significance level).⁴³ Moreover, a 5-year follow-up period, comparing women with newly diagnosed breast cancer with women not developing breast cancer, should be tracked. Sufficient statistical power would then be expected to answer questions related to the potential impact of personal use of hair dyes on breast cancer risk. As a cheaper and faster alternative, a large scale case control study can be envisaged in the same population, i.e., women undergoing breast cancer screening, comparing women with a new diagnosis of breast cancer with women without breast cancer and collecting retrospectively detailed information on lifetime exposure to hair dye products. Such a study should be best conducted in several countries with different baseline cancer risk and environmental diversity. The baseline category information must be accurately recorded and potential confounding factors must be accounted for in a multivariate analysis.

CONCLUSION

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

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

Study Type/Methodology	Results	Reference
<i>Bladder Cancer</i>		
Population-based case-control study in the Netherlands. Cases diagnosed between 1975 and 2009 for a total of 246 female cases with 2587 female controls; Analyses were not performed for the men selected for the study because less than 5% reported ever using hair dyes.	<p>No association between bladder cancer and ever/never use of permanent hair dyes – permanent OR 0.87 (95% CI 0.65-1.18); temporary OR 0.7 (95% CI 0.58-1.02)</p> <p>No association between bladder cancer and duration of use, number of times used per year, total number of times used over a lifetime, dying all the hair or only part of the hair, or dye color (none of the subjects reported use of black dye).</p> <p>No association found when patients stratified by aggressiveness of the cancer.</p>	Ros et al (2012) ⁷
<p>Population-based case-control study in Maine, Vermont, and New Hampshire. Cases diagnosed 2001 to 2004 for a total of 1193 cases (911 male and 282 female) with 1418 controls (1039 male and 378 female).</p> <p>Genotyping done for NAT2, NAT1, GSTM1, and GSTT1.</p>	<p>No association between ever/never use of hair dyes and bladder cancer – women OR 0.7 (95% CI 0.5-1.0); men OR 0.7 (95% CI 0.4-1.0).</p> <p>No association between hair dye use, NAT2 phenotype or NAT1 genotype and bladder cancer risk.</p> <p>Increased risk of bladder cancer with permanent hair dye use in a subgroup of women with a college degree, but no dose-response for color, duration of use, or total lifetime uses. NAT2 phenotype was associated with a suggestive, but not statistically significant, increased risk when college-degreed women were stratified by education – this was based on 15 cases and 6 controls.</p>	Koutros, et al. (2011) ⁸
Population-based case-control study of bladder cancer in Iran with 692 cases and 692 controls (identified using the Iranian cancer registry).	<p>Overall (male and female) OR for hair dye use and bladder cancer was 1.99 (95% CI 1.02-3.82).</p> <p>When women and men were analyzed separately, no significant association with hair dye use and bladder cancer was reported.</p>	Shakhssalim et al. (2010) ⁹
<i>Prostate Cancer</i>		
<p>Hospital-based case-control study of prostate cancer in Taiwan with 296 cases and 296 controls</p> <p>Another 608 incident prostate cancer cases were investigated to determine the rate of prostate cancer survival.</p>	<p>The prevalence of hair dye use was higher in the cases than the controls (95/296 = 32.1% vs. 64/296 = 21.6%, $p < 0.05$), and the hair dye users had increased odds of prostate cancer when compared with the non-users (adjusted OR 2.15; 95% CI 1.32–3.57). Personal hair dye use increased risk of prostate cancer with a dose-response effect.</p> <p>Of the 608 cases, 26.4% (161/608) reported having used hair dyes. The use of hair dye did not affect cumulative incidence estimates of prostate cancer-specific deaths ($p=0.753$).</p>	Tai et al. (2016) ¹⁰

<i>Lymphoma and Leukemia</i>		
Cohort or case-control study of leukemia in North America, Europe and Asia.	Multivariate analysis: Based on 20 studies, ever use of any type of personal hair dye was associated with a non-statistically significant increased risk of leukemia, when compared to no use of hair dye (meta-RR=1.09; 95% CI 0.97–1.22). A model restricted to case-control studies yielded a statistically significant increased RR of 1.13 (95% CI 1.00–1.28), while a model including cohort studies yielded an RR of 1.00 (95% CI 0.85–1.19). When restricted to studies that adjusted for smoking history, use of any hair dye was not associated with leukemia (RR= 0.99; 95% CI 0.76–1.29).	Towle et al. (2017) ¹³
Population-based case-control study of leukemia and non-Hodgkin's lymphoma (NHL) in Italy. There were 161 cases (120 lymphoid and 41 myeloid) and 84 randomly-selected controls among women in the population studied.	Multivariate analysis: Hair dye use for at least 15 years was associated with NHL (OR=2.3; 95% CI 1.0-4.9), but hair dye use for less than 15 years was not associated with NHL (OR=1.4; 95% CI 0.6-3.1). Leukemia was not associated with using hair dye for at least 15 years (OR=2.7; CI 0.9-7.9) or for less than 15 years (OR=2.7; CI 0.9-8.4).	Parodi et al. (2016) ¹⁴
Hospital-based case-control study of lymphoproliferative cancers in Egypt. There were 130 cases (107 NHL and 23 chronic lymphocytic leukemia) and 130 age- and sex-matched controls.	Multivariate analysis: No increase in the risk of lymphoproliferative disorders with history of using hair dyes (χ^2 , $p>0.05$).	Salem et al. (2014) ¹⁸
Hospital-based case-control study of myelodysplastic syndromes (MDS) in China. There were 403 cases and 806 controls.	Univariate analysis: OR for hair dye use (≥ 2 times per year) and all MDS was 1.46 (95% CI 1.03-2.07). Multivariate analysis: OR was 1.31 (95% CI 0.88-1.93).	Lv et al. (2010) ¹⁹
Hospital-based case-control study in Shanghai of NHL. There were 649 cases and 1298 controls	No increased risk of NHL, with an OR of 0.93 (95% CI 0.75-1.16). For chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), the authors reported a significantly lower risk associated with hair dye use with an OR of 0.37 (95% CI 0.18-0.76).	Wong et al. (2010) ²⁰
Re-evaluated tissue samples from an NHL case-control study in males from Iowa and Minnesota using FISH (fluorescence in situ hybridization) cytogenetic technique to evaluate both <i>t</i> -positive and <i>t</i> -negative NHL subtypes.	An association between ever/never use of hair dyes and <i>t</i> (14;18)-negative NHL (OR 2.9; 95% CI 1.6-5.0) and <i>bcl</i> -2 positive NHL (OR 2.2; 95% CI 1.4-3.4), but not with <i>t</i> (14;18)-positive NHL (OR 1.3; 95% CI 0.6-2.6) or <i>bcl</i> -2 negative NHL (OR 1.4; 95% CI 0.5-3.8).	Chang et al. (2010) ²¹
Hospital-based case-control study of acute myeloid leukemia (AML) in Shanghai, China. There were 722 cases and 1,444 controls.	No increase in the risk of AML with personal use of hair dyes; OR = 0.98 (95% CI 0.8-1.2).	Wong et al. (2009) ²²
<i>Breast Cancer</i>		
Population-based case-control study of breast cancer in African American and European American women in New York city and 10 counties in New Jersey. There were 1508 African American and 772 European American cases and 1290 African American and 715 European American frequency-matched (by age and county of residence) control subjects.	Increase in the odds of breast cancer in African American women who reported using dark permanent hair dyes (1.52; 95% CI 1.21-1.91), African American women who typically had their hair dyed in a salon (1.30; 95% CI 1.03-1.63), and European American women who had a history of both hair dyes and chemical hair relaxers (2.21; 95% CI 1.26-3.86). Women who started using hair dyes before 1980 were not distinguished from women who started in 1980 or thereafter.	Llanos et al. (2017) ²⁴
Population-based case-control study of breast cancer in Finland. There were 6,567 cases and 21,598 age-matched controls.	Increase in the odds of breast cancer in women who ever used hair dyes, compared with those who never used hair dyes (OR=1.28; 95% CI 1.10-1.48). Statistically significant trend in ORs for cumulative use of hair dyes (1.07 and 1.31 for 1-2 episodes and 35-89 episodes, respectively). In comparison, the OR decreased from 1.28 (10 - 34 dye episodes) and 1.31 (35 - 89 dye episodes) to 1.25 (≥ 90 dye episodes).	Heikkinen et al. (2015) ²⁵

<i>Breast Cancer (continued)</i>		
Prospective population-based cohort study of breast cancer in China. Cases of breast cancer include 234 hair dye users and 358 non-users.	No increase in the relative risk of breast cancer in women who ever used hair dyes, compared with never used hair dyes (RR=0.93; 95% CI 0.78-1.09). Stratification by menopausal status indicated no association between breast cancer and hair dye use in either pre- or post-menopausal women.	Mendelsohn et al. (2009) ²⁶
Hospital based case-control study in the UK. There were 191 cases and 561 age matched controls. 73 cases and 213 controls had ever used hair dyes.	A non-statistically significant increase in the relative risk of breast cancer in women who ever used hair dyes, compared with never used hair dyes (RR=1.01). There was no evidence of an increasing risk for breast cancer with increasing duration of use of hair dyes or with use beginning more than four or more than nine years before diagnosis.	Kinlen et al. (1977) ⁵¹
Hospital based case-control study in Canada and London. There were 85 cases and 170 controls, both over two locations.	A non-statistically significant increase in the odds of breast cancer in women who ever used hair dyes, compared with never used hair dyes (London: RR=1.3; 95% CI, 0.6-2.50 and Toronto, Ontario: RR=1.1; 95% CI, 0.5-2.4). Further statistical analyses, allowing for smoking habits, family history of cancer and age at first birth, showed no significant relationship between hair-dye use and breast cancer incidence.	Stavraky et al. (1979) ²⁸
Hospital based case-control study in New York City with 398 cases and 90 randomly selected, age-matched controls.	No increase in the odds of breast cancer in women who ever used hair dyes, compared with never used hair dyes (OR=0.8; 95% CI 0.6-1.1). There was also no statistically significant difference between those who report using hair dyes at least once and those who reported more than 100 uses.	Koenig et al. (1991) ²⁹
Hospital-based case-control study in Iran with 526 newly diagnosed breast cancer cases and 526 randomly selected, age-matched controls.	Multiple factors contribute to the risk of breast cancer, such as hair coloring, stress, and smoking. The OR of breast cancer from hair dye use on a regular basis compared to no use was 1.93 (95% CI, 1.41-2.62).	Dianatinasab et al. (2017) ⁴⁴

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, CIR Toxicologist
Date: November 09, 2018
Subject: Draft Revised Aerosols Precedents Document

Enclosed is a draft of the CIR Precedents – Aerosols document (*aeroso122018rep*), the transcripts of the discussion of the CIR Precedents – Aerosols document (*aeroso122018min.doc*), and the presentations by Dr. Nazarenko (*aeroso122018data_1*) and Dr. Singal (*aeroso122018data_2*) at the September 2017 meeting. In addition, enclosed are three papers titled “Principles for the safety evaluation of cosmetic powders” (*aeroso122018pub_1*), “Skin exposure to deodorants/antiperspirants in aerosol form” (*aeroso122018pub_2*), and “Principle considerations for the risk assessment of sprayed consumer products” (*aeroso122018pub_3*), which are authored by Dr. Steiling and her colleagues.

New comments have been received from the CIR Science and Support Committee (CIR SSC), which are identified as *aeroso122018pcpc.pdf* in the packet. At the September 2017 meeting, the Panel requested additional information on spray product particle size for hair spray and deodorants. Data are included in this submission, and have been added to the document. In addition, the CIR SSC provided the following recommendations for the document revision:

- Revise the CIR Aerosols Precedents document to clearly outline a tiered approach to assess inhalation exposure and risk assessment.
- Reference the updated particle/droplet size data in the Precedents document. These data are generally consistent with earlier data. Importantly, particle/droplet size data are generally not needed when assessing the inhalation safety of an ingredient in a spray cosmetic product.
- Revise the boilerplate language to reflect less reliance on particle size and more emphasis on exposure levels from spray cosmetic products by the inhalation route. These exposure levels are generally *de minimus*.

The enclosed document has been updated (**highlighted** in the text) to address the comments from CIR SSC, as well as include the information from the presentations at the September 2017 meeting that cover the topics of exposure assessment of nanomaterial-containing aerosols from cosmetic spray and powder products and considerations for inhalation safety assessments.

At the September 2017 meeting, the Panel noted that the document should be corrected to replace the assumption that 5% of the particle-size distribution released from propellant deodorant sprays consist of respirable particles with the assumption that 50% of the particles are respirable. The document has been revised to address this issue. In addition, inhalation exposures to a pump/propellant hair spray or propellant deodorant spray are recalculated with updated respirable particle size data by implementing the tiered approach.

The Panel should determine how, and to what extent, the attached draft of the CIR Precedents – Aerosols document should be revised further, based on the information provided by the presentations and the papers and the comments from CIR SSC.

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...

Day 1 of the April 10-11, 2017 CIR Expert Panel Meeting – Dr. Belsito's Team

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

DR. SNYDER: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. BELSITO: I think we have to.

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

before we respond.

DR. BELSITO: We are going to respond.

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

DR. BELSITO: Yes.

DR. BOYER: Exactly.

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

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

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

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

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

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

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

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

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

DR. ANSELL: Carbon black.

DR. LIEBLER: Carbon black.

DR. ANSELL: Certain titanium and zinc.

DR. BELSITO: Yeah.

DR. ANSELL: Sunscreens.

DR. BELSITO: There are sunscreens.

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

DR. ANSELL: But pigmentary grade because...

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

DR. ANSELL: No. And these have undergone review by SCCS in accordance with European

regulations. But there's very few actually facilities.

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

DR. ANSELL: No. FDA has --

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

DR. SNYDER: There's no aerosol usage.

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

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

DR. LIEBLER: Right.

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

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

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

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

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

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

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

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

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

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

DR. LIEBLER: Yeah, right.

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

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

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

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

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

DR. BOYER: Correct.

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

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

DR. BELSITO: Who?

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

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

DR. BELSITO: Right.

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

DR. LIEBLER: I think we're probably going to circle back to this issue again. I want to come back to the general comment that Ms. Scranton made, which was the first bold font thing you had, which was really the Epidemiology association of respiratory disease in hairdressers and beauticians. To what extent do we need to deal with that?

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

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

DR. BELSITO: Well it's the same as the hair dyes where there's some evidence of bladder cancer in hairdressers and barbers. And we say that it's not our purview, that they're exposed to multiple other chemicals, that it's not our purview to regulate workplace exposures. That would be OSHA. But from the data that we have in consumers, there is no strong data. The data is not strong. It's not conclusive. It's not pointing in any one direction that can tell us that this is or is not a concern. That the data seems to indicate that for beauticians there may be for bladder cancer, but of course one of my questions when we're looking at, and we're going to go to hair dye again with some new studies and I didn't have time to actually read through the studies, but how well are these controlled

for confounding factors. Because we know that beauticians smoke more than the average population. And smoking is a bladder cancer risk. So how well do they control the beautician smoking habits, how well do they control the breast cancer? We know that breast cancer is linked to diet. We know that from the Japanese studies when the Japanese moved from Japan to Hawaii their incidents of breast and colon cancer goes up astronomically and it's thought to be related to the fat in their diet.

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

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

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

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

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

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

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

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

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

DR. ANSELL: Like two paragraphs.

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

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

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

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

paragraph from her letter and put quotes on it to put that right there in place of the new paraphrased version.

So do you want to go on to specific comments?

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

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

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

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

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

DR. BOYER: Correct.

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

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

But I think for her I would just kind of generalize it like that. The committee is looking into this,

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

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

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

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

DR. KLAASSEN: No kidding?

DR. BOYER: Yeah.

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

DR. BOYER: There's not a lot. In fact the Nazarenko papers that she found were really the only substantial papers that have come out since then that speak specifically to this issue.

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

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

DR. BOYER: We didn't reference those.

DR. BELSITO: For powders.

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

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

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

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

DR. ANSELL: Yeah. I mean the major exposure to the small particles in the household come

from vacuum cleaning and using gas-fired appliances.

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

DR. LIEBLER: PM 2.5.

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

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

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

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

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

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

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

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

least we're using something that's considered acceptable standard in the field with its caveat.

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

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

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

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

DR. BOYER: No.

DR. KLAASSEN: Maybe it should be something.

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

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

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

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

DR. LIEBLER: Which would bother me.

DR. BELSITO: Right.

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

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

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

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

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

DR. BELSITO: Well I think we are re-challenging the foundations. We're saying that there's some new science that hasn't been brought in and we need to look at it. I mean I would like to see the more recent data on powder formation. I think she has a good point that we're basing our assumptions only on a couple different products that were tested and not on a range of products. I think she has a good point that the size of underarm deodorants, which of all the sprays are probably more in your breathing zone than a hairspray, because when women use a hairspray they're using looking in a mirror going like this. And when you're using an underarm spray, you're usually going like that. So I think she raised a lot of very valid points. And it may be that we continue to use our

foundations as our foundations, but I mean these are very valid points. In the end we're responsible. I'm responsible. Every voting member or the panel is responsible for saying that we thought that it was safe despite lack of significant inhalation data, because we didn't think it was going to be respirable. And this woman has raised a lot of questions in my mind as to whether that data is in fact totally correct, or that assumption that we've made is totally correct. And it may be. But I do think we need to relook at it.

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

DR. SYNDER: Worst case scenario.

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

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

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

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

DR. ANSELL: It dropped to zero in minutes.

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

DR. SYNDER: Not anymore.

MR. 8: Oh yeah?

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

MR. 8: Who is doing inhalation?

DR. SYNDER: I don't know.

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

MR. 8: In Rochester.

DR. LIEBLER: The end of an era.

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

DR. LIEBLER: Greg [inaudible]

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

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

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

DR. LIEBLER: And I don't know. This is not so much respiratory per se, the issues we're talking about are actually particle behavior and particle measurements.

DR. BELSITO: Okay.

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

DR. ANSELL: It's classic analytical methodology.

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

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

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

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

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

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

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

DR. LIEBLER: She says it's not.

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

DR. LIEBLER: She uses some of our numbers.

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

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

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

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

DR. LIEBLER: That's correct.

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

DR. LIEBLER: What's the distribution like.

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

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

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

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

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

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

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

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

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

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

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

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

DR. LIEBLER: Nazarenko?

DR. BELSITO: Yeah.

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

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

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

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

DR. LIEBLER: Who's presenting on this?

DR. BELSITO: Ivan.

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

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

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

142d COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

Tuesday, April 11, 2017

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 pharmaceuticals industry in terms of the work that's being done. And that will end up having numerous consequences. But I didn't really have a sense of, in terms of other than putting something flashy on the label, nano delivery or something, how much activity in the cosmetic and personal care product.

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

DR. HILL: Yeah.

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

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

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

DR. HILL: Mm-hmm.

DR. SADRIEH: -- in cosmetics.

DR. HILL: Yeah.

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

DR. HILL: Yeah.

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

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

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

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

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

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

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

DR. BERGFELD: Thank you very much.

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

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

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

DR. BERGFELD: Mm-hmm.

DR. MARKS: Okay.

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

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

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

143d COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

Monday, September 11, 2017

Dr. Marks' team

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 ubiquitous 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.

Dr. Belsito's team

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.

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

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.

COSMETIC INGREDIENT REVIEW

CIR Precedents

Aerosols

12/2018

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

Sprays/Powders

Update 12/2018

BACKGROUND

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

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

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

The physical parameter most strongly associated with the deposition pattern of an aerosol in the respiratory tract is the aerodynamic equivalent diameter (d_{ae}).^{6,7} The d_{ae} of a droplet/particle is defined as the diameter of a hypothetical, smooth sphere of unit density (e.g., 1 g/cm³) that has the same gravitational settling velocity as the droplet/particle in calm air, regardless of its actual geometric size, shape and density.^{5,8}

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

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

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

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

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

One industry survey provides volume weighted particle size distribution data, measured using laser diffraction, for propellant hair sprays and propellant deodorant/antiperspirant sprays.²² Data are reported as volume diameter defined by 10% , 50% (volume median), and 90% of the cumulative volume undersize (Dv_{10} , Dv_{50} , and Dv_{90} , respectively). The 90% particle sizes (Dv_{90}) of droplets/particles released from propellant hair sprays are distributed within the size range of $23.5 - 409 \mu\text{m}$, whereas the mean (SD) values of Dv_{50} and Dv_{10} 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 Dv_{90} , Dv_{50} and Dv_{10} 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 ($\% < 10 \mu\text{m}$) is 3.24 ± 4.48 and 26.6 ± 13.4 (mean \pm SD) for propellant hair sprays and deodorant/antiperspirant sprays, respectively.

These differences in droplet/particle size distributions between pump and propellant spray products, and between the few hair spray and deodorant spray products tested, are important considerations for evaluating the safety of cosmetics ingredients that may be 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.^{1,17} Simulation studies revealed that all of the droplets/particles released from both pump sprays and propellant sprays settle quickly after spraying, including the respirable and inhalable fractions, which substantially reduces the overall potential for inhalation exposure.^{5,8,17-19} Specifically, about 35% of the airborne droplets/particles drop away from the breathing zone in the first minute, 60% in the second minute, 90% in six minutes, and 95% in eight minutes after spraying.¹⁷ The droplets/particles are likely to be undetectable in the breathing zone within 10 minutes after spraying.

Due to the compressed format and low usage amounts, inhalation exposure to compact powders is not expected at use conditions.²³ 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.^{24,25} 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).²³ 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 askew the size distributions, of the particles released from these products, outside of the respirable range.²⁴

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,²⁶ although the mechanism(s) of overload-induced tumor formation is not completely understood.²⁶⁻²⁹ The European Union's current threshold for protecting workers from pulmonary overload during occupational exposure to respirable dust particles is 1.5 mg/m^3 8 hour time-weighted average. In comparison, inhalation exposures to aerosols from cosmetic sprays will be much lower than this threshold, primarily because of the much shorter exposure duration associated with cosmetic spray use (i.e., only a few minutes).^{1,17}

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

Similarly, industry can minimize airborne particles from cosmetic powder products by controlling the milling of the ingredients and adding binding materials, such as oils, waxes or hygroscopic ingredients to the formulations.³⁰ The binding materials foster the agglomeration of the ingredients and substantially increase their cohesivity. These measures increase the size of the particles in the product.

However, characterizing the particle size distributions released from finished powder products under use conditions is difficult. This is because the methods used to measure the particle sizes of powder products involve dispersing the powder in a solvent or applying a pressure differential to break up the agglomerated particles.³⁰ 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 $20 \text{ }\mu\text{m}$,^{25,31} which does not cover the full spectrum of particle sizes typically released from cosmetic sprays (with the largest portion being in the $50 - 300 \text{ }\mu\text{m}$ 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.²³ Organic particles or a more complex mixture are hard to detect using electron microscopy.²⁴ 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.^{24,40}

A conservative estimation indicates up to 50% of the particle size distribution released from propellant deodorant sprays consist of respirable particles.^{12,18} 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.^{23,24,32,33} 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.³⁴

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 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.^{23,34} 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.

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.³⁵ 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 m³ 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.

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 tanning, foot and deodorant sprays, and loose powders) would substantially increase confidence in safety assessments of ingredients in products that may be aerosolized.

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

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

For example, conservative estimates indicate that inhalation exposures for once-a-day application of a pump hair spray, propellant hair spray or propellant deodorant spray containing 2% of an ingredient would be no more than 1.5, 4.7, and 6.8 µg/kg/day, respectively.^{35,36} 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, respectively³⁷
- Respirable fraction: 1%, 5%, 50% for pump-hair, propellant-hair and deodorant spray, respectively

The percentage of particles/droplets with $d_{ae} < 10 \mu\text{m}$, measured for deodorant/antiperspirant spray products, is 26.6 ± 13.4 (mean \pm SD).³⁵ 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:³⁸⁻⁴⁰

- Concentration of respirable particles: 0.19 to 2.03 mg/m³ 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.^{41,42} 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,⁴³ based on a conservative estimate use of face powder at 510 mg per application per day.⁴⁴

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.⁴⁵ 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.⁴¹

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.^{35,38,40} 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/m³) 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/m³ for an 8-hour workplace.²³ 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.²³ However, it is important to remember that even such small inhalation exposures may be significant for an ingredient that has the potential to act as a potent systemic or local respiratory tract toxicant or to accumulate in the body.

On the other hand, the Panel noted that inhalation toxicity studies on test animals are often conducted using high concentrations of droplets/particles with size distributions well within the respirable range and long exposure durations to ensure that the potential for pulmonary or systemic toxicity will be

detected. In contrast, the concentrations of respirable droplets/particles and the inhalation exposure durations from the use of cosmetic products will be much less than those of the animal studies. Thus, the adverse effects reported in such studies may have little or no relevance for evaluating the inhalation safety of cosmetic ingredients.

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

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

Precedent language for specific report sections:

Cosmetic Use Section

[INGREDIENT(S)] was/were reported to be used in [LIST TYPE(S) OF SPRAY PRODUCT(S), e.g., [cosmetic sprays, including hair, deodorant, foot, and other propellant and pump spray products](#)], and could possibly be inhaled. [NOTE THE HIGHEST MAXIMUM USE CONCENTRATION OF THE INGREDIENT IN A SPRAY PRODUCT IF THIS INFORMATION IS AVAILABLE, e.g., [These ingredients are reportedly used at concentrations up to 4% in spray products](#)] In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters $>10 \mu\text{m}$ [IF PRODUCT(S) MAY INCLUDE BOTH PROPELLANT AND PUMP SPRAYS, ADD: [, with propellant sprays yielding a greater fraction of droplets/particles below \$10 \mu\text{m}\$ compared with pump sprays](#)]. (Rothe et al 2011, Bremmer et al 2006, Rothe 2011, Johnsen 2004).^{1,12,17,46} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount. Rothe et al 2011, Bremmer et al 2006).^{1,12} [IF PRODUCT(S) INCLUDE DEODORANT SPRAY(S), ADD: [There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable \(Bremmer et al 2006\).](#)¹² However, data is 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 data under consumer use conditions are 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. \(Stelling et al 2014, CIR SSC 2018\)](#)] [IF PRODUCTS INCLUDE POWDER(S), ADD: INGREDIENT(S)] was/were reported to be used in [LIST TYPE(S) OF POWDER PRODUCT(S), e.g., [baby powders, dusting powders, talc powders, face powders, foot powders](#)],

and could possibly be inhaled. [NOTE THE HIGHEST MAXIMUM USE CONCENTRATION OF THE INGREDIENT IN A POWDER PRODUCT IF THIS INFORMATION IS AVAILABLE, e.g., [These ingredients are reportedly used in loose powder products at concentrations up to 4%](#)]. Conservative estimates of inhalation exposures to respirable particles during the use of loose-powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace. ([Aylott et al 1979](#), [Russell et al 1979](#), [CIR SSC 2015](#)).³⁸⁻⁴⁰]

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

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

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

[ADDRESS PARTICLE SIZES IN COSMETICS, **IF POSSIBLE**; [EXAMPLES: \(1\) The Expert Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. Thus, the adverse effects reported using high doses of respirable particles in the inhalation studies do not indicate risks posed by use in cosmetics OR \(2\) The particle sizes of these ingredients was reported to range from 0.05 – 1000 \$\mu\text{m}\$ with the largest portion being in the 50 – 300 \$\mu\text{m}\$ 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) They noted the lack of systemic toxicity at high doses in several acute and subchronic oral exposure studies and one chronic oral exposure study, little or no irritation or sensitization in multiple tests of dermal and ocular exposure, the absence of genotoxicity in multiple Ames tests and a Chinese hamster ovary test, and lack of carcinogenicity in a lifetime oral exposure study OR (2) They noted the lack of irritation or sensitization in tests of dermal exposure, no systemic toxicity at 5000 mg/kg, and the absence of genotoxicity in an Ames test of a related chemical.]

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

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

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Unpublished references are available for viewing upon request to CIR.



Exposure Assessment of Nanomaterial-Containing Aerosols from Spray and Powder Products

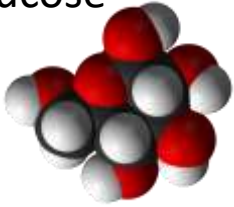
Cosmetic Ingredient Review Panel
Washington, DC, September 11, 2017

Yevgen Nazarenko, Ph.D.

Department of Atmospheric and Oceanic Sciences, McGill University
805 Sherbrooke St. West, Montreal, QC H3A 0B9
Tel: +1-514-431-4115; Fax: +1-514-398-6115
E-mail: YevgenNazarenko@gmail.com; Yevgen.Nazarenko@mcgill.ca

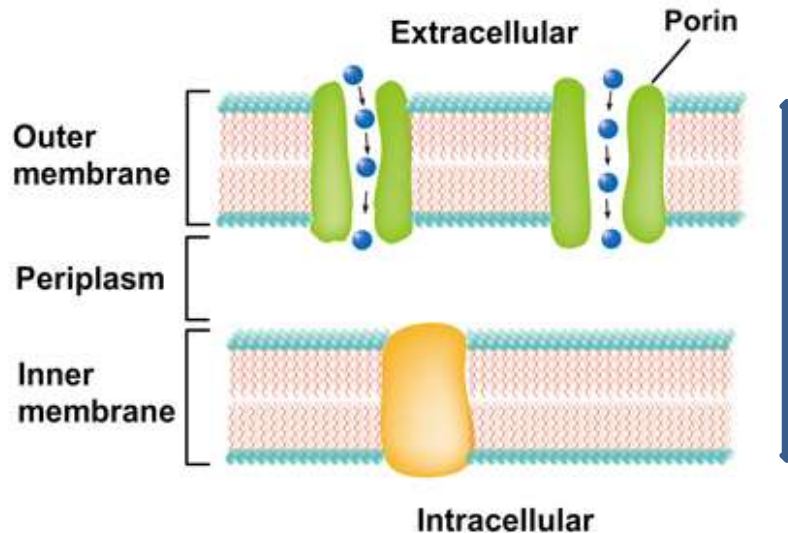
1 – 100 nm in Perspective

Glucose



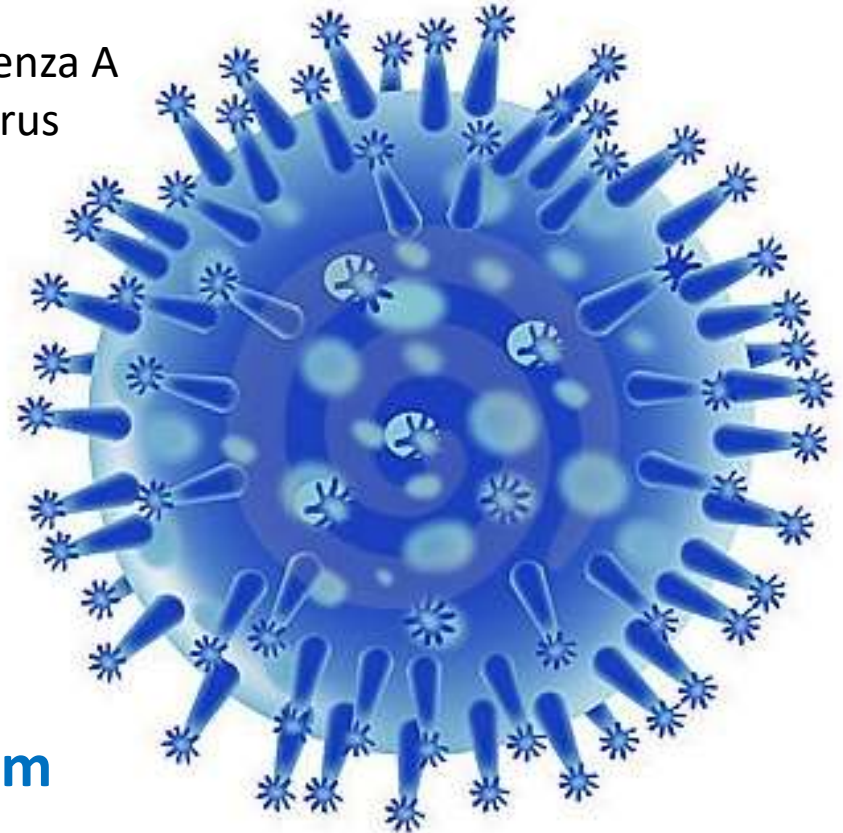
~1 nm

Double membrane of Gram-negative bacteria



~10 nm

Influenza A Virus



~100 nm

Nano-sized Particles and Materials

The US National Nanotechnology Initiative (NNI) defines nanotechnology as “the understanding and control of matter at dimensions between **approximately 1 and 100 nanometers**, where unique phenomena enable novel applications” (National Science and Technology Council, 2007).

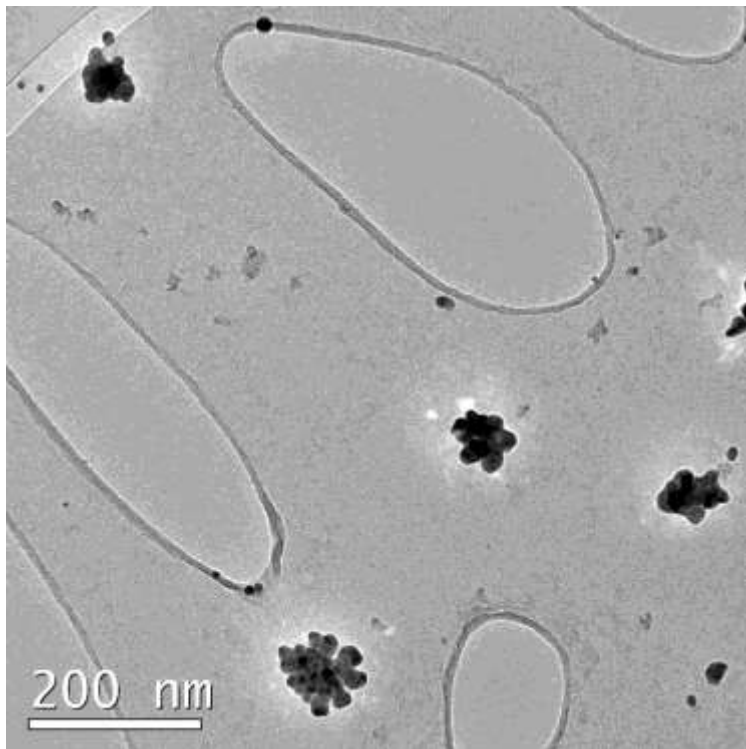
Under the EU’s “Recommendation on the definition of a nanomaterial (2011/696/EU)”

*“A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range **1 nm - 100 nm**.”* *Includes some < 50 % and < 1 nm.

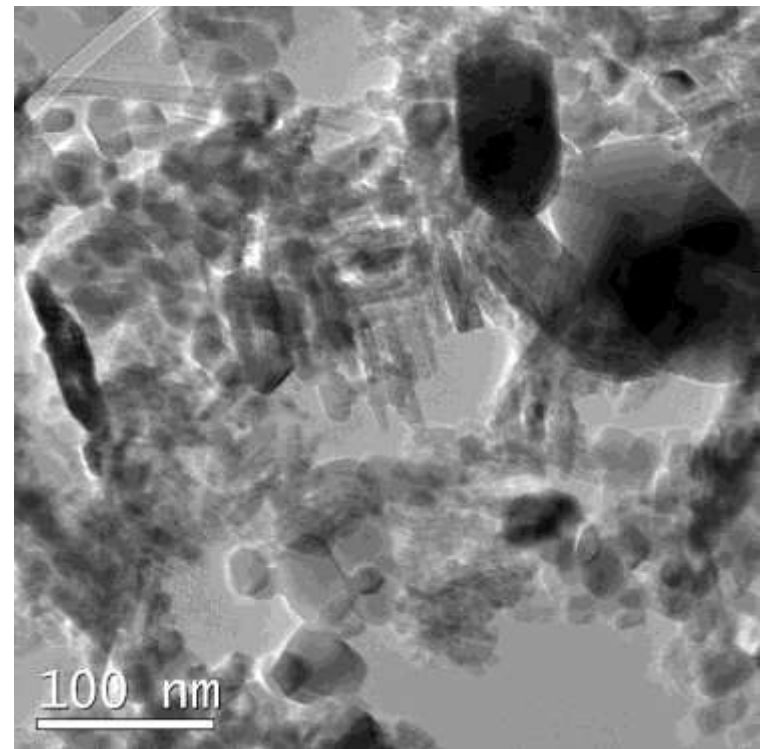


Nano-objects \neq Nanomaterials

- Nano-objects can exist both as free nanoparticles and their agglomerates / aggregates or be attached to / incorporated into larger particles

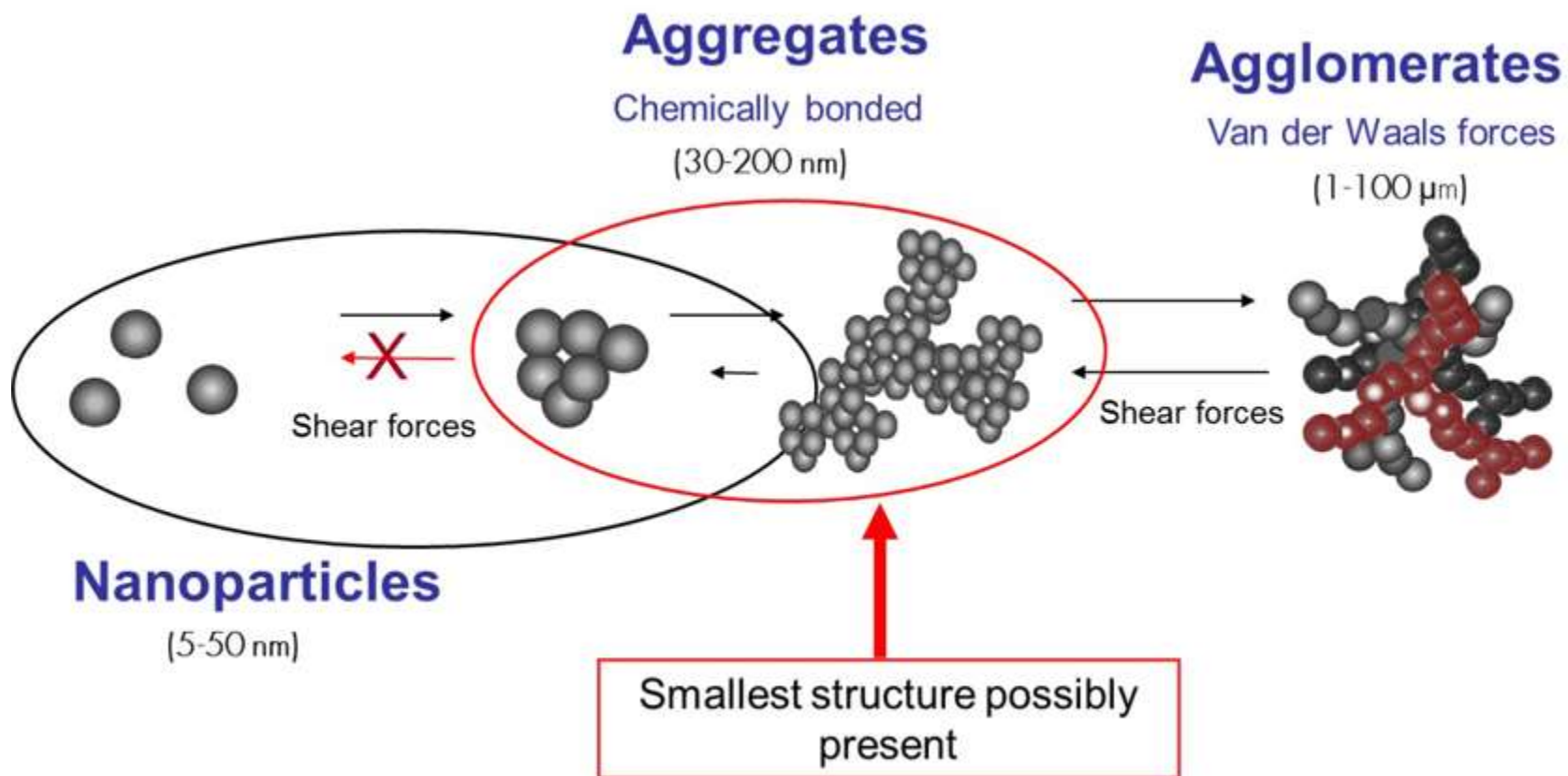


Sample 1



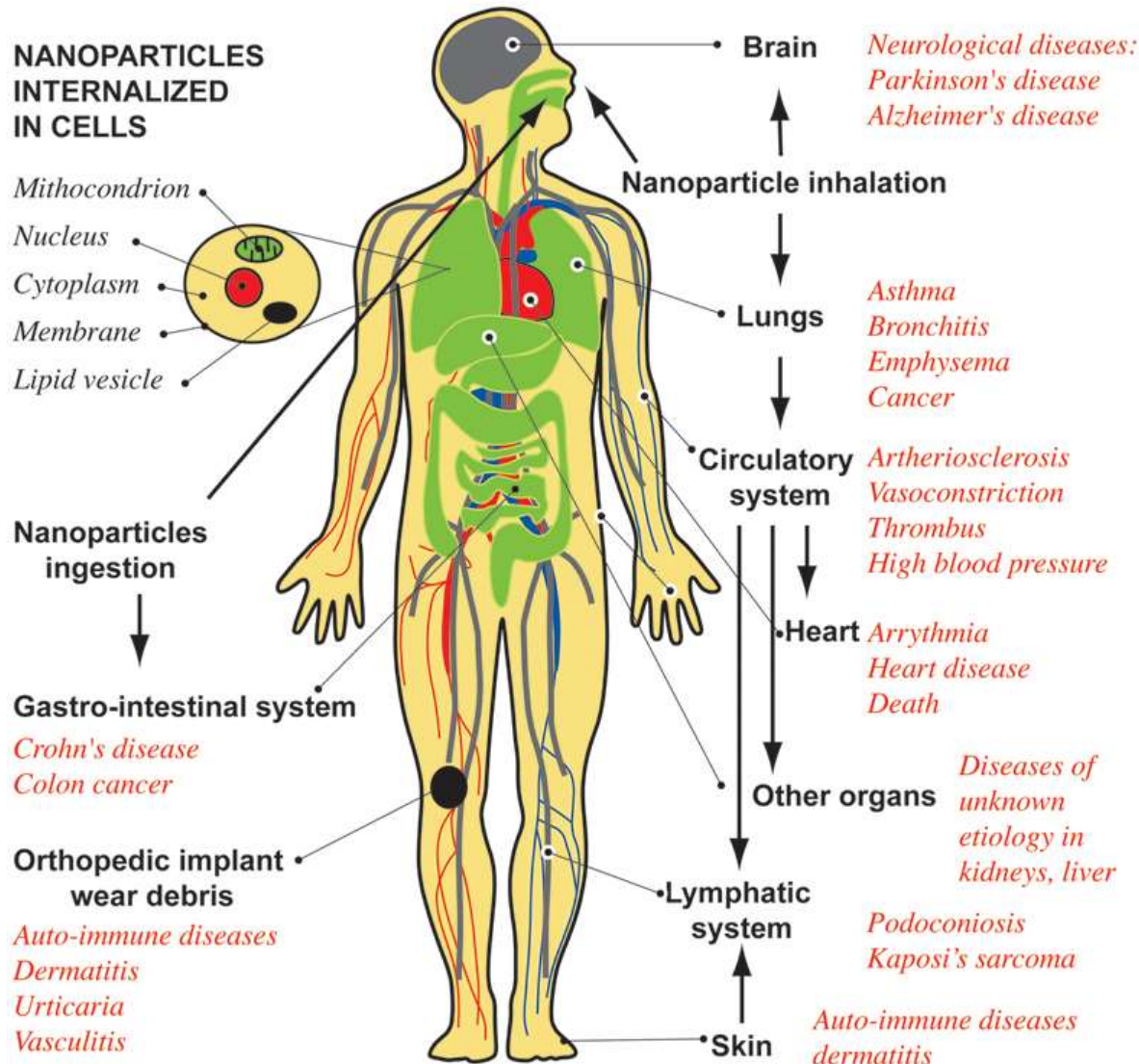
Sample 2

NOAA: Nano-objects, agglomerates and aggregates



Human Exposure to Nanomaterials

C. Buzea, I. Pacheco, & K. Robbie, *Nanomaterials and nanoparticles: Sources and toxicity, Biointerphases 2 (2007) MR17-MR71*

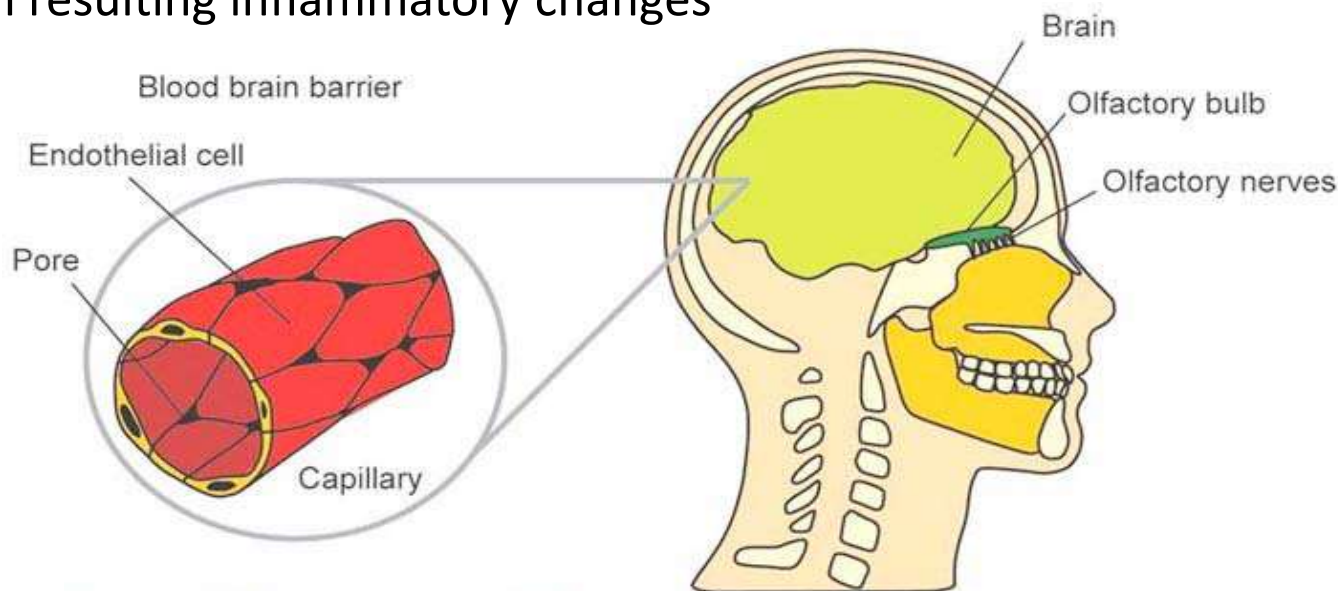


- Human exposure to nanomaterials is associated with **potential health risks**;
- Different routes of this exposure are possible: **ingestion, dermal, inhalation**

Health Concerns of Nanomaterial Exposure

The size distribution and structural state of matter at the nanoscale affects its toxicity and associated biological and health effects relative to mass dose of chemically the same substance:

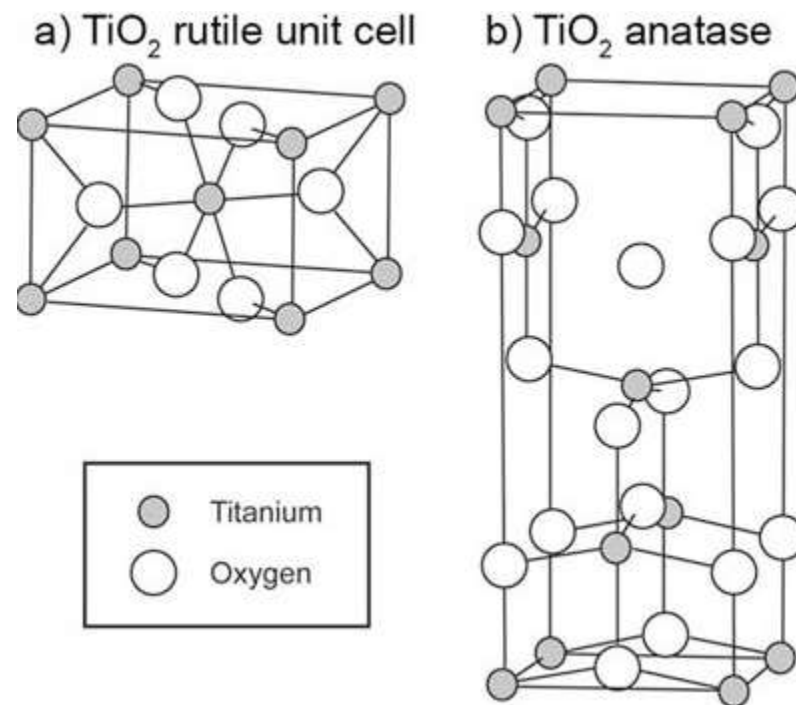
- **Example 1:** graphite-derived carbon nanoparticles (median diameter 36 nm) were found to translocate from the respiratory system to the olfactory bulb of the rat central nervous system. The same effect was found for the manganese oxide nanoparticles (median diameter 30 nm) with resulting inflammatory changes*



Health Concerns of Nanomaterial Exposure

Toxicity of nanomaterials can differ even for small variations of particle size and crystal structure:

➤ **Example 2:** following intranasal instillation, a more intense inflammation response resulted in mice exposed to 21-nm anatase/rutile nano-TiO₂ compared to 5-nm anatase nano-TiO₂.*

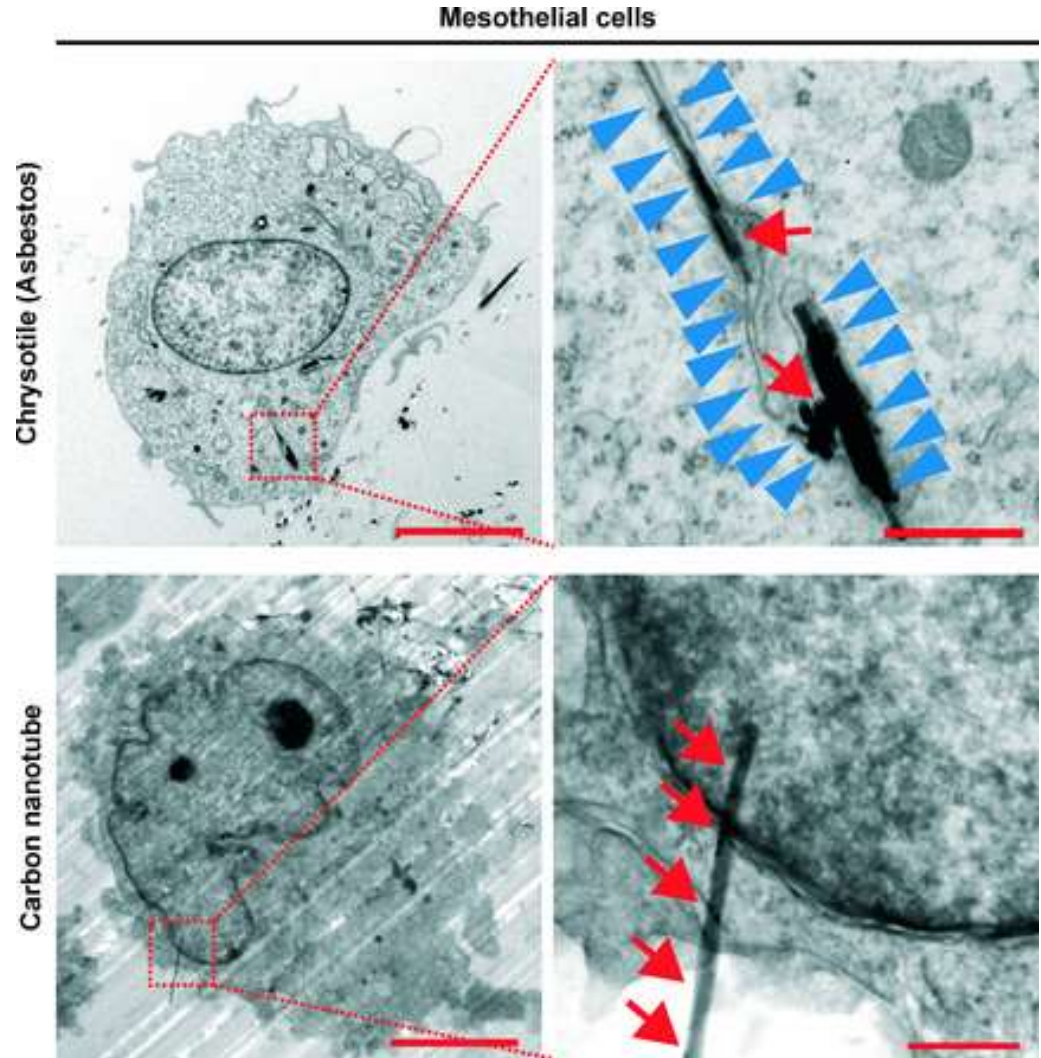


*Grassian VH, Adamcakova-Dodd A, Pettibone JM, O'Shaughnessy PT, Thorne PS. 2007. Inflammatory response of mice to manufactured titanium dioxide nanoparticles: Comparison of size effects through different exposure routes. *Nanotoxicology* 1(3): 211-226;
 Buzea, C., Pacheco, I.I., Robbie, K. 2007. Nanomaterials and nanoparticles: Sources and toxicity. *Biointerphases*, 2(4): MR17-MR172.

Health Concerns of Nanomaterial Exposure

Differences and similarities between carbon nanotubes and asbestos fibers during mesothelial carcinogenesis:

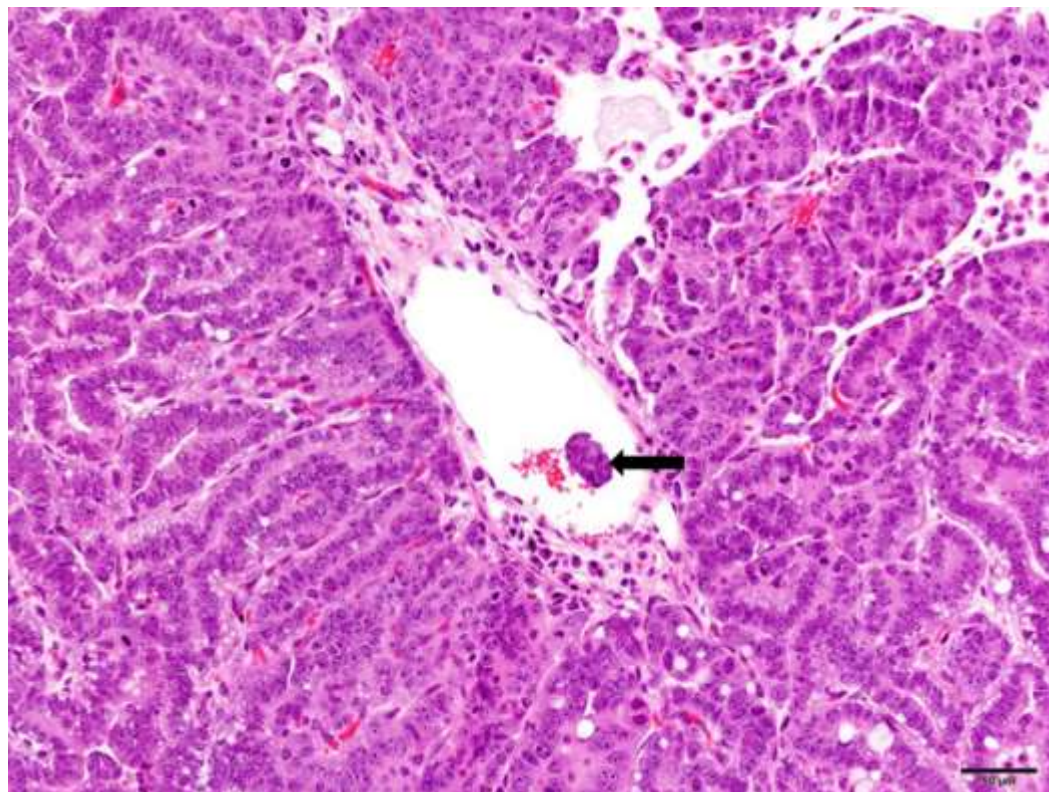
The mechanism of fiber entry into the cells



Health Concerns of Nanomaterial Exposure

Mice receiving both a known cancer initiator, methylcholanthrene, plus inhalation exposure to multiwalled carbon nanotubes (MWCNT)¹ were significantly more likely :

1. to develop tumors – **90% incidence and larger tumors**;
2. have **more tumors** than mice receiving the initiator chemical alone: all mice developed tumors (~3.3 tumors/mouse lung) vs. only 50% of mice developed tumors with ~1.4 tumors/lung).



Alveolar Bronchiolar Carcinoma of the Lung with Metastases in a Blood Vessel (arrow).

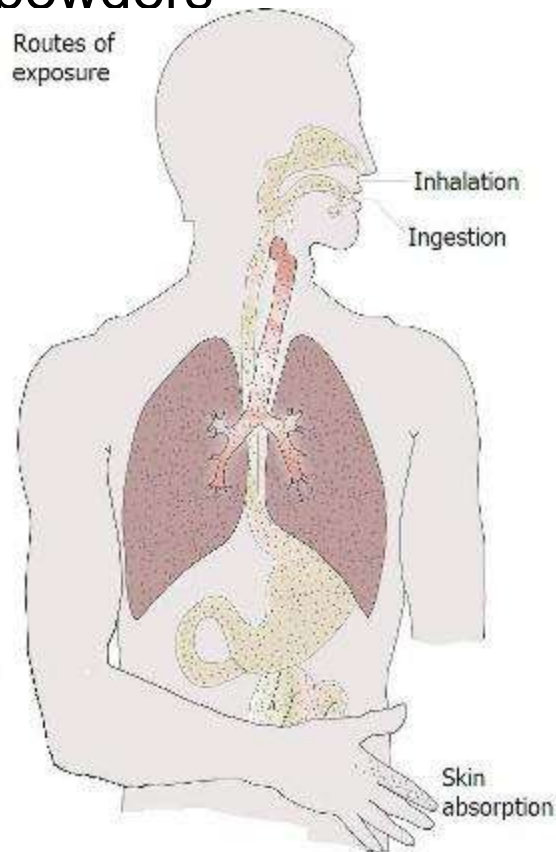
¹ Inhalation exposure at 5 mg/m³ for 15 days, 5 hrs. per day

Health Concerns and Regulation

- Nanoparticles can be found ubiquitously in industrial and consumer products, claimed to contain nanomaterials and products not marketed as nanotechnology-based (regular products). **Nanomaterial exposure is possible - both occupational and end-user?**
- It is a challenge for modern analytical techniques to **determine if nanoparticles, found in the products, are engineered or derived from natural ingredients**. Manufacturers do not usually disclose such information about ingredients in their products. **Some regulations mandate disclosure of this information? Future regulations will likely require it too.**
- Inconsistency between advertising and marketing and the *de facto* “nano-status” of products that exist in the absence of regulations mandating accurate reporting of this information.

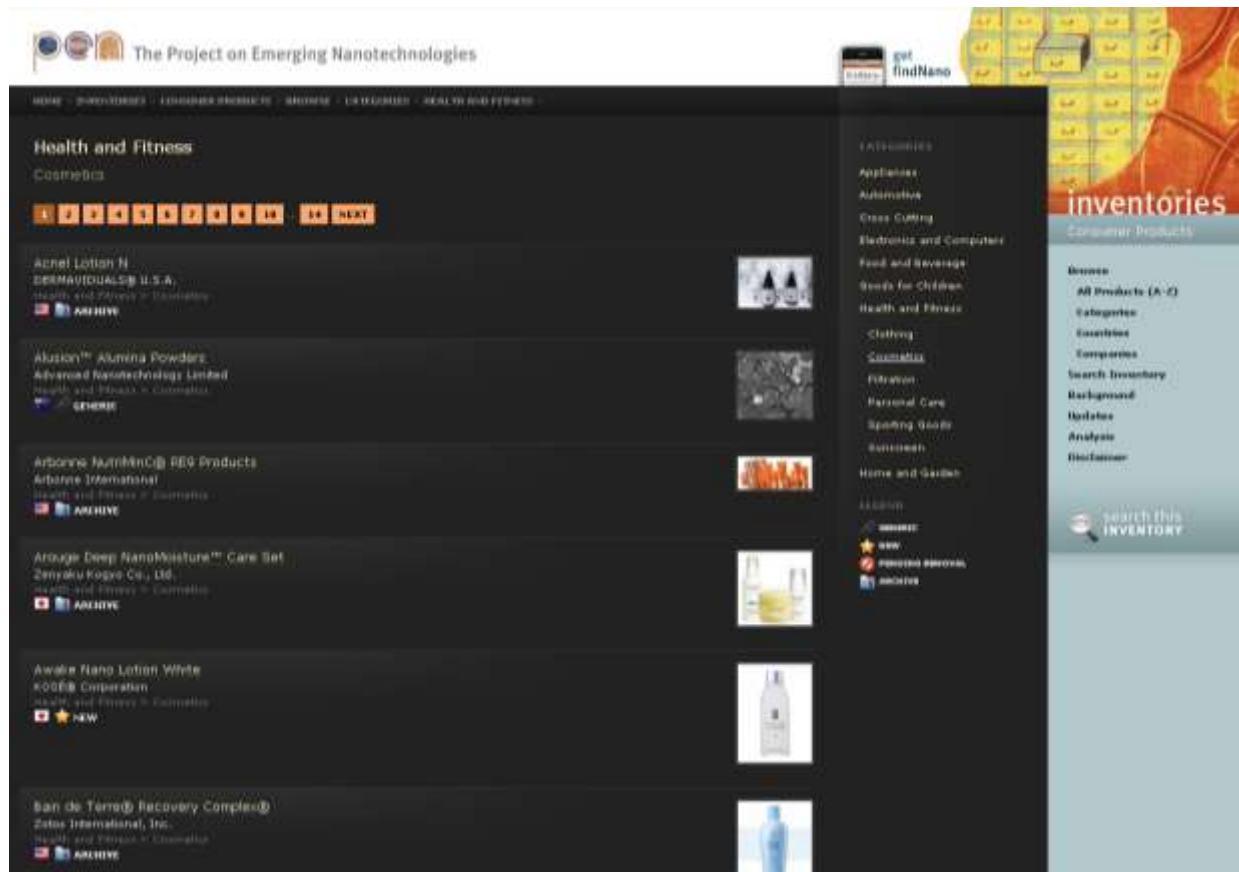
Nanotech Products → Exposure

- Dermal and inhalation exposure may be especially high from nanotechnology-based consumer sprays and cosmetic powders



Our Research: Nanoproduct Selection

- The nanotechnology-based products were selected from the Woodrow Wilson Nanotechnology Consumer Products Inventory* that currently contains **>1300 such products**



Non-Nanotech Products

- We added **Regular** products in our studies to study if and how their particulate composition and potential for inhalation exposure differ from the nanotechnology-based products



<http://chemistscorner.com/wp-content/uploads/2009/12/new-cosmetic-products.jpg>



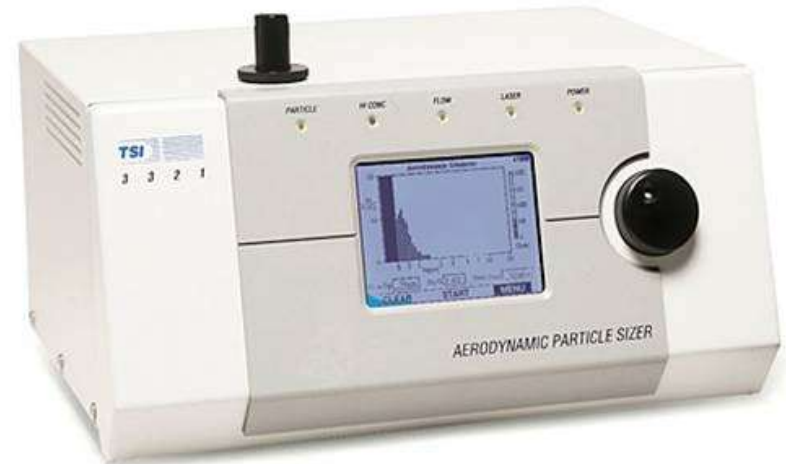
<http://www.studioidirectcosmetics.com/cosmetics/pressed-powder-2.jpg>

Problems Our Work Aimed to Address

- **Presence and content of nanomaterials** in consumer products on the market were largely unknown;
- **Potential of human exposure** to nanomaterial-containing aerosol particulate matter, released during use of nanotechnology-based products was unknown;
- **Doses of nanomaterials** that may result from the above-mentioned exposure were unknown.

Aerosol Measurement Techniques

- High importance of nanomaterials in all size fractions (both 1 – 100 nm and above in the agglomerated form) → we need to use **more than one measurement technique**, e.g. SMPS and APS



- **SMPS**: Scanning Mobility Particle Sizer
- **APS**: Aerodynamic Particle Sizer

Methods: All Aims

- Transmission Electron Microscopy (JEOL 2010F) to analyze particle **size, shape, and agglomeration** in the consumer sprays and cosmetic powders



Image from: <http://www.virginia.edu/ms/images/JEOL2010.jpg>

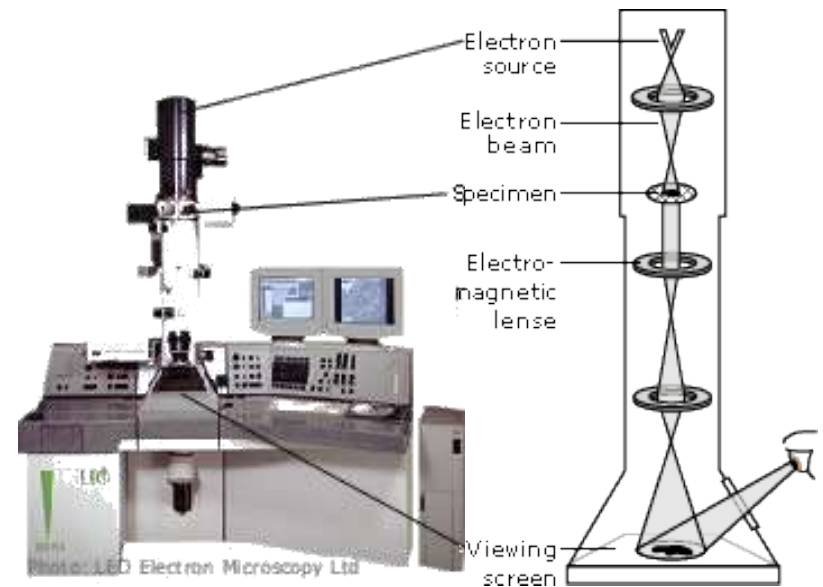


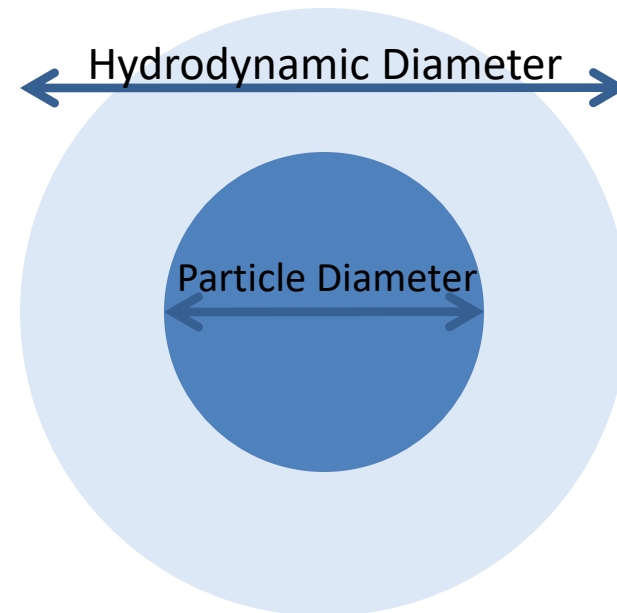
Image from: http://nobelprize.org/educational_games/physics/microscopes/tem/index.html

Methods: Consumer Sprays

- Photon Correlation Spectroscopy (Brookhaven ZetaPALS 90Plus Particle Size Analyzer) to obtain particle size distributions in spray products



<http://www.wrrc.hawaii.edu/lab/ZetaPALS-250px.jpg>



- Hydrodynamic diameter (HD) corresponds to the equivalent sphere with the same diffusion coefficient as that of the real particle

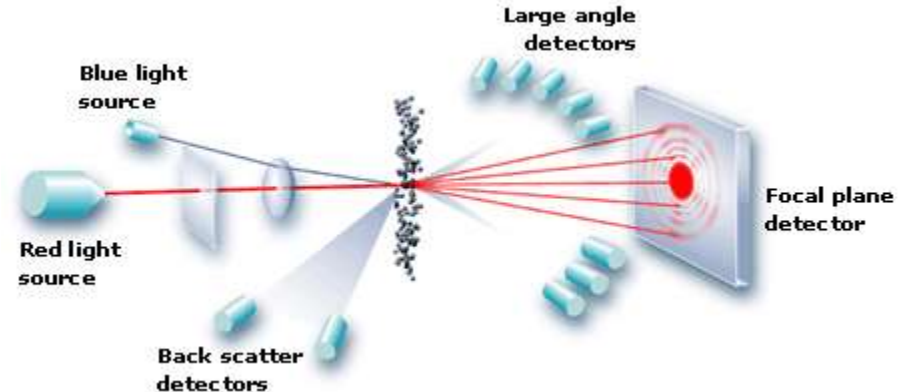
→ Additional Explanation of HD

Methods: Cosmetic Powders

- Laser Diffraction Spectroscopy (Malvern Mastersizer 2000) was used to obtain particle size distributions in cosmetic powders



<http://www.leeds.ac.uk/particletechnology/Images/mastersizer.jpg>



http://www.malvern.de/LabGer/technology/laser_diffraction/particle_sizing.htm

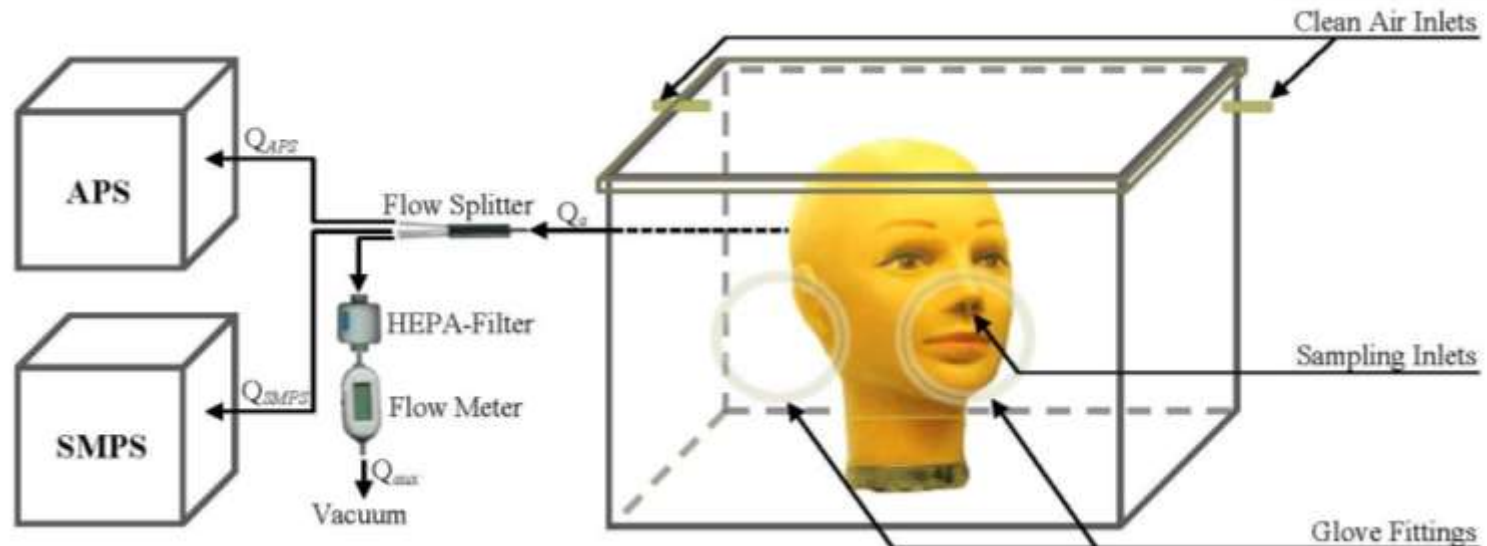
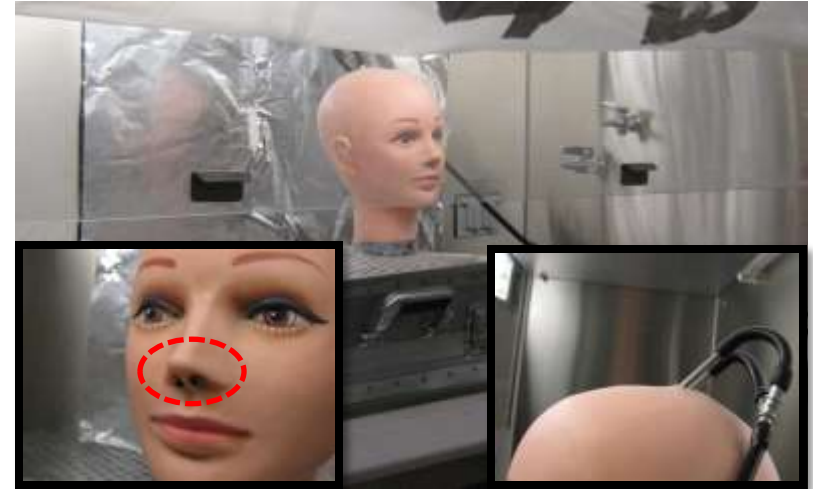
- Particles passing through a laser beam scatter light at an angle that is directly related to their size.

→ Additional Explanation of the Principle of Operation

Methods: Cosmetic Powders

➤ Realistic exposure scenario:

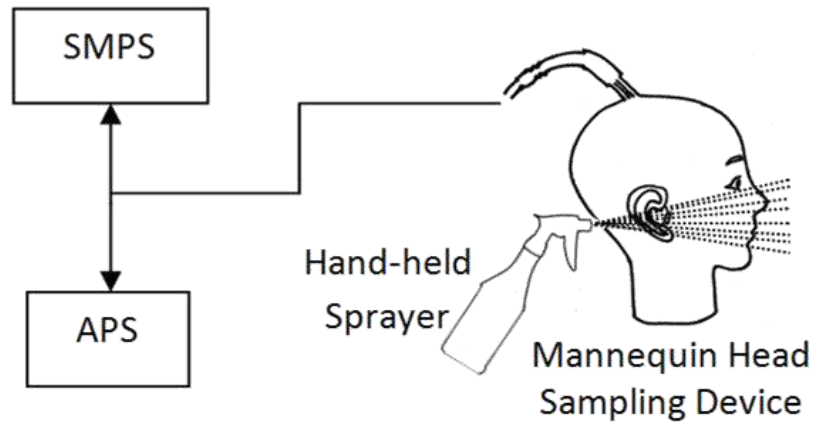
- application of the cosmetic powders with the supplied applicators and sampling in the way that mimics real life application and inhalation.



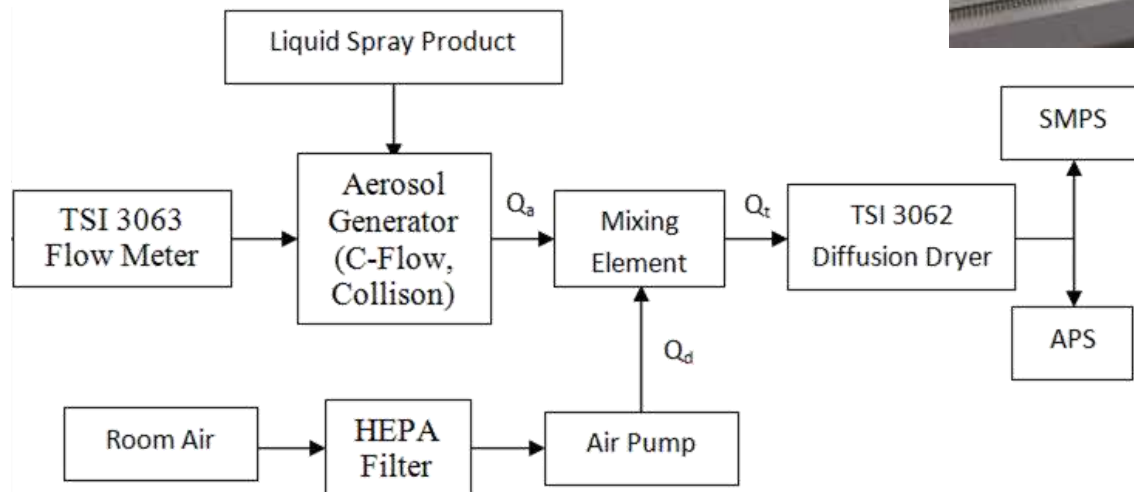
→ Justification of the Sampling Flow Rate

Methods: Consumer Sprays

Realistic Spray Use



Standard Nebulizers



Tested Consumer Sprays

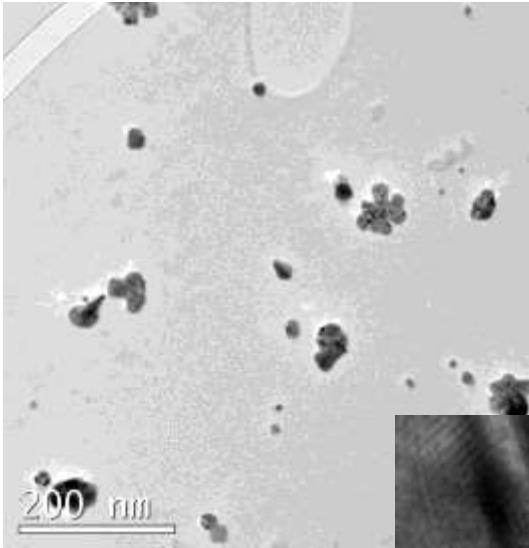
Nanoproduct	Regular Product
Silver Nanospray*	Regular Silver Spray
Facial Nanospray*	Regular Facial Spray
Hair Nanospray*	Regular Hair Spray
Disinfectant Nanospray*	Regular Disinfectant Spray
Skin Hydrating Nanomist*	Regular Skin Hydrating Mist
Wheel Nanocleaner*	<i>No Alternative Tested</i>

*Nanoproduct as per the Woodrow Wilson Nanotechnology Consumer Products Inventory

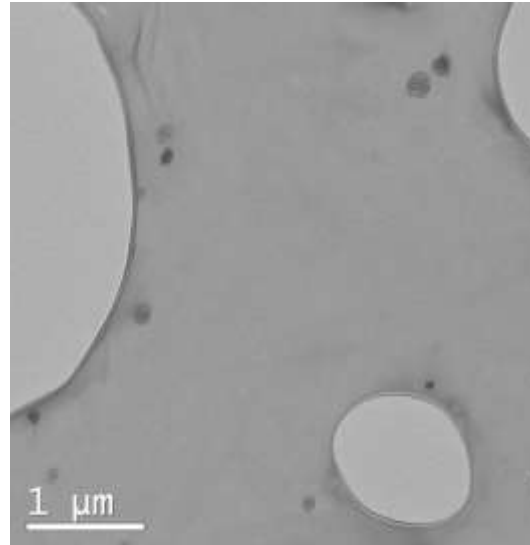


Results: TEM of Nano Consumer Sprays

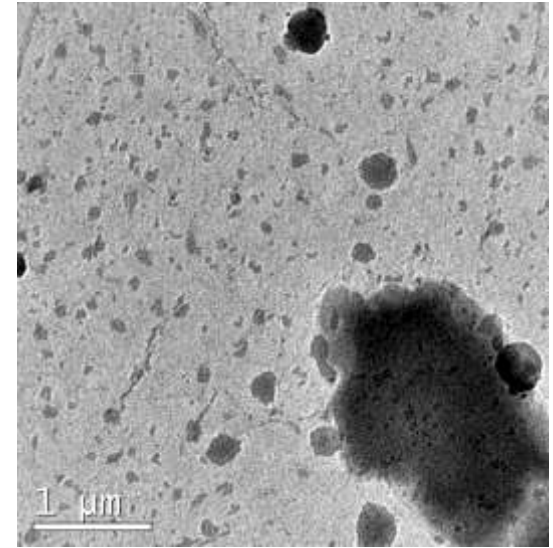
Nanotechnology-based Sprays



Silver **Nano**spray



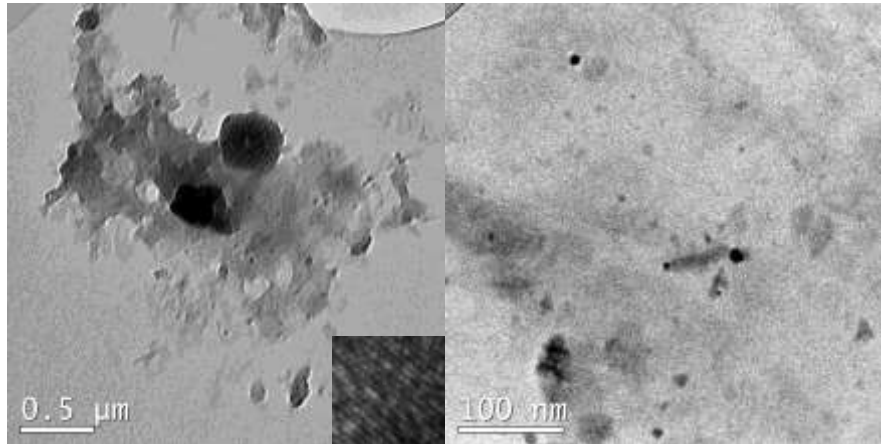
Disinfectant **Nano**spray



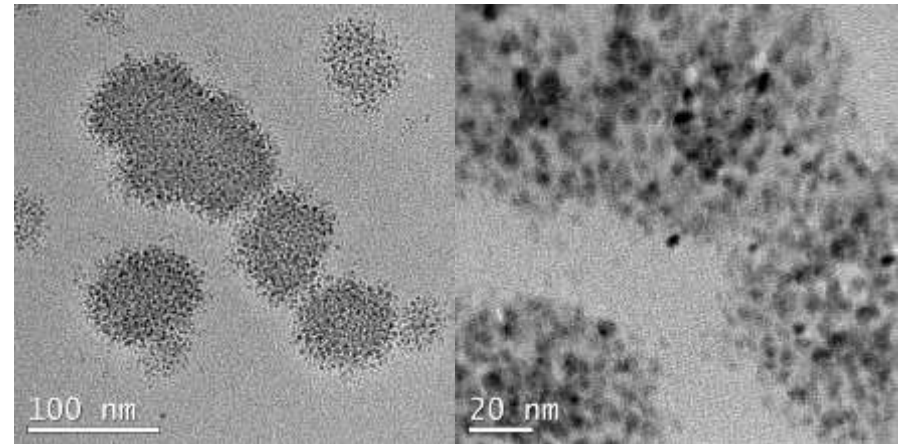
Wheel **Nano**cleaner

Results: TEM of Regular Consumer Sprays

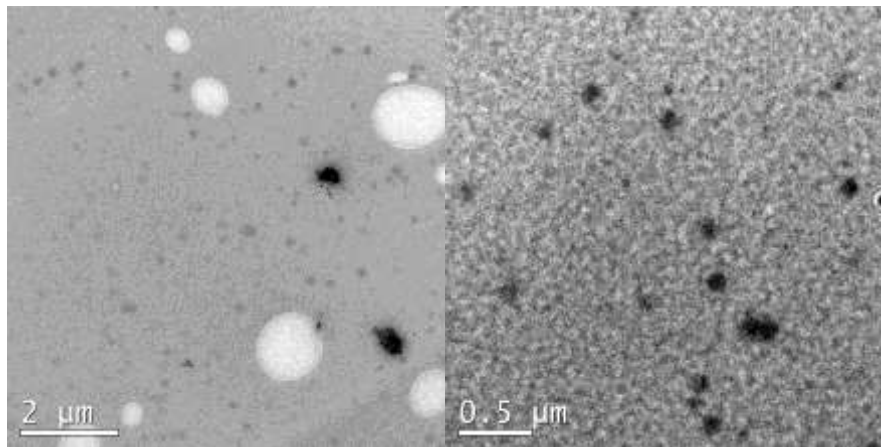
Regular Sprays



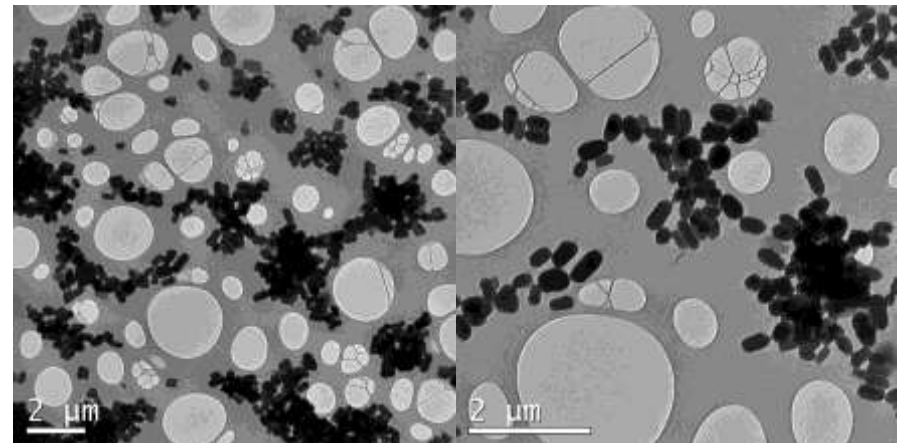
Regular Silver Spray



Regular Disinfectant Spray



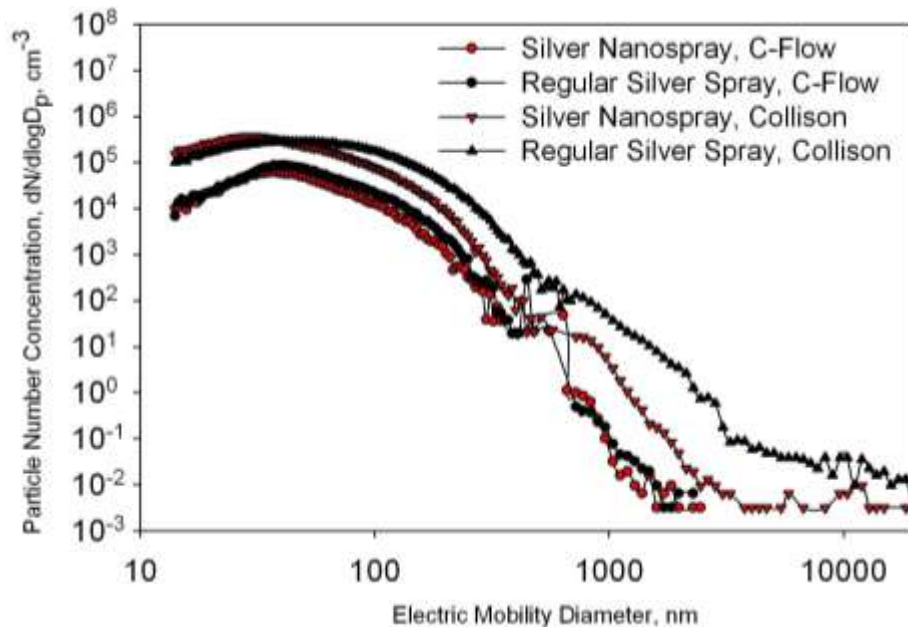
Regular Hair Spray



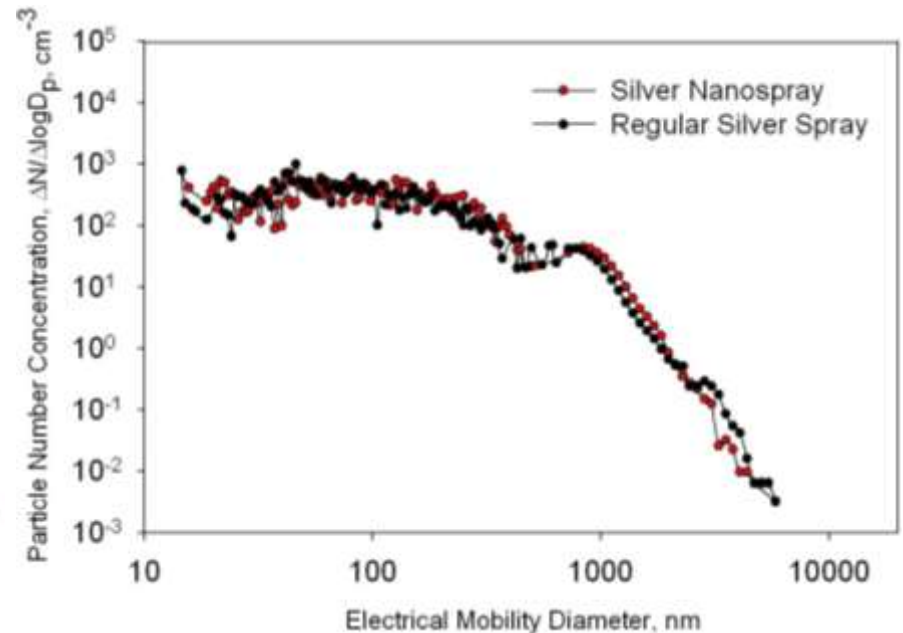
Regular Facial Spray

Results: Consumer Sprays

- The size distributions of aerosol particles and droplets likely to be inhaled during product application are different depending on the spraying technique



Using nebulizers



Handheld sprayer; Mannequin sampler

Selected Results: Nano Consumer Sprays

Product / Method	TEM	C-Flow Nebulizer Mode Diameter	Collison Nebulizer Mode Diameter
Silver Nanospray	3 - 65 nm, single particles and agglomerates, spheroidal, solid, beam insensitive	37 nm	30 nm
Facial Nanospray	No particles detected	98 nm	61 nm
Hair Nanospray	No particles detected	311 nm	No data (foaming)
Disinfectant Nanospray	71 - 214 nm, single particles, spheroidal, solid, beam insensitive	85 nm	No data (foaming)
Skin Hydrating Nanomist	No particles detected	157 nm	113 nm

Results: Regular Consumer Sprays

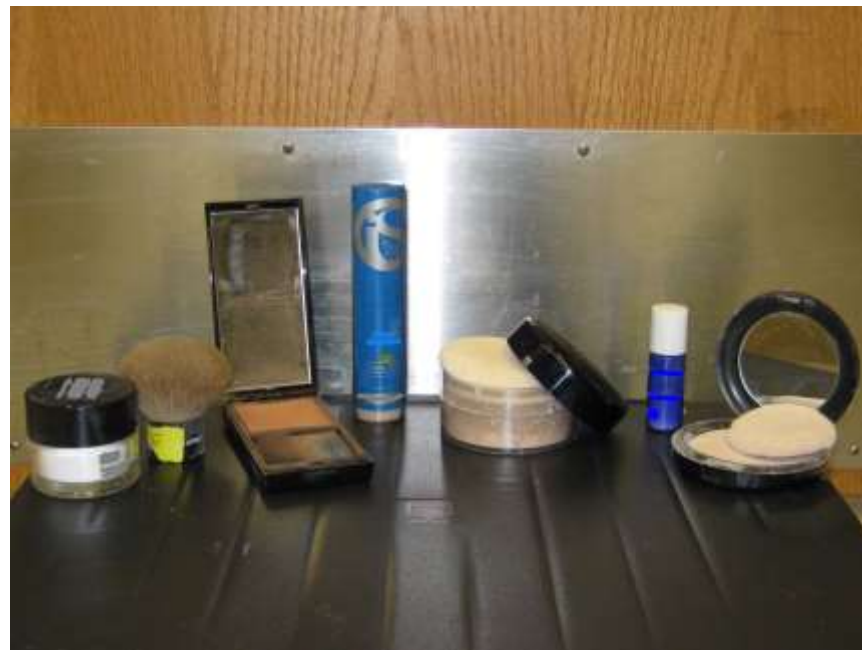
Product Method	TEM	C-Flow Nebulizer Mode Diameter	Collison Nebulizer Mode Diameter
Regular Silver Spray	<3 - 435 nm, agglomerates and single particles, various shapes, solid, beam insensitive	41 nm	41 nm
Regular Facial Spray	82 - >6000 nm, single particles and agglomerates, spheroidal and elliptical, beam sensitive	102 nm	No peak (concentration below water background)
Regular Hair Spray	16.5 – 683 nm, single particles and agglomerates (two types), spheroidal, solid, beam insensitive	429 nm	334 nm
Regular Skin Hydrating Mist	146 - >2500 nm, single particles and agglomerates, spheroidal and elliptical, beam sensitive	102 nm	No peak (concentration below water background)

Tested Cosmetic Powders

Product	Purpose**
Nanopowder M*	Moisturizer
Nanopowder D*	Blusher
Nanopowder K*	Sunscreen
Powder F	Blot Powder
Powder G	Blot Powder
Powder E	Cosmetic Powder

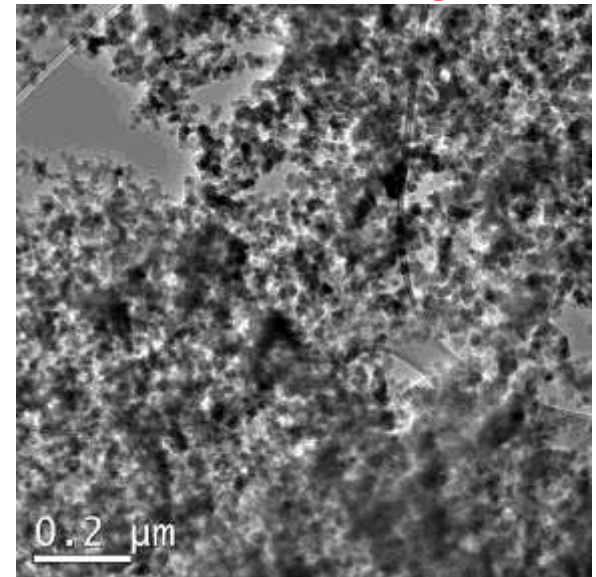
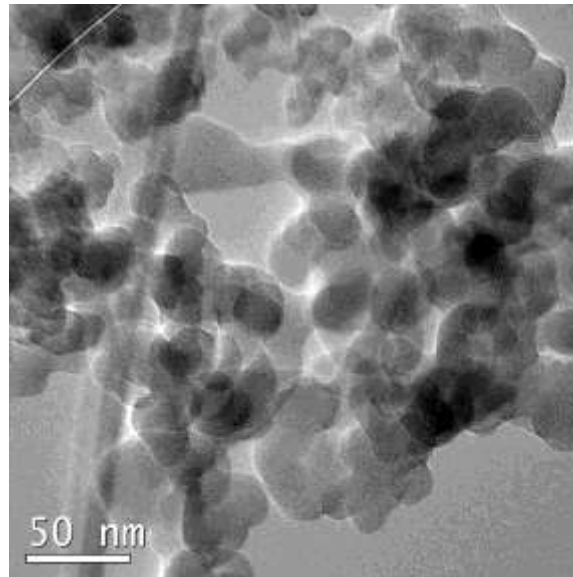
*Nanoproduct as per the Woodrow Wilson Nanotechnology Consumer Products Inventory

**As per manufacturer

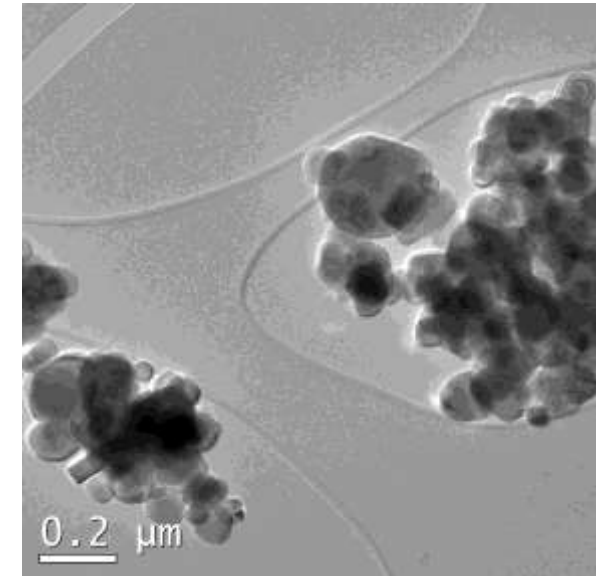
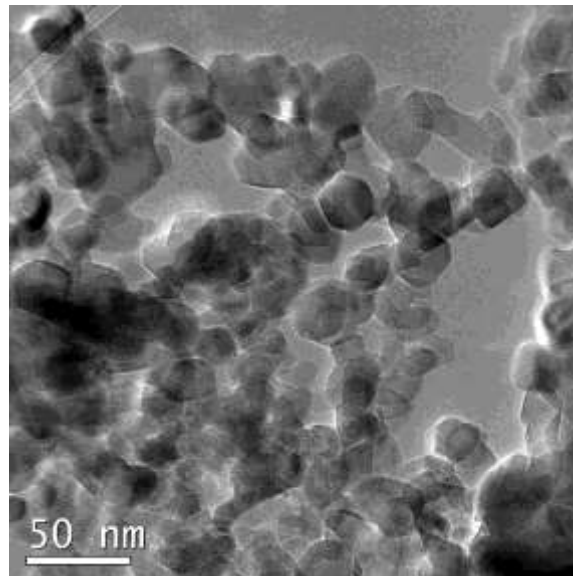


Cosmetic Powders, Confirmed as Nano by TEM

Nanopowder M
(Moisturizing Powder)

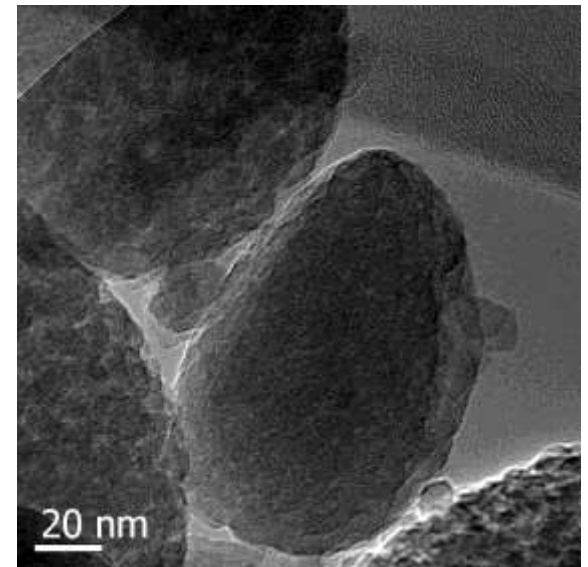
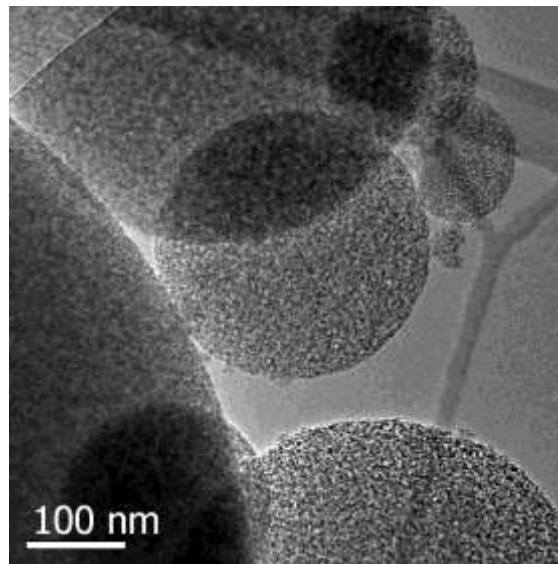
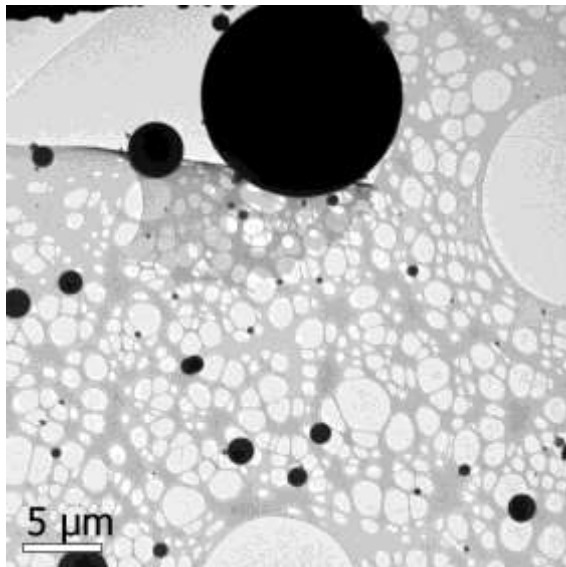


Nanopowder K
(Sunscreen)



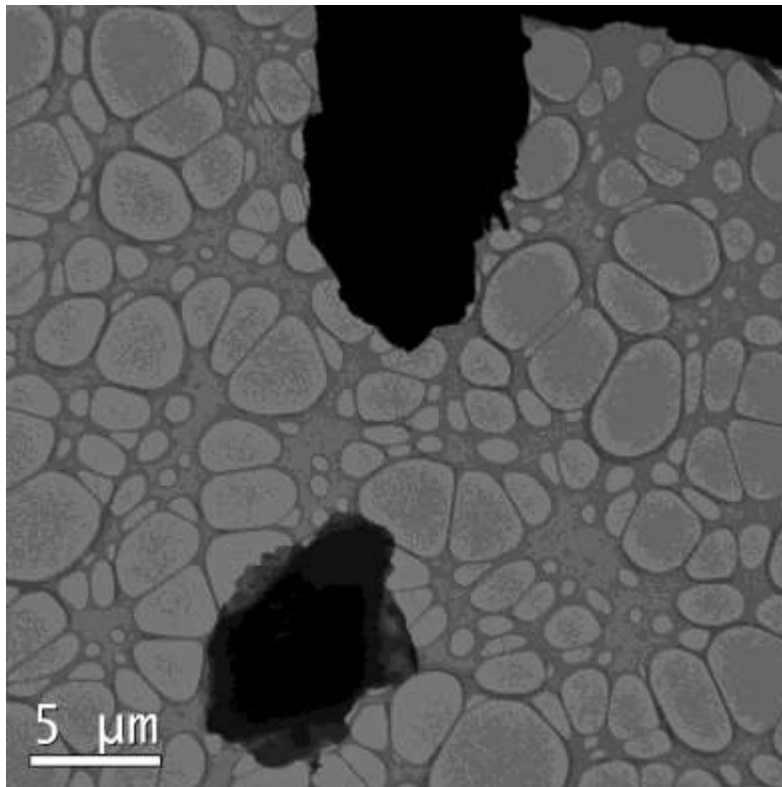
Cosmetic Powders, Confirmed as Nano by TEM

Regular Powder E (Cosmetic Powder)

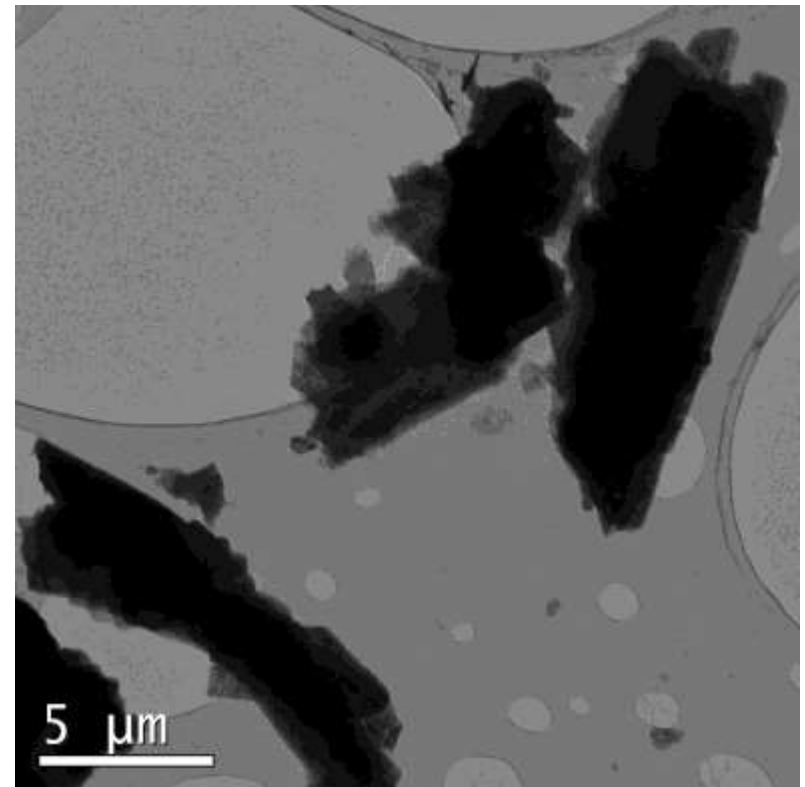


Cosmetic Powders, NOT Shown as Nano by TEM

- Similarities between certain nano and regular cosmetic powders;
- The “Nano” status of a product does not necessarily mean it contains detectable nanoparticles.



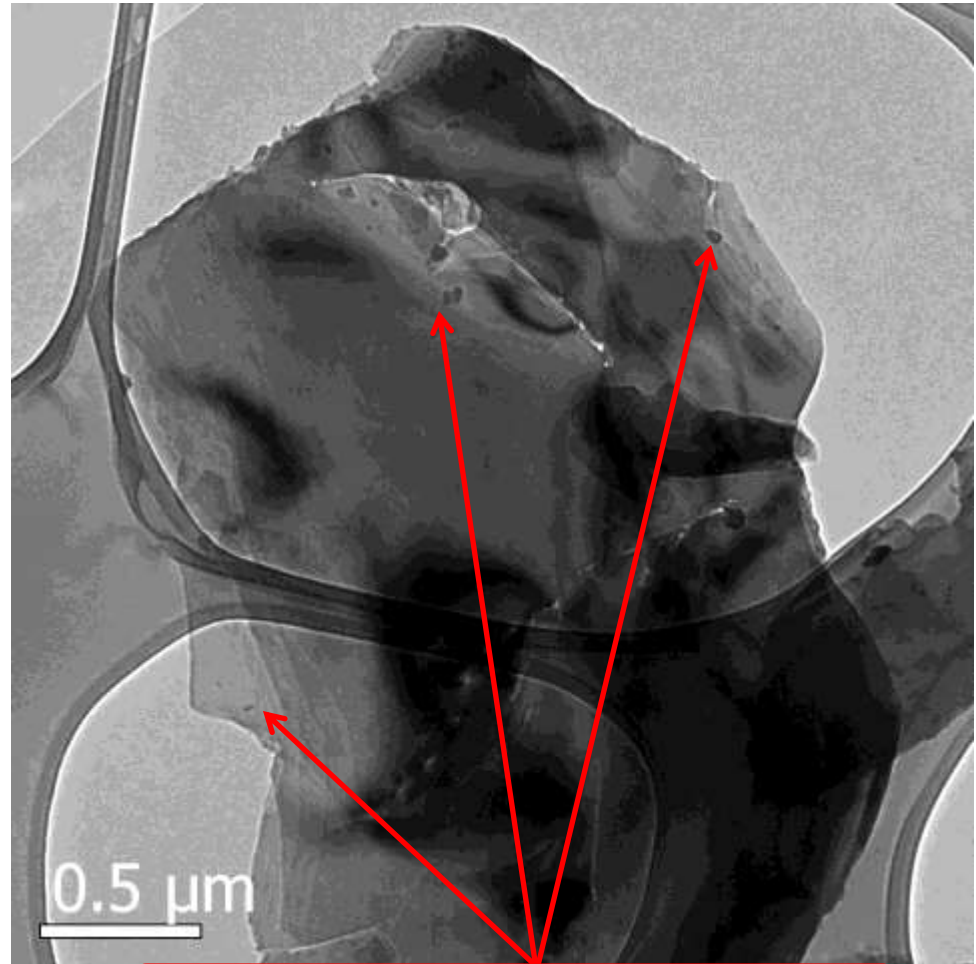
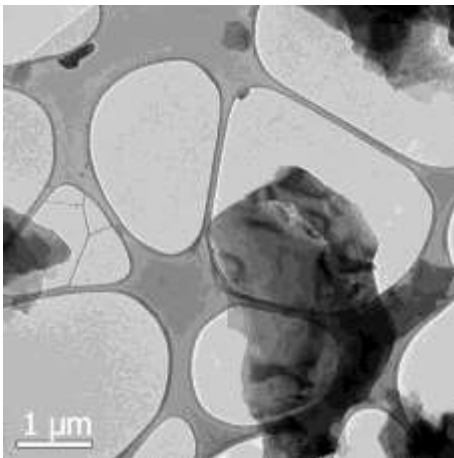
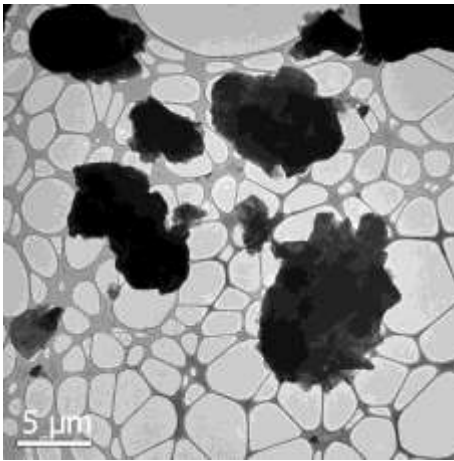
Nanopowder D (Blusher)



Regular Powder G (Blot Powder)

Cosmetic Powders, a Special Case – by TEM

Regular Powder F (Blot Powder)



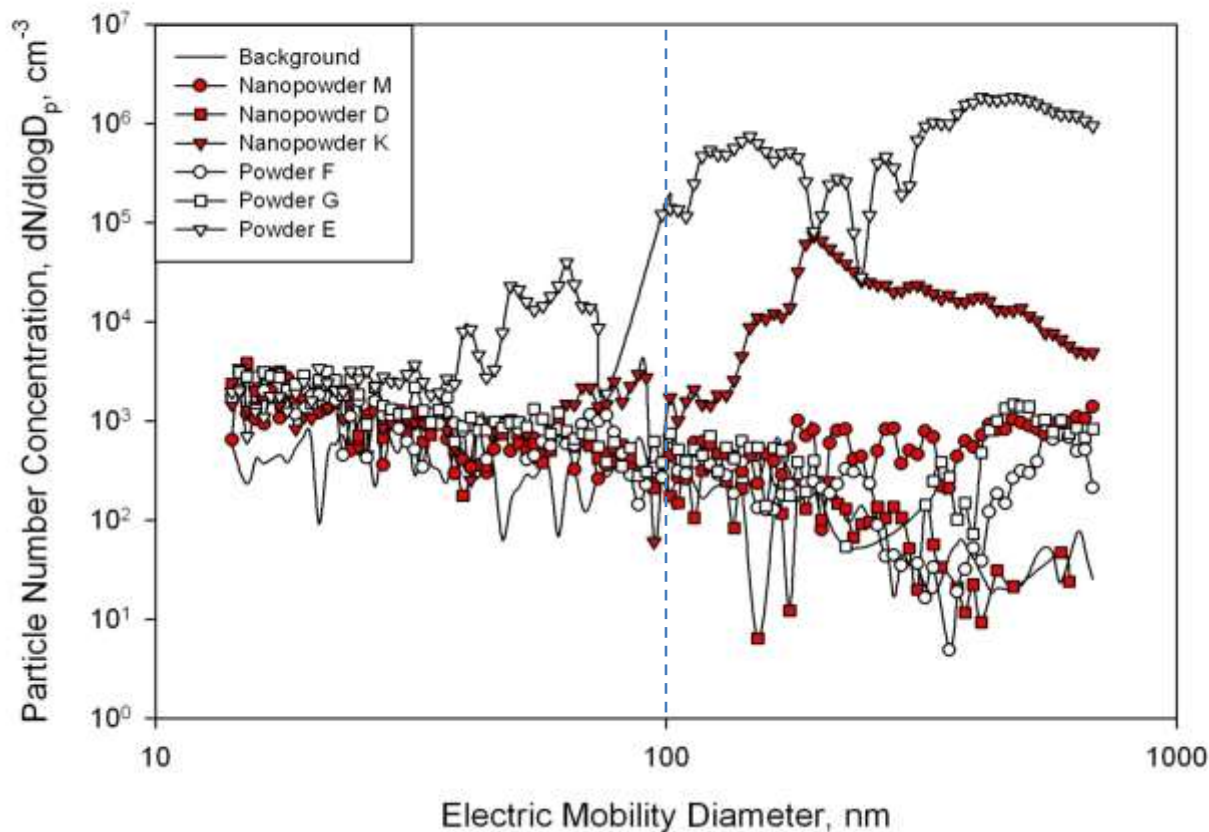
Nanoscale inclusions, unclear if on the surface or inside larger particles

Results: Cosmetic Powders (TEM)

Product	TEM Range of Particle Diameters, Agglomeration, Shape, Structure, Electron Beam Sensitivity	Presence of particles <100 nm
Nanopowder M	6 – 45 nm	No separate, all particles are <100 nm and agglomerated
Nanopowder D	> 5 µm, single particles , irregular, solid, beam insensitive	No separate, no agglomerated
Nanopowder K	7 nm - > 3 µm, only agglomerates, angular spheroidal, solid, beam insensitive	No separate, many agglomerated
Powder F	12 nm – > 8.8 µm, single particles and agglomerates, angular composite, beam insensitive	No separate, many in composites within large particles
Powder G	62.5 nm – > 10 µm, single particles and agglomerates, irregular, solid, beam insensitive	Very few separate, unclear if larger particles are or are not agglomerates of nanoparticles
Powder E	23.3 nm – > 12.8 µm, single particles and agglomerates, spheroidal, solid, beam insensitive	No separate, many agglomerated and attached to the surface of large particles

Results: Cosmetic Powders

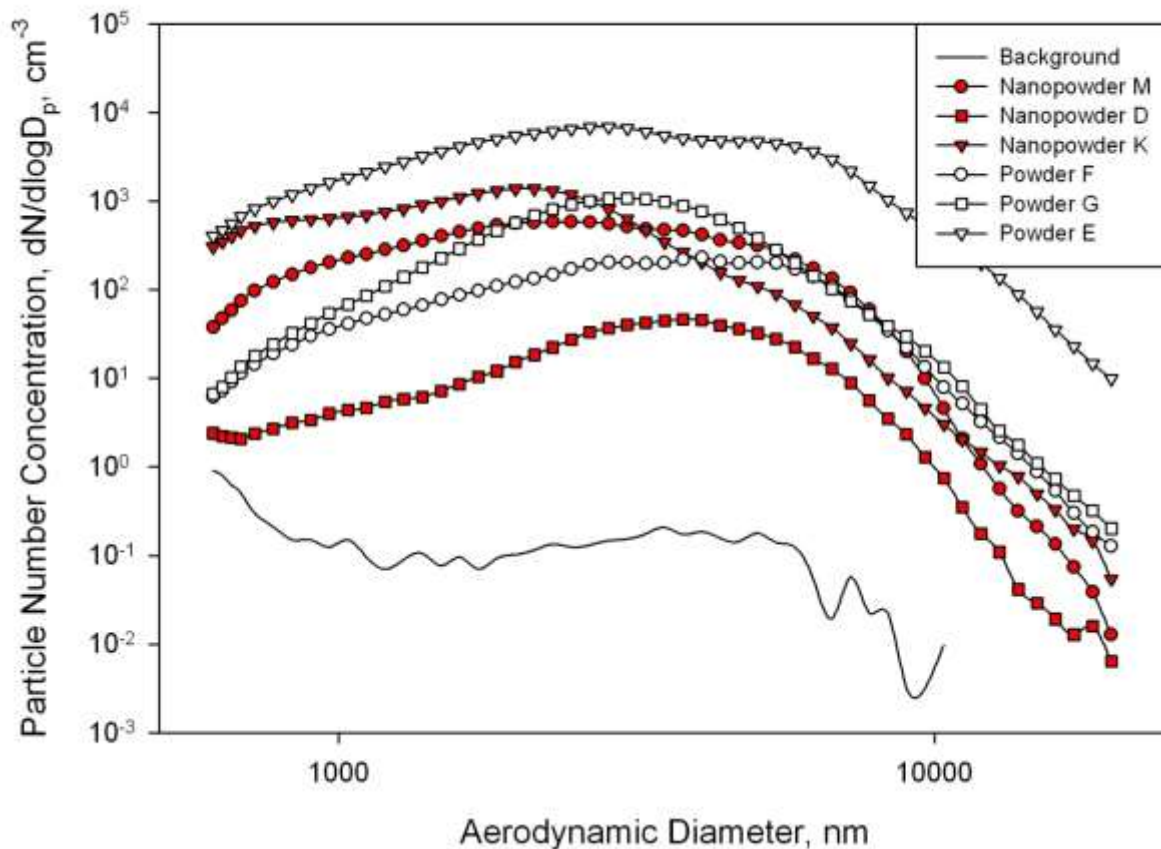
Airborne Particle Size Distributions of the Cosmetic Powder Products



- In the nanosize range of the **SMPS** (14.1 nm – 98.2 nm), the aerosol particle size distribution for 4 cosmetic powders was very similar. Nanopowder K and especially Regular Powder E differed.

Results: Cosmetic Powders

Airborne Particle Size Distributions of the Cosmetic Powder Products



- In the **APS** measurement range (0.6 – 19.8 μm), the simulated inhaled particle concentrations resulting from the application of different powders **differed substantially from each other.**

Results: Cosmetic Powders (SMPS, APS)

Product	Purpose**	SMPS, Mannequin Head Sampler: Mode(s) Diameter	APS, Mannequin Head Sampler: Mode Diameter
Nanopowder M	Moisturizer	Not prominent < 100 nm	2.5 µm
Nanopowder D	Blusher	Not prominent < 100 nm	3.8 µm
Nanopowder K	Sunscreen	88.2, 194.6 nm	2.1 µm
Powder F	Blot Powder	Not prominent < 100 nm	4.0 µm
Powder G	Blot Powder	Not prominent < 100 nm	3.0 µm
Powder E	Cosmetic Powder	63.8, 145.9, 414.2 nm	2.8 µm

Nanomaterial Dose Assessment

- Performed for the cosmetic powders
 - Calculated for a **typical consumer** – a female 18 – 60 years old
 - Covered the total **14 nm – 20 μm** aerosol particle size range
 - Calculated how much particulate matter (PM) would be inhaled and how much would deposit in different regions of the human respiratory system: “**inhaled dose**” and “**deposited dose**” per 1-minute cosmetic powder application



Methods: Nanomaterial Dose Assessment

Inhaled Dose

$$I_{inh} = f_{nano} \cdot C_{inh} \cdot IH_{air} \cdot T_{contact} / Bw \quad (1),$$

where:

I_{inh} – inhaled dose of particulate matter per application (**ng/kg bw/application**);

C_{inh} – mass concentration of particulate matter in inhaled air (ng/L);

IH_{air} – inhalation flow rate for a given gender/activity scenario (L/min);

$T_{contact}$ – duration of contact per application (min);

Bw – body weight (kg);

f_{nano} – mass fraction of nanomaterial(s) in the inhaled aerosol.

$$C_{inh} = IF \cdot C_{air}$$

where:

C_{air} – mass concentration of aerosol particulate matter in the personal breathing cloud;

IF – inhalability fraction.

It is assumed that the concentration of nanomaterial(s) in the initial product is proportional to the concentration of nanomaterial in the inhaled aerosol.

Methods: Nanomaterial Dose Assessment

Deposited Dose = DF_{region of respiratory system} · Inhaled Dose

$$DF_{HA} = \left(\frac{1}{1 + \exp(6.84 + 1.183 \ln d_p)} + \frac{1}{1 + \exp(0.924 - 1.885 \ln d_p)} \right) \quad (4),$$

$$DF_{TB} = \frac{\left(\frac{0.00352}{d_p} \right) \left[\exp(-0.234(\ln d_p + 3.40)^2) + 63.9 \exp(-0.819(\ln d_p - 1.61)^2) \right]}{1 - 0.5 \left(1 - \frac{1}{1 + 0.00076 d_p^{2.8}} \right)} \quad (5),$$

$$DF_{AL} = \frac{\left(\frac{0.0155}{d_p} \right) \left[\exp(-0.416(\ln d_p + 2.84)^2) + 19.11 \exp(-0.482(\ln d_p - 1.362)^2) \right]}{1 - 0.5 \left(1 - \frac{1}{1 + 0.00076 d_p^{2.8}} \right)} \quad (6),$$

$$DF = \left(0.0587 + \frac{0.911}{1 + \exp(4.77 + 1.485 \ln d_p)} + \frac{0.943}{1 + \exp(0.508 - 2.58 \ln d_p)} \right) \quad (7)$$

where:

d_p – particle size (μm);

DF_{HA} – deposition fraction for the head airways;

DF_{TB} – deposition fraction for the tracheobronchial region;

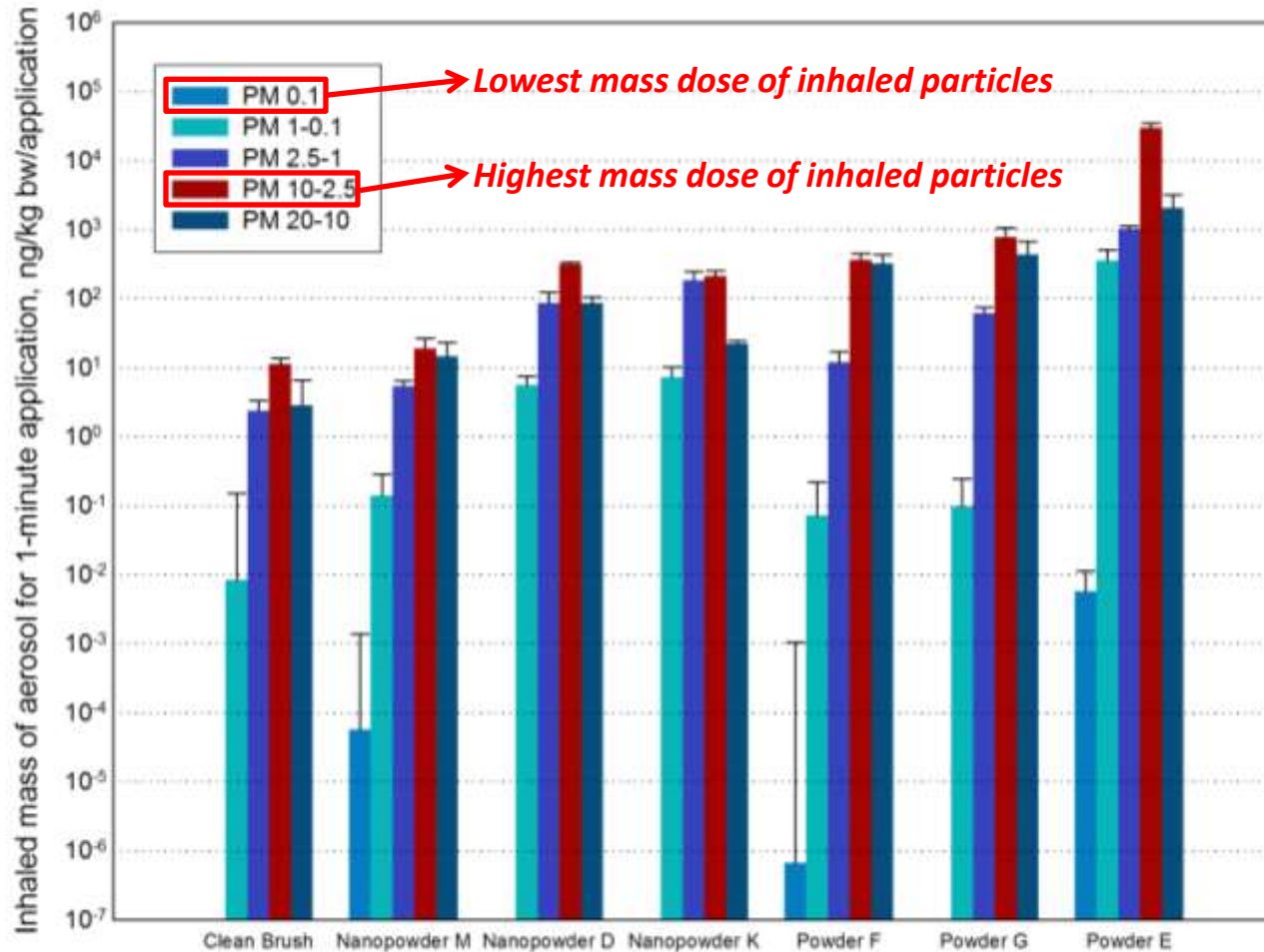
DF_{AL} – deposition fraction for the alveolar region;

DF – the total deposition fraction of the inhaled particulate matter.

Equations (2, 4, 5, 6, 7) from Hinds, W.C. (1999) Aerosol technology: properties, behavior, and measurement of airborne particles. New York, NY: John Wiley & Sons, Inc., 483pp

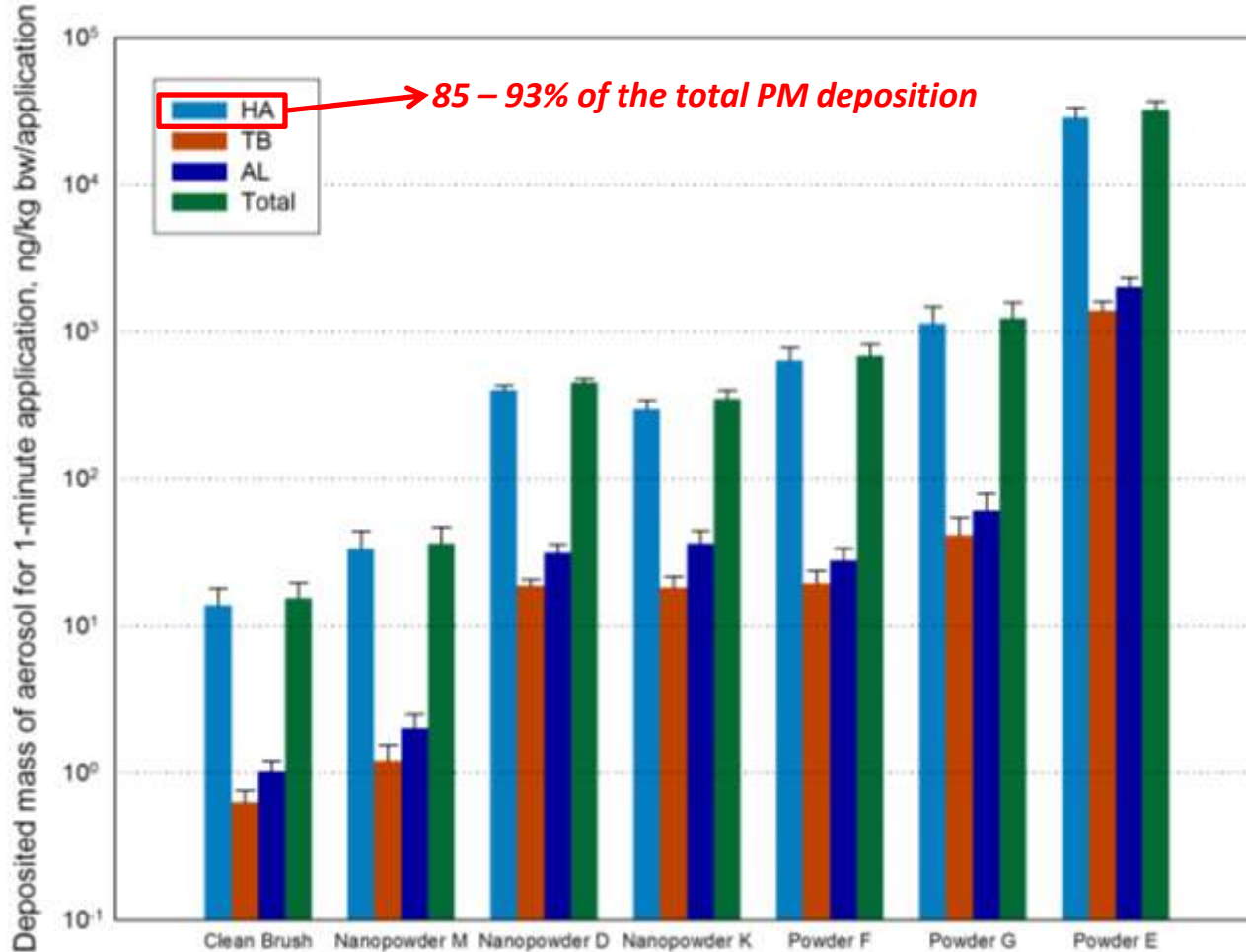
Results: Nanomaterial Dose Assessment

Inhaled Dose from 1-minute application of cosmetic powders



Results: Nanomaterial Dose Assessment

Deposited Dose from 1-minute application of cosmetic powders



→ Deposited Dose as Percentage of Total PM Deposition

Conclusions I

- Exposure to ultrafine including engineered nanoparticles can cause or contribute to **adverse health effects**;
- **Nanoparticles can be found ubiquitously** in consumer products, claimed to contain nanomaterials as well as “regular” (not marketed as nanotechnology-based) products;
- Use of nanotechnology-based consumer products can lead to **inhalation exposure** to single and agglomerated nanoparticles;
- Existing sampling and analytical techniques do **allow collection and characterization** of ultrafine particles including engineered nanomaterial particles;

Conclusions II

- By mass, inhaled dose of the aerosol fractions above 100 nm is much higher (3-8 orders of magnitude) than of individual nanoparticles or their agglomerates **smaller than 100 nm (nanoagglomerates)**;
- By mass, between **85 and 93%** of the total deposition of inhaled particulate matter occurred **in the HA region** of the human respiratory system in the case of the cosmetic powders we investigated;
- **The head airways and, to a lesser extent, the tracheobronchial region** are important in addition to the alveolar region as the **deposition sites** of nanomaterial-containing particulate matter.

Conclusions III

- The particle size distributions in the products and the derived aerosol are different;
- For the consumer spray products, different spraying (aerosolization) techniques produce different aerosol particle size distributions;
- It is currently hard or impossible to determine if nanoparticles, found in the products are engineered or derived from natural ingredients, especially when manufacturers do not disclose this information;
- Both natural and engineered nanomaterials are currently subject of the “**U.S. EPA Nanotechnology Reporting and Record-keeping Requirements Rule**” under TSCA section 8(a) and will likely be subject of future regulations.

Conclusions IV

- The European Union **already regulates nanotechnology-based cosmetic products**. It is unclear if and how the US will follow in the EU's footsteps, but it may so happen that the issue of inhalation exposure from cosmetic products in general could become subject of regulations in the US.
- **Both natural and engineered** nanomaterials are currently subject of the “**U.S. EPA Nanotechnology Reporting and Record-keeping Requirements Rule**” under TSCA section 8(a) and will likely be subject of future regulations.

Questions?

Yevgen Nazarenko, Ph.D.
Department of Atmospheric and Oceanic Sciences
McGill University
Room 726, Burnside Hall
805 Sherbrooke Street West, Montreal, QC H3A 0B9
E-mail: yevgennazarenko@gmail.com; yevgen.nazarenko@mcgill.ca
Tel: (732) 470-0201
Fax: (514) 398-6115

Considerations for Inhalation Safety Assessment: Approaches and Application

Madhuri Singal, PhD, RRT, DABT
Inhalation Toxicologist, Senior Consumer Safety Associate
Reckitt Benckiser, LLC
CIR Expert Panel Meeting, Washington, D.C.
September 11th, 2017



HEALTH • HYGIENE • HOME

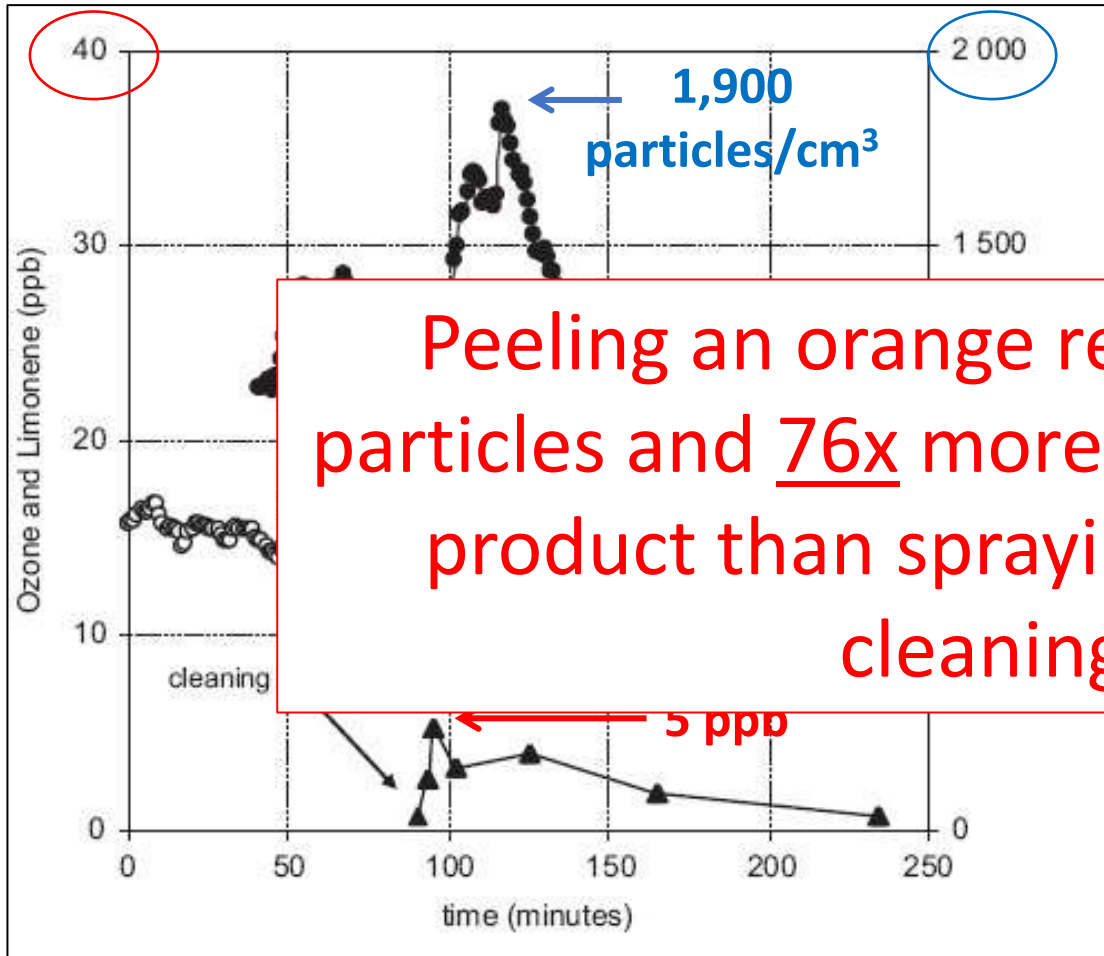
Objectives

- Inhalation exposure assessment paradigm
- Gases, vapors, and droplets/particles
- Particle specifications
- Air exposure versus deposition and bioavailability
 - 2-Box Air Dispersion Model
 - Multiple Path Particle Deposition Model
- Translating air concentration to systemic dose
 - Local effects versus systemic toxicity
- Data assessment and evaluation of exposure margin of safety

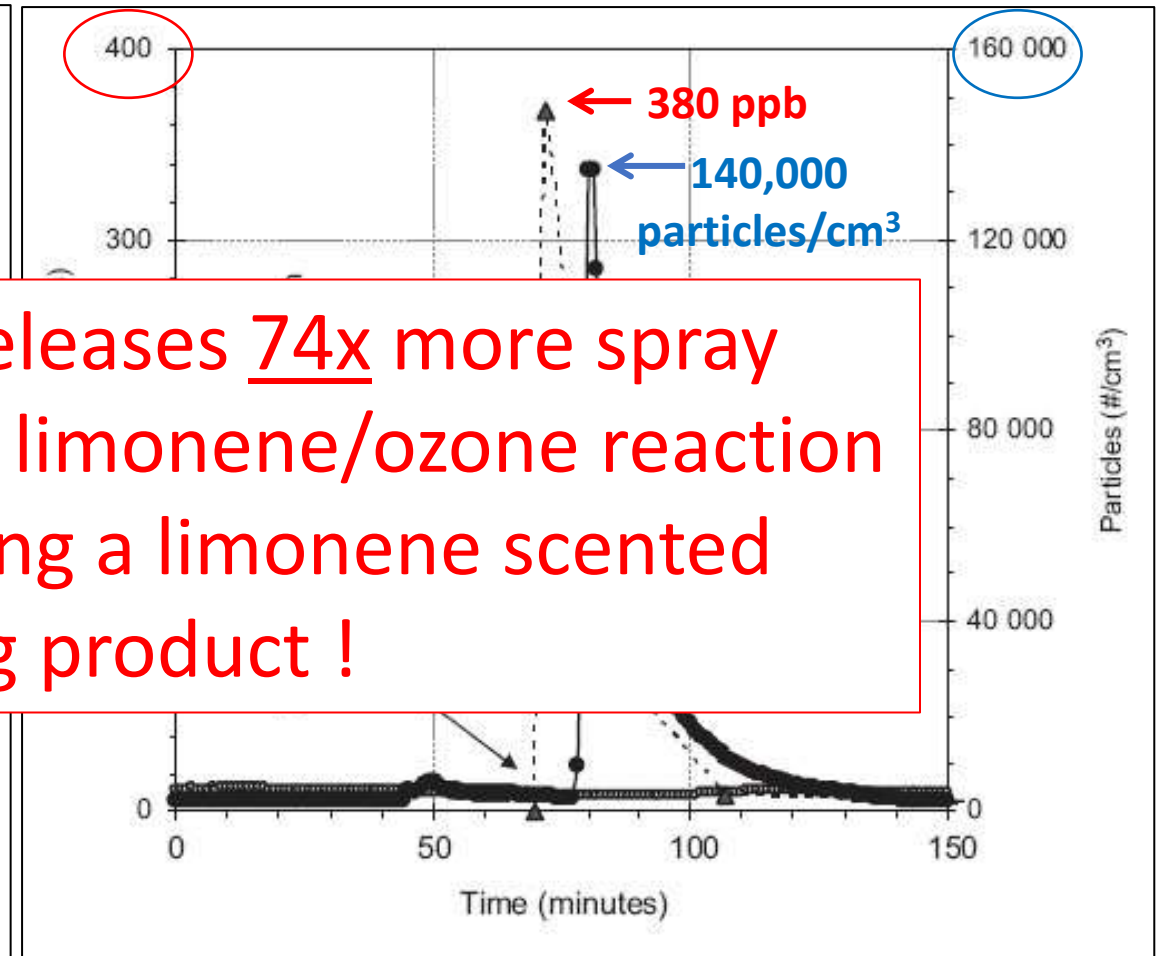


Exposure, Air Concentration and Context

Lemon Cleaning Product



Whole Fruit Orange



Peeling an orange releases 74x more spray particles and 76x more limonene/ozone reaction product than spraying a limonene scented cleaning product !

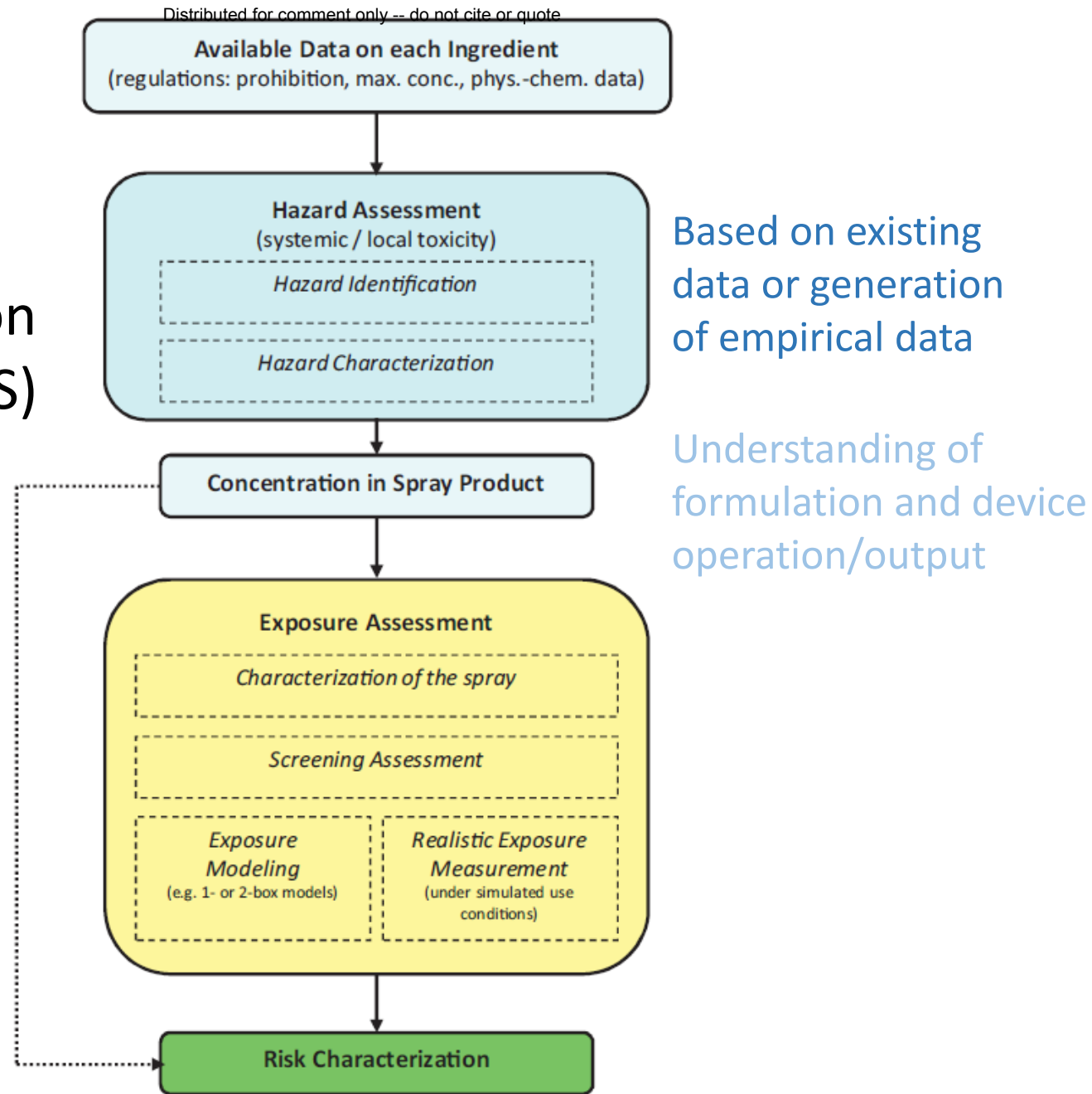
Langer, et al., Atmospheric Environment, 2008

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Inhalation Safety Assessment per EU Scientific Committee on Consumer Safety (SCCS)

Application of parameters for
formulation and device using
in silico prediction methods

Comparison to existing data or
toxicological threshold of
concern (in absence of data)



SCCS, 2012

Defining Inhalation Assessment Parameters

- Airborne concentration (mg/m³)
- Air Exchange Rate (ACH)
 - $N = (60 * Q) / Vol$
 - Where:
 - N = number of air changes per hour
 - Q = Volumetric flow rate of air
 - Vol = Space volume L × W × H
- Particle/Droplet size distribution (MMAD and GSD)
- Respiratory rate and tidal volume
 - Based on age, activity and health
- Duration of exposure
- Chemical, physical or biological properties of the hazardous



What's in the Air? - Distinct Characteristics

- Gases, vapors, and particles/droplets
 - Low vapor pressure compounds (droplet phase and solid particles)
 - Medium vapor pressure compounds (mixture of vapor and particle phases)
 - High vapor pressure compounds (vapor phase)
 - Nanosize droplets/particles are modeled by MPPD as the vapor component emulates nanosized droplets/particle behavior
 - Nanoscale is defined as a dimension between 1-100 nm (ISO, 2008)
 - Nanoparticle – having a mean mass aerodynamic diameter of 1-100 nm
 - Nanomaterial – an aerosol dispersion containing >50% droplets/particles characterized as nanoscale

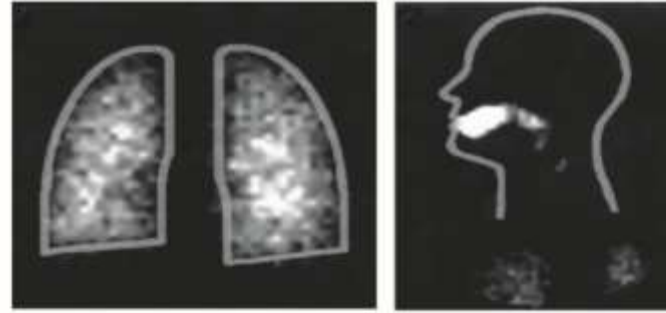


Particle/Droplet Specifications

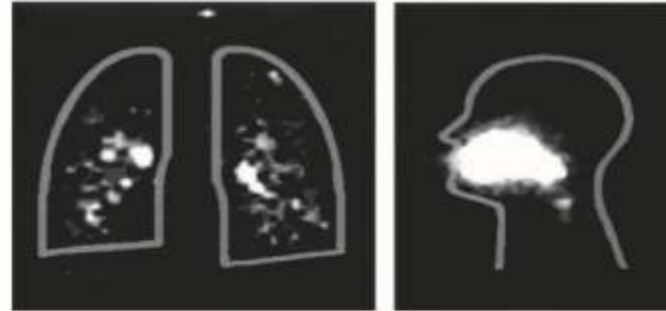
- Mean mass aerodynamic diameter and geometric standard deviation
 - Size dictates depth of deposition
 - Cells affected will determine impact of exposure
- Biochemical reactivity
 - Interaction with phospholipid bilayer of the cell membrane
 - Potential for paracellular transport and interaction with internal cellular processes
 - Activation of oxidant-mediated systems
- Structure and solubility
 - Mass per surface area
- Surface charges



HFA



CFC

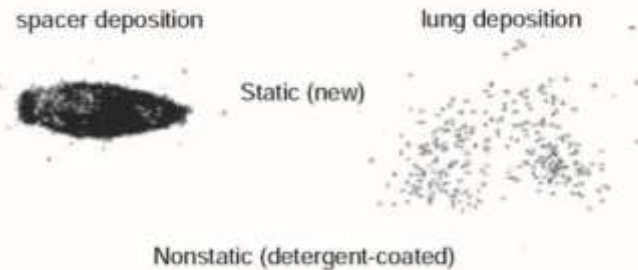


Evaluation of deposition efficiency and impact of propellant

HFA = hydrofluoroalkane

CFC = chlorofluorocarbon

Static



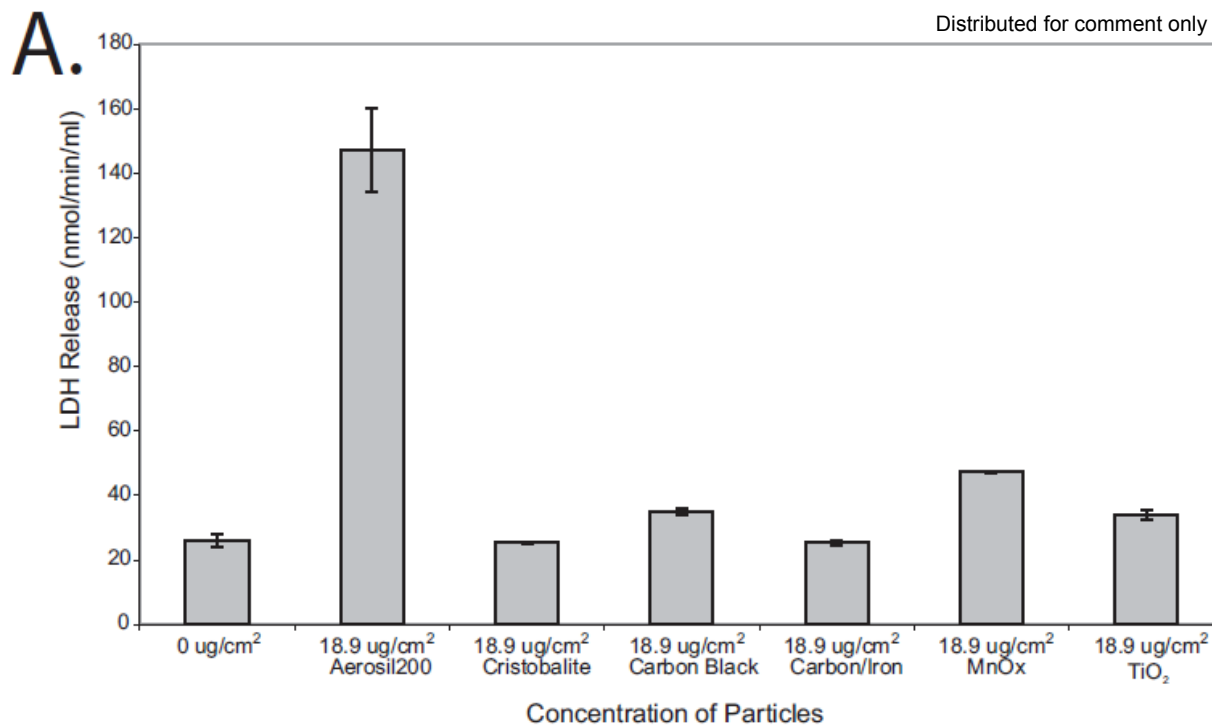
Non-Static



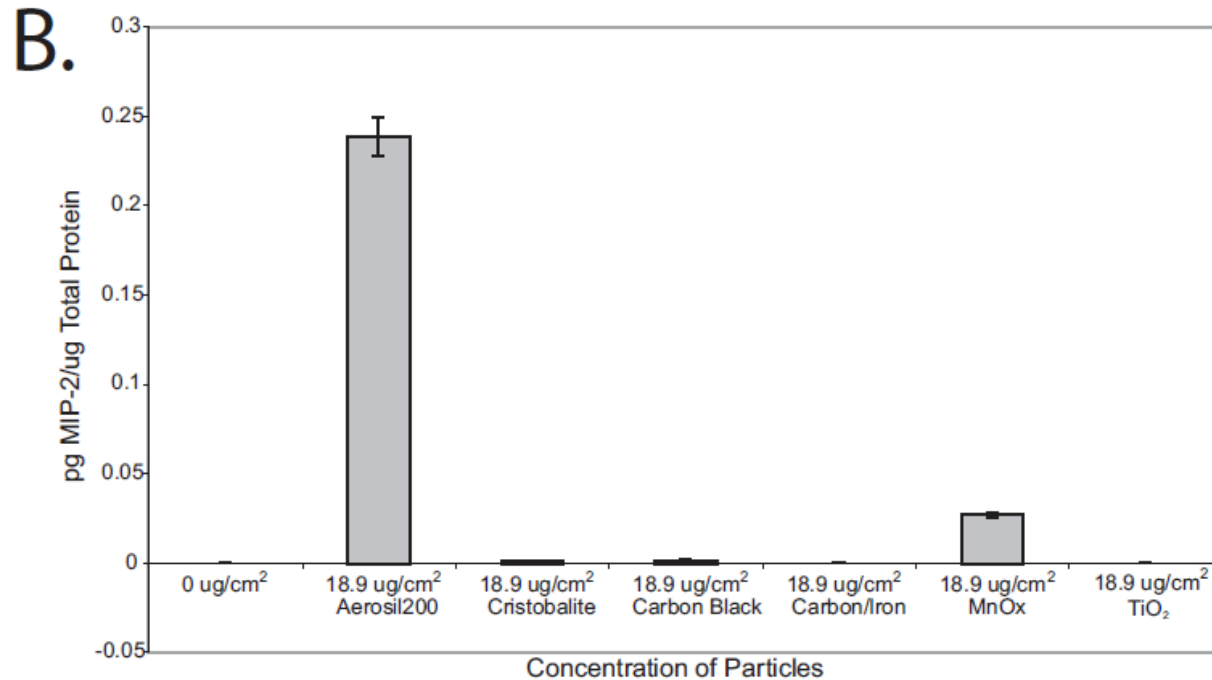
Evaluation of deposition efficiency and impact of surface static charge

Hess, et al., Respiratory Care Journal, June 2008



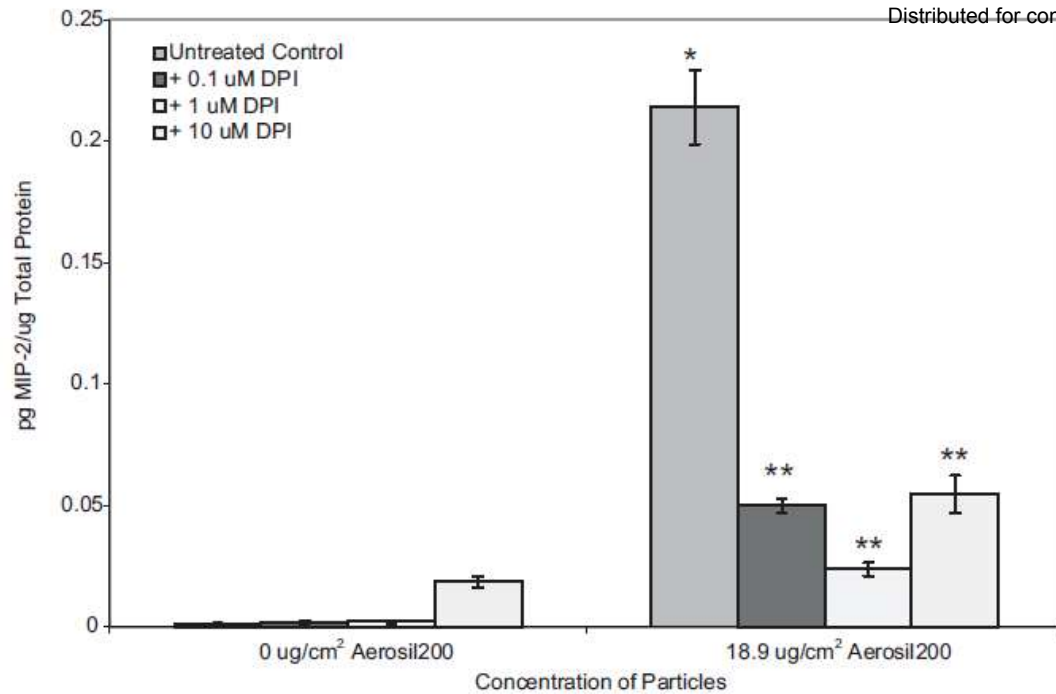


Evaluation of cytotoxicity induced by exposure to solid particles of differing structure and/or charge status

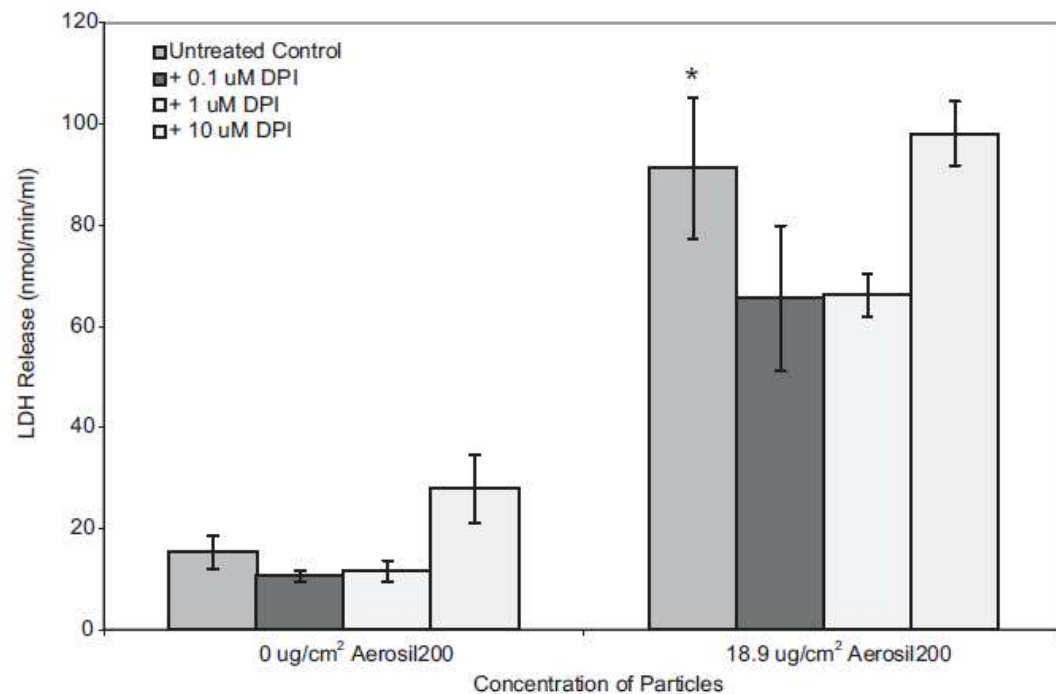


Quantification of inflammatory mediator response following exposure to solid particles of differing structure and/or charge status

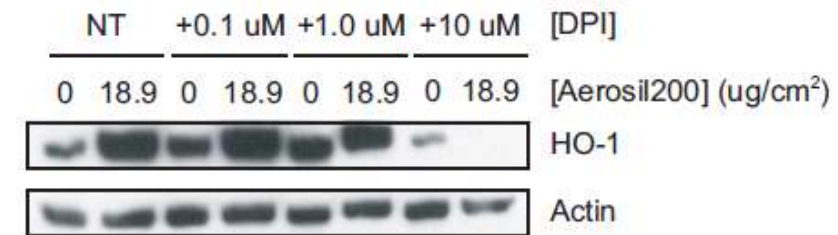


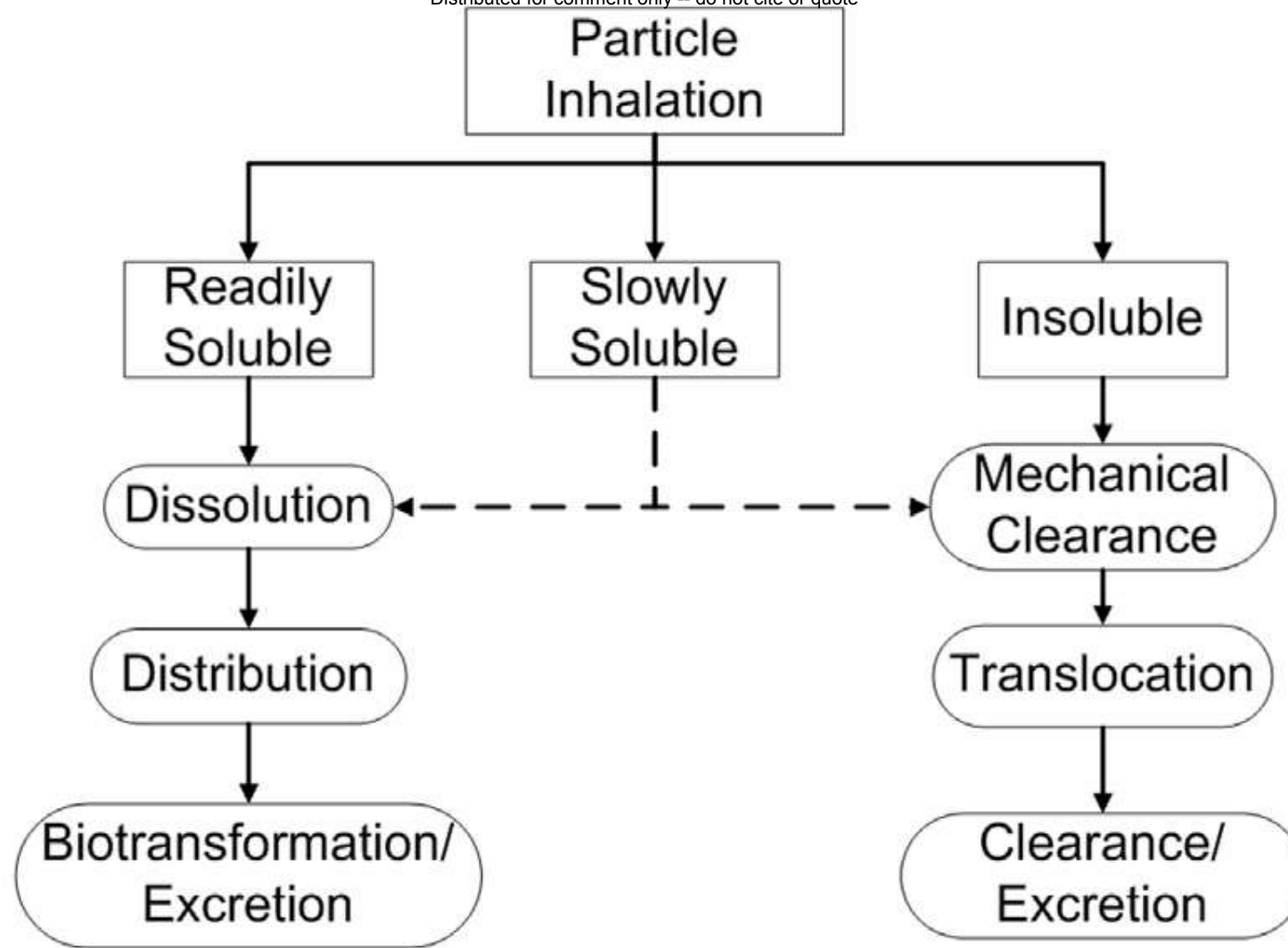


B.



C.

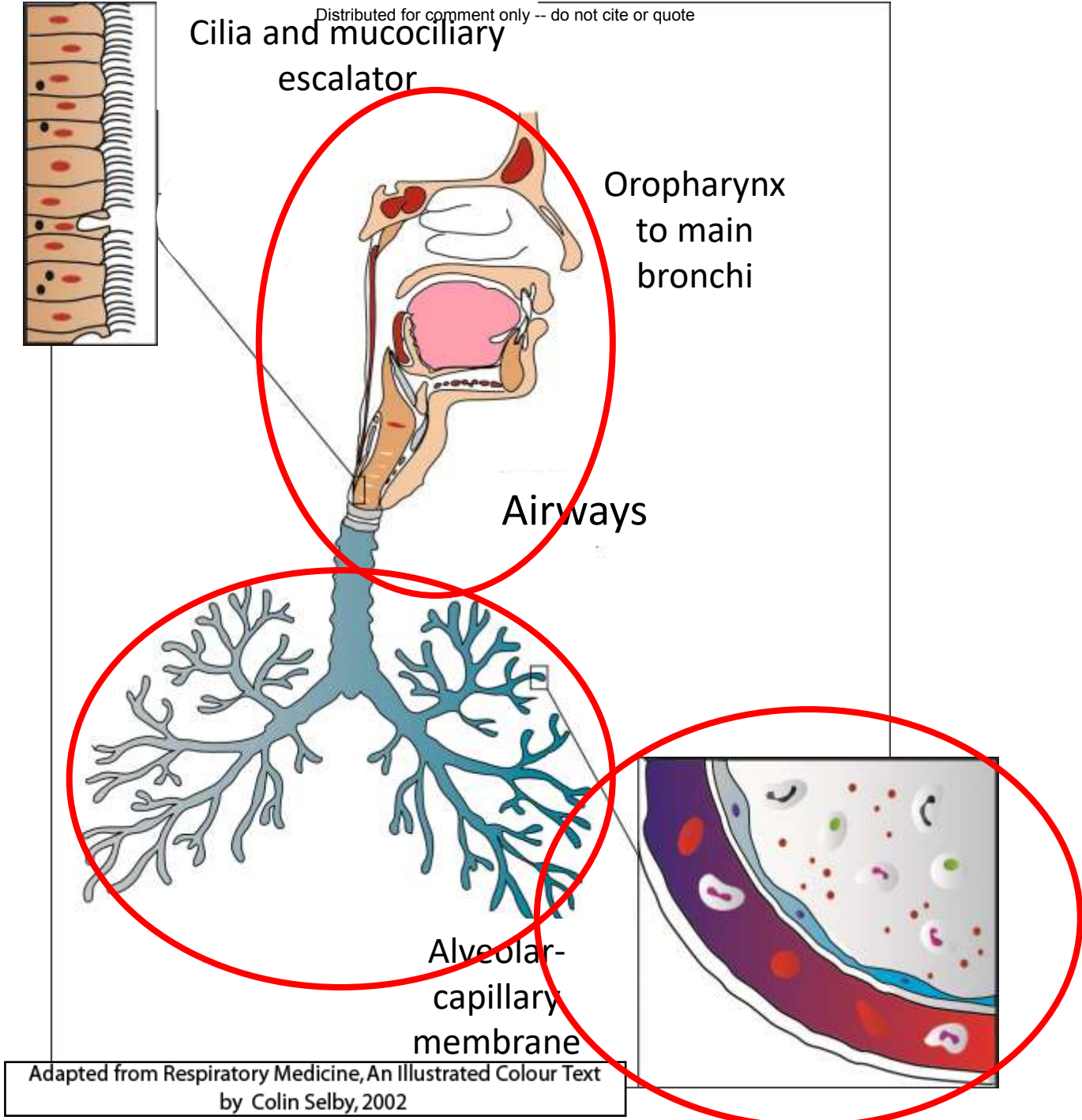




Molecular/Ionic Form

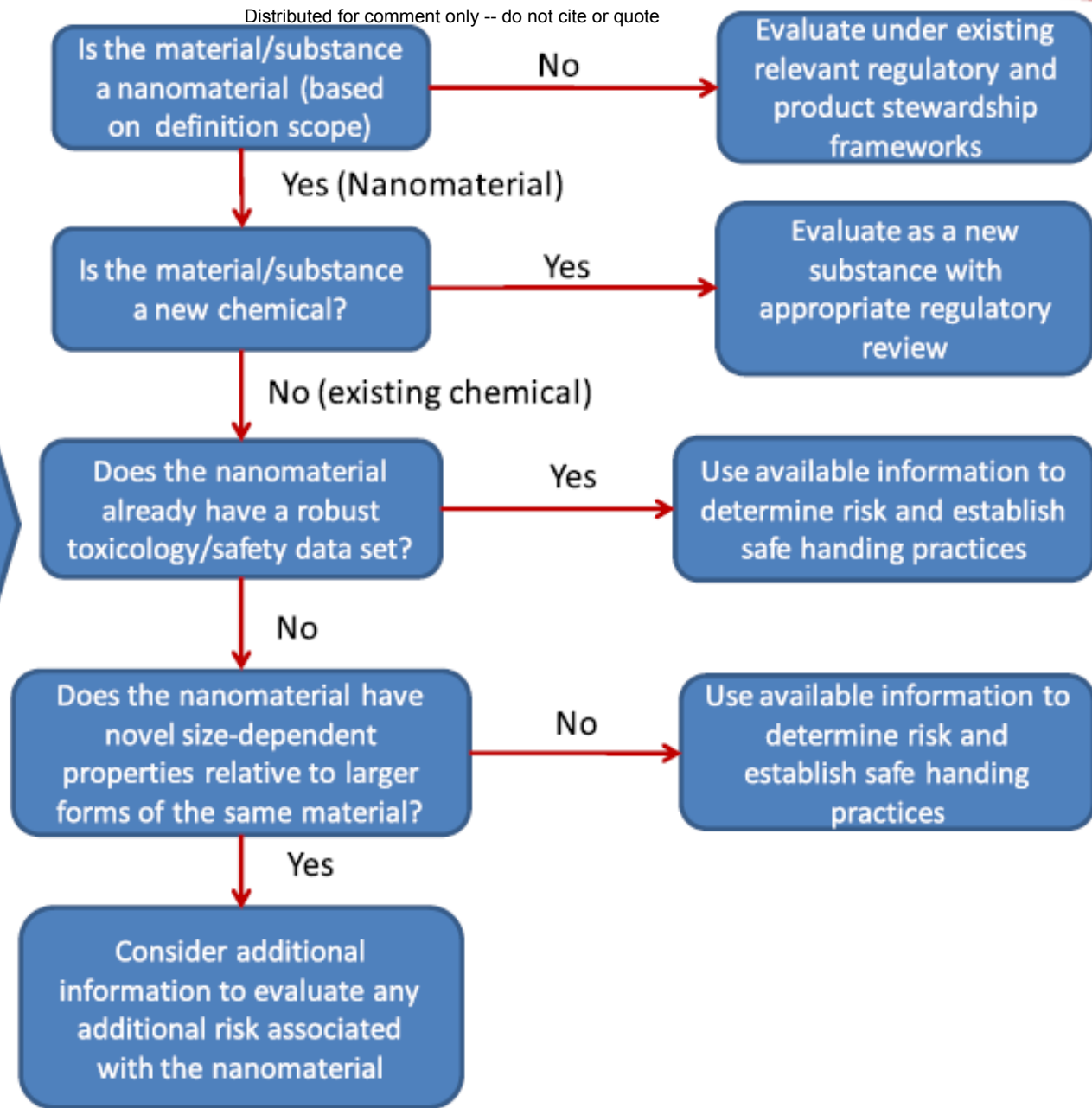
Particulate Form

Boverhof, D. et al., Regulatory Toxicology and Pharmacology 73 (2015) 137-150



Elements to consider in the identification and evaluation of nanomaterials

- Size & distribution
- Intentionally manufactured
- Aggregates
- Agglomerates
- Solubility/Dissolution rate
- Size dependent properties



Ensure products are safe for their intended use

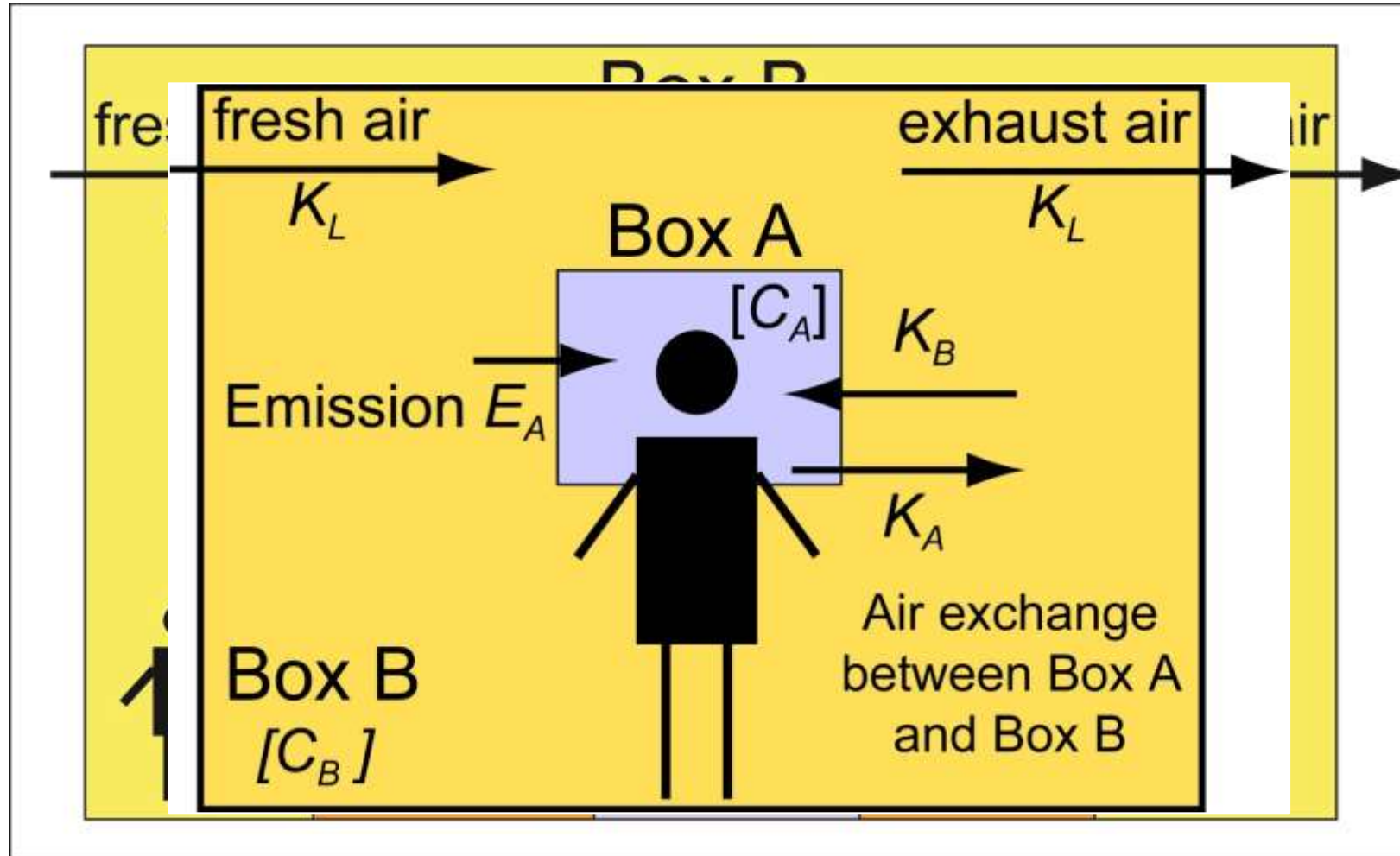


Air Exposure vs. Deposition and Bioavailability

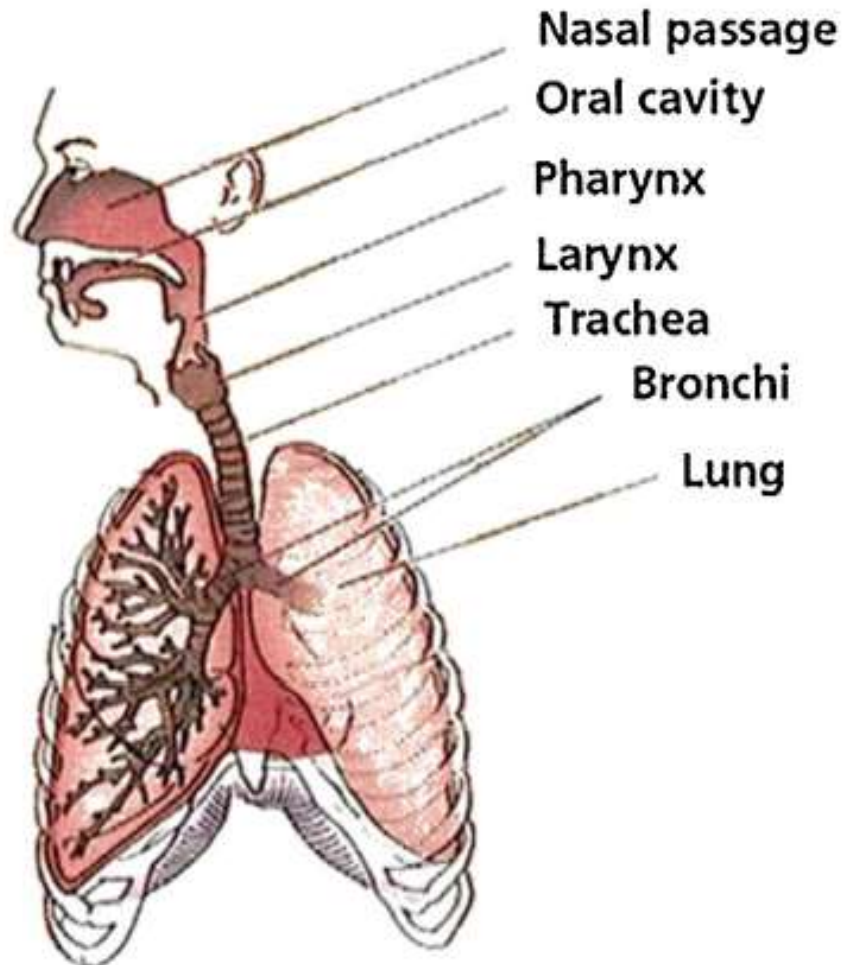
- 2-Box Air Dispersion Model, ConsExpo, IKW, BAMA, MCCCEM
 - All evaluate possible exposure under defined conservative consumer and/or occupational scenarios
 - Basic assumptions include:
 - Homogeneous distribution of emitted concentration
 - 100% potential for inhalation of airborne concentration
- Multiple Path Particle Deposition Model
 - Allows refinement of the exposure assessment by evaluation of regional deposition in the respiratory tract
 - Models include ages 3 months old to adult
 - Pulmonary condition can be modeled to emulate disease (asthma, COPD)
 - Tissue disposition can also be evaluated



2-Box Air Dispersion Model - Field Analysis



Regional Deposition



Nasopharyngeal region

Deposition: impaction, diffusion
Clearance: mucociliary, sneezing/blowing
Targeted by: $>30\ \mu\text{m}$ particles
highly reactive, water soluble gas,
"inhalable fraction"

Tracheobronchial region

Deposition: impaction, sedimentation, diffusion
Clearance: mucociliary, coughing
Targeted by: $10\text{--}30\ \mu\text{m}$ particles, $200\ \mu\text{m}$ fibres,
"thoracic fraction"

Pulmonary region (parenchyma)

Deposition: sedimentation, diffusion
Clearance: phagocytosis, solubilisation,
interstitial
Targeted by: $<10\ \mu\text{m}$ particles, $10\text{--}12\ \mu\text{m}$ fibres
less reactive/water soluble gas,
"respirable fraction"

W. Steiling et al., Toxicology Letters 227 (2014) 41–49

Predictive Power of Dosimetry Modeling

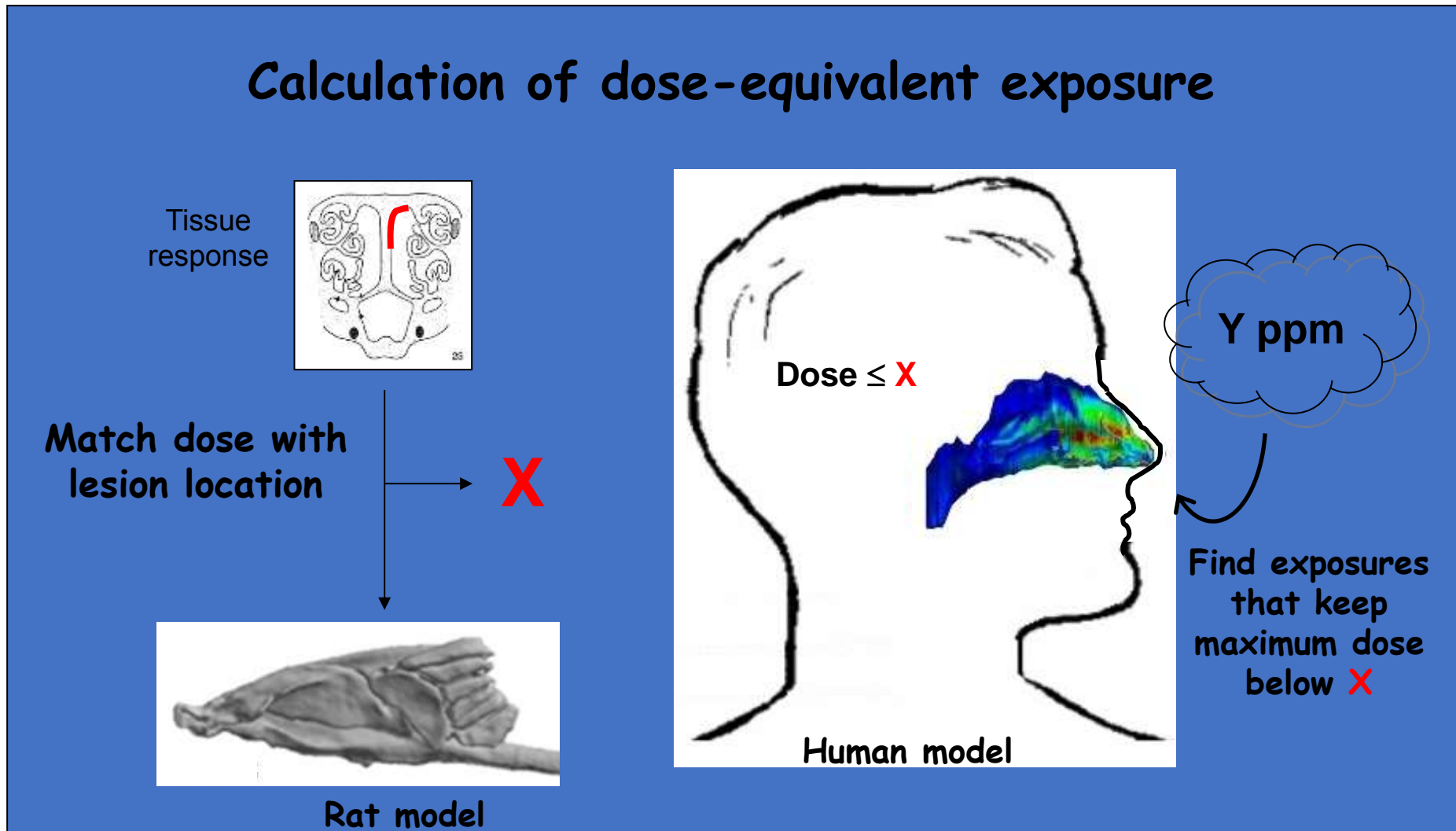
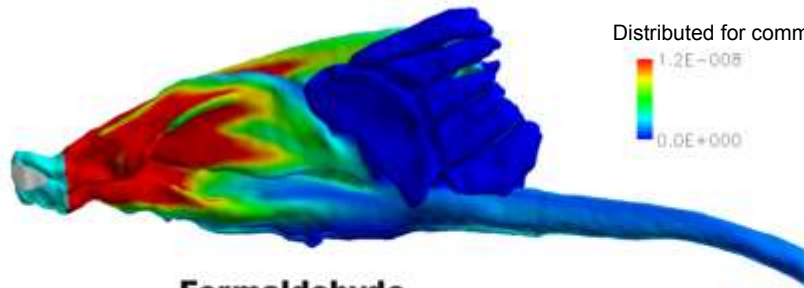


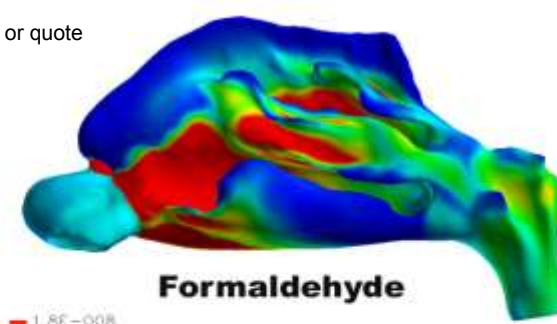
Image courtesy of Dr. Jeffry Schroeter, Applied Research Associates

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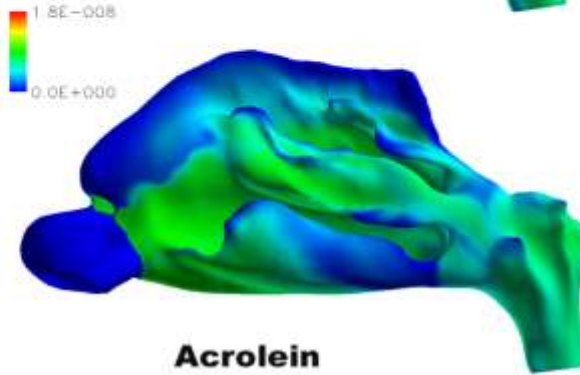
Formaldehyde



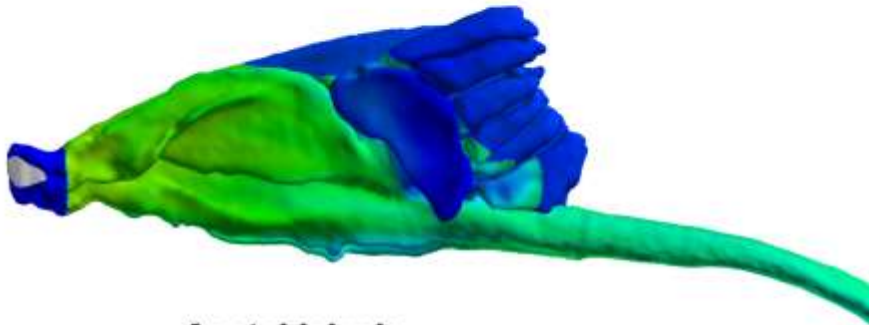
Formaldehyde



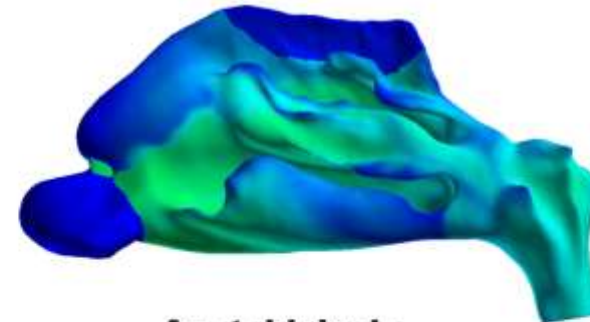
Acrolein



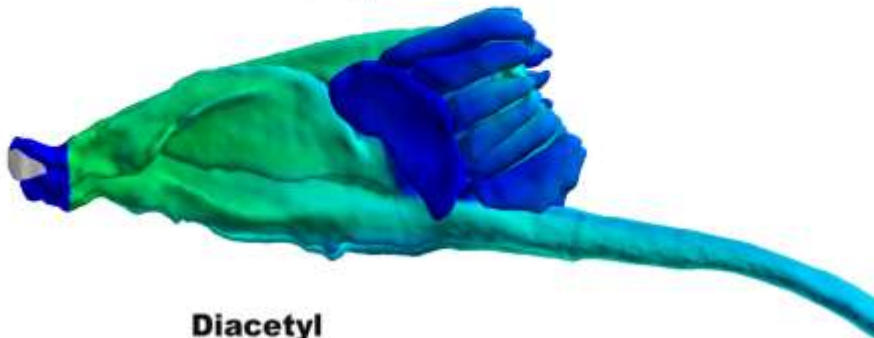
Acrolein



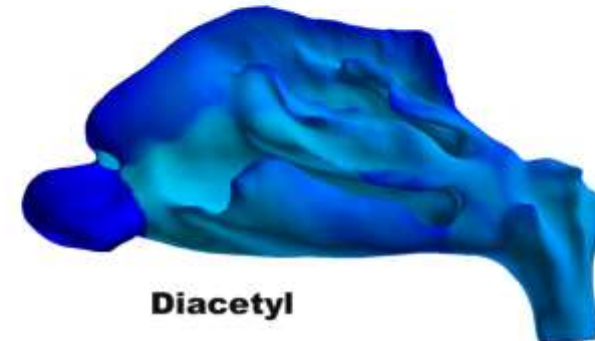
Acetaldehyde



Acetaldehyde



Diacetyl



Diacetyl



Acetaldehyde Model Predictions Match Published Experimental Data

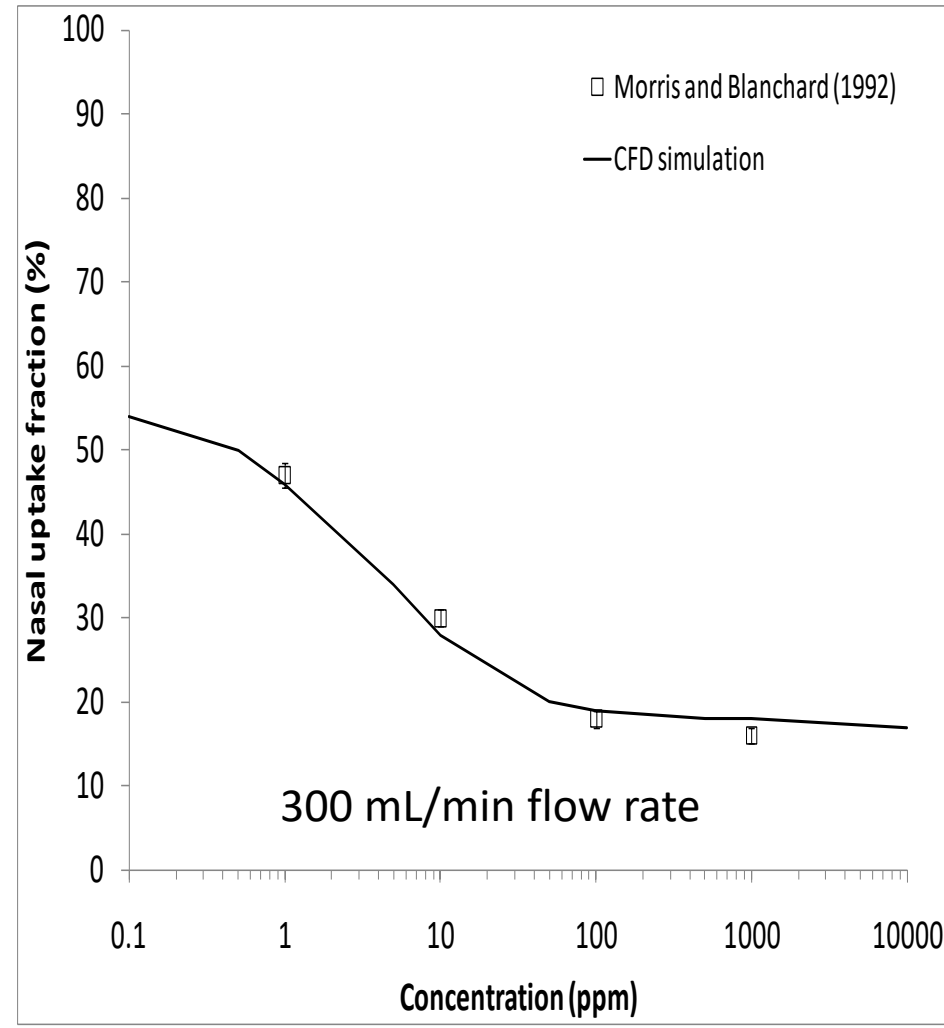
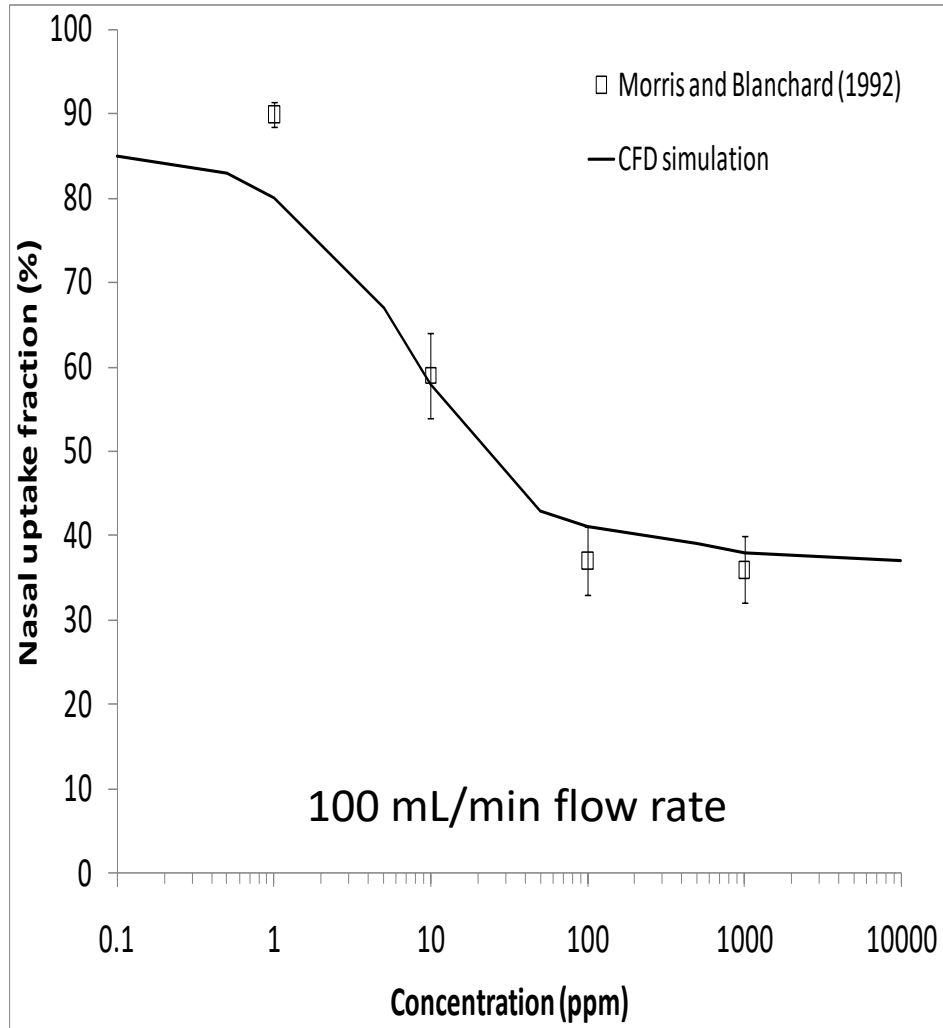


Image courtesy of Dr. Bahman Asgharian, Applied Research Associates

Human Nasal Deposition Patterns

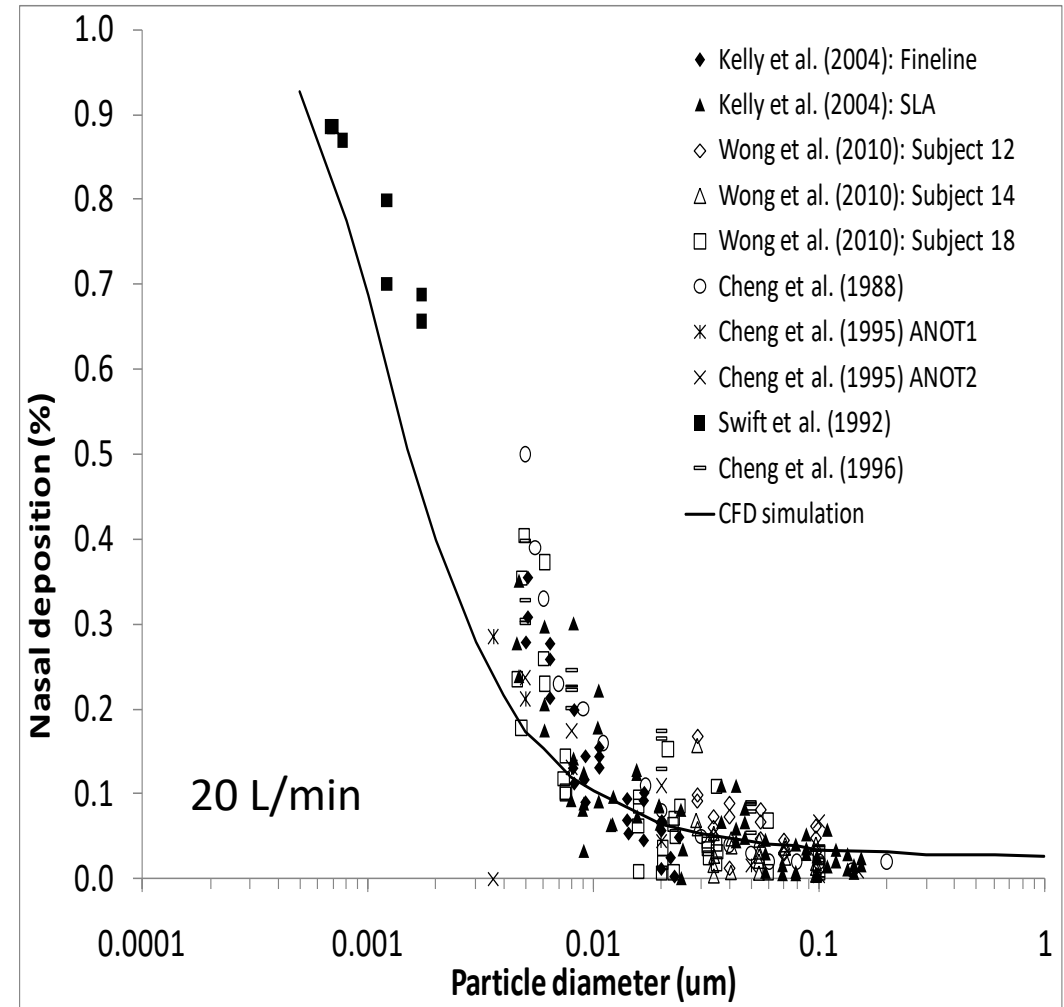
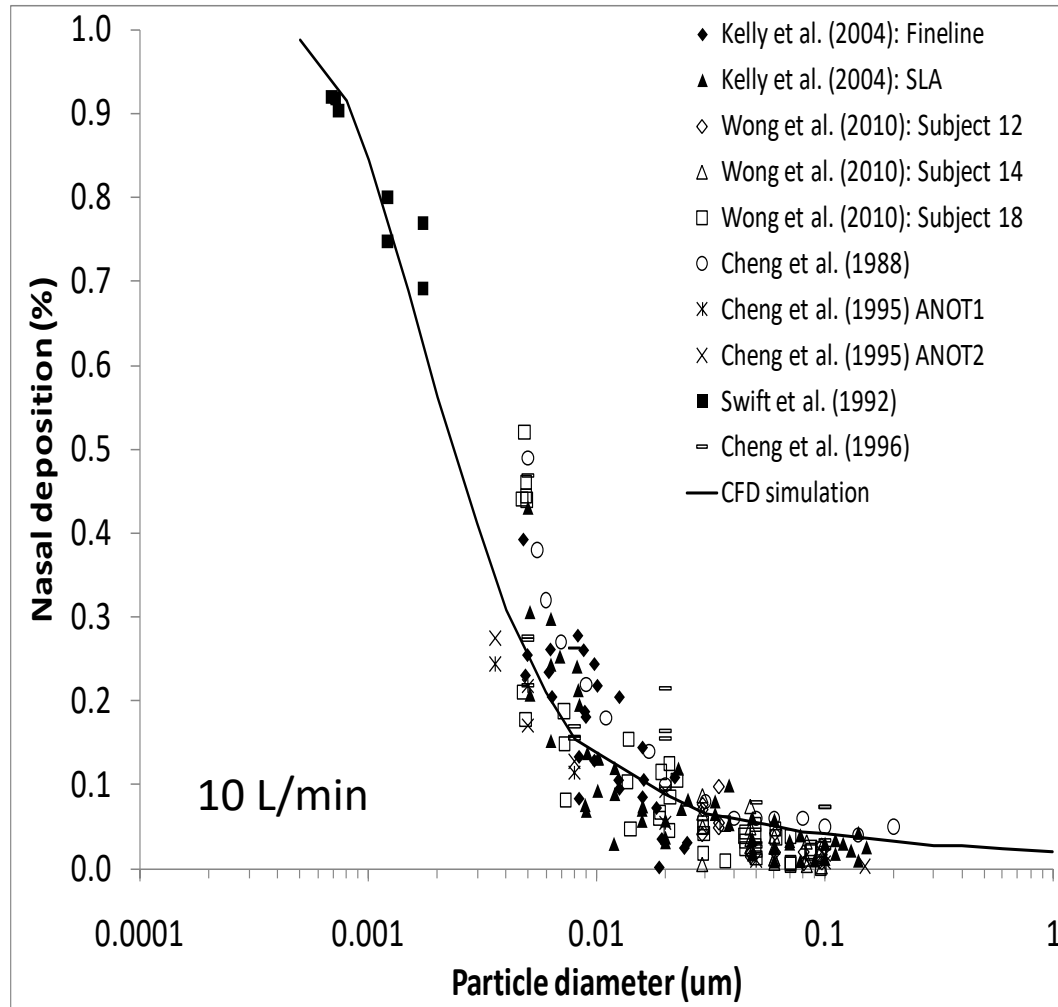
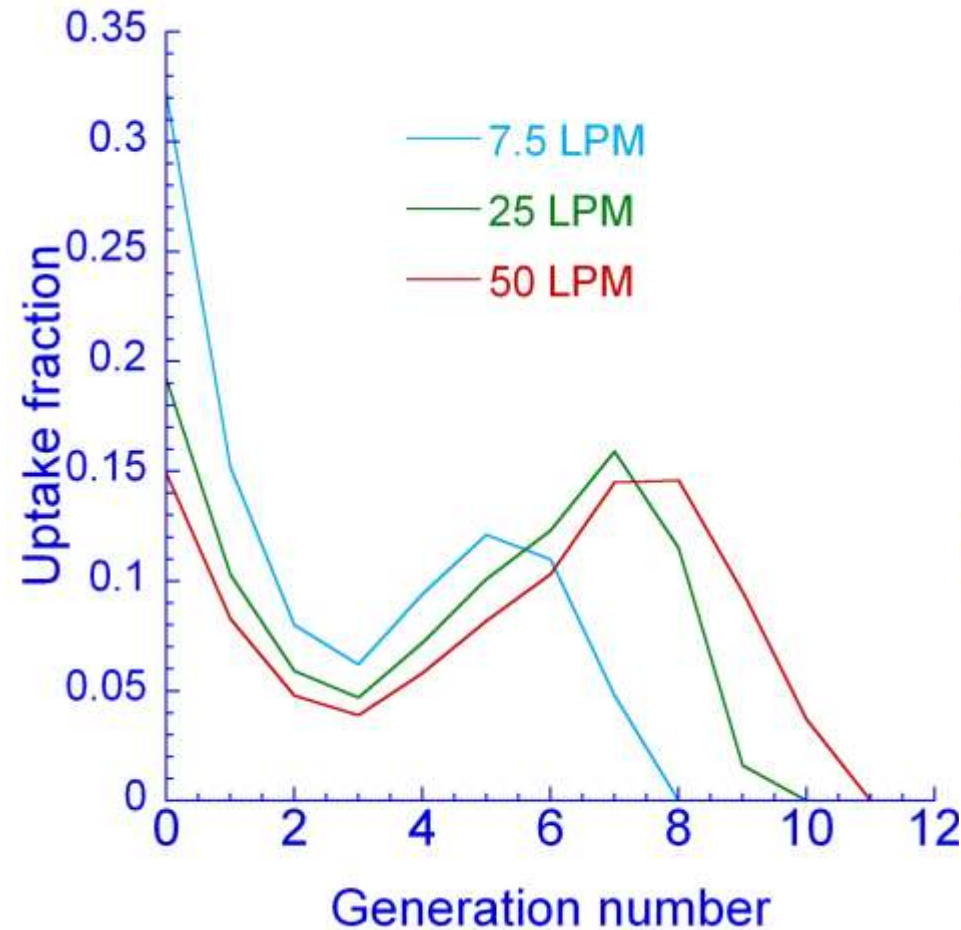


Image courtesy of Dr. Jeffry Schroeter, Applied Research Associates

Percent of Vapor Uptake in the Lower Airway

FORMALDEHYDE



DIACETYL

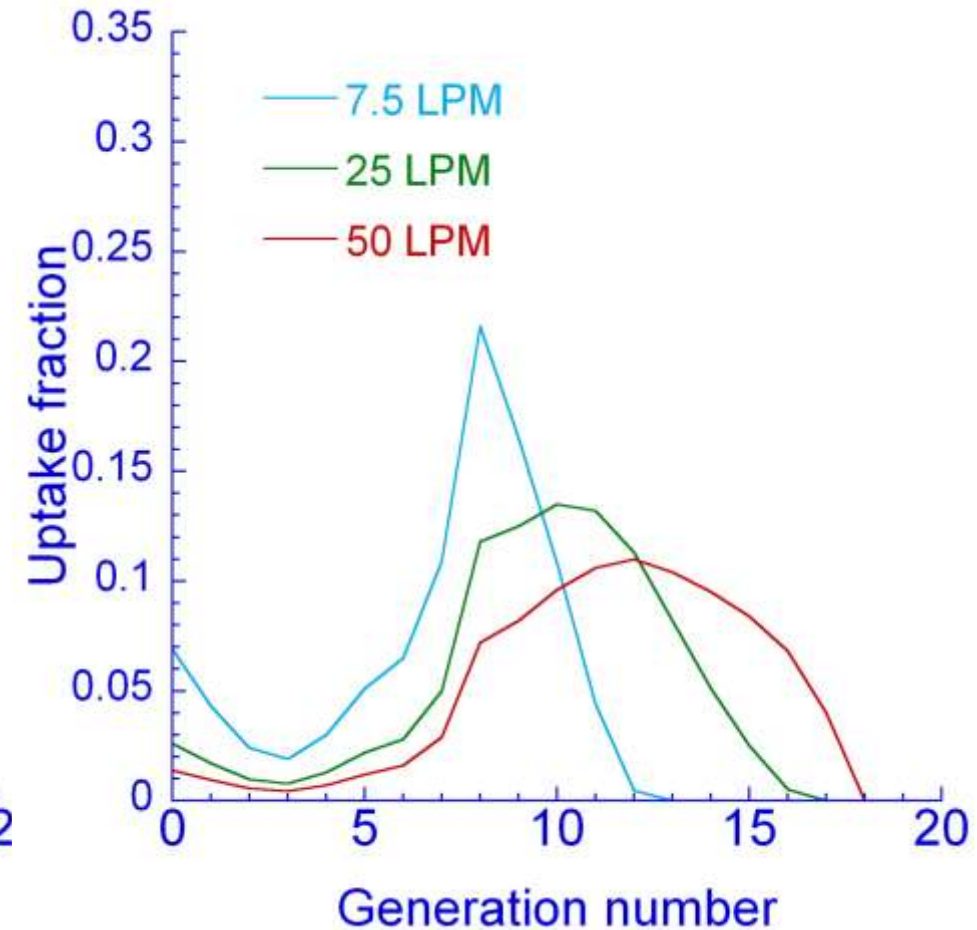


Image courtesy of Dr. Bahman Asgharian, Applied Research Associates

Absorption in the Lower Airway

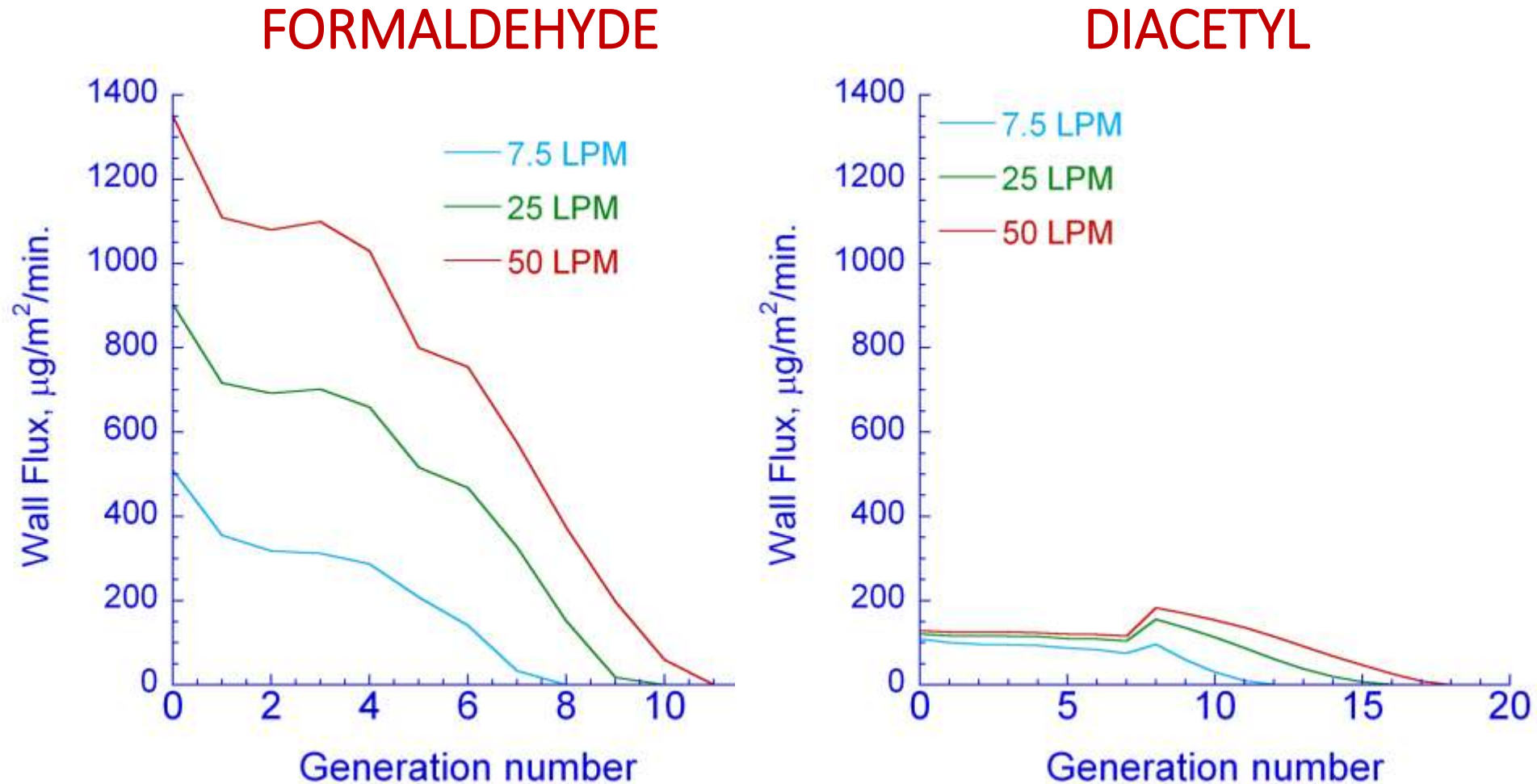
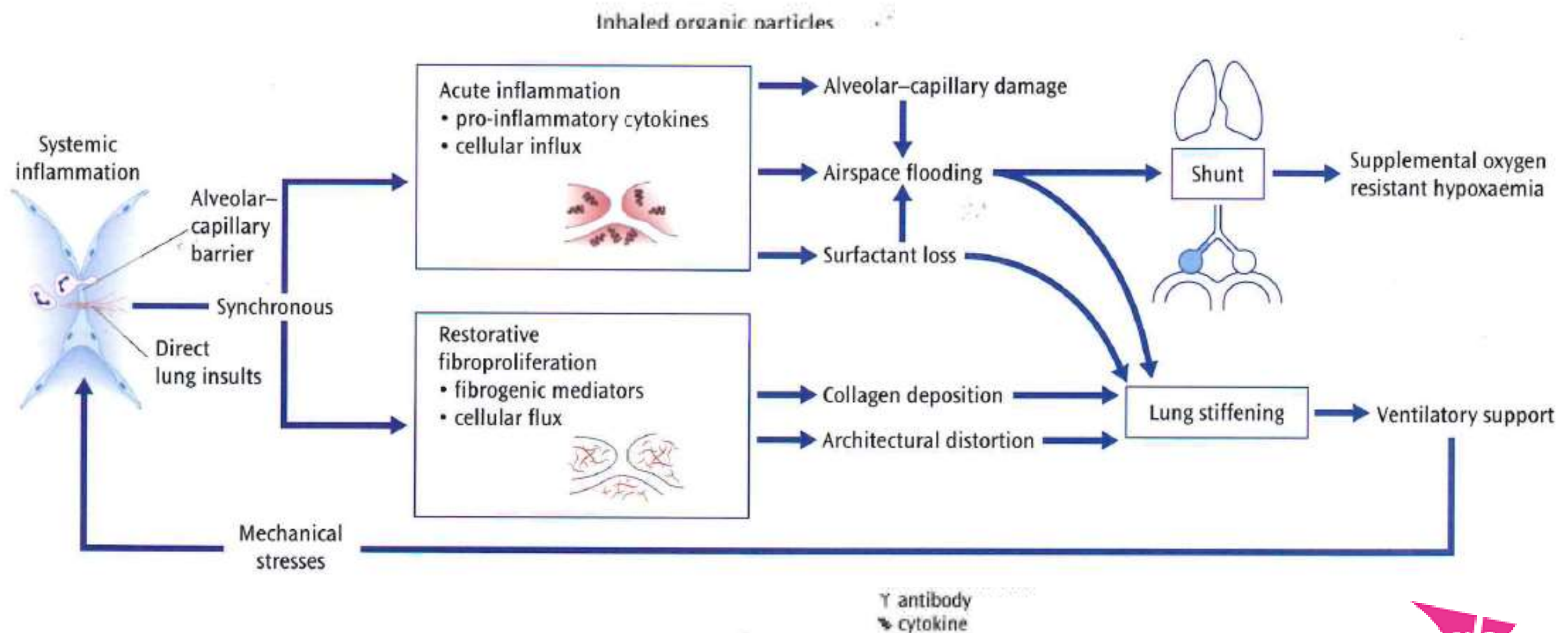


Image courtesy of Dr. Bahman Asgharian, Applied Research Associates

Acute Inhalation vs. Long-term Inhalation Toxicity



Translating Air Concentration to Systemic Dose

- The output from an exposure-only model is applied as the anticipated human systemic dose (mg/kg/day)

$$\text{mg/kg/day} = \frac{(\text{mg/L/day})(A)(D)(MV)}{BW}$$

- A conservative, route non-specific approach for MOE calculation:

$$\text{MOE} = \frac{\text{NOAEL (mg/kg/day)}}{\text{Anticipated Human Exposure (mg/kg/day)}}$$



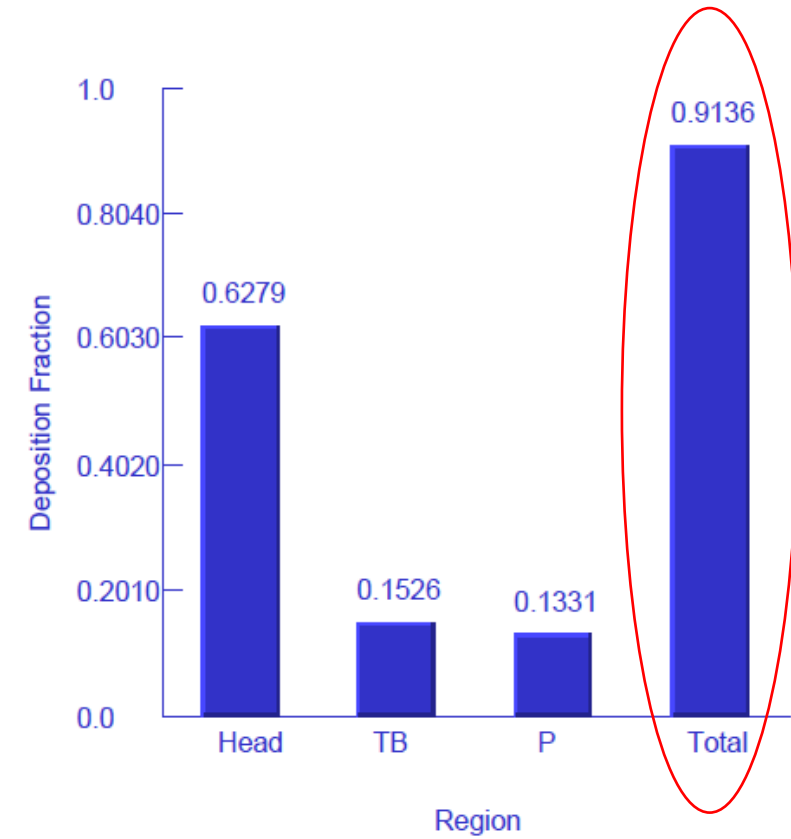
$$\text{MOE} = \frac{(\text{NOAEL})(\text{DAF})(D_A)}{(\text{Human exposure})(D_H) \left[\frac{(\text{Human MV}_{\text{actual}})}{(\text{Human MV}_{\text{rest}})} \right]}$$

- NOAEL – No observed adverse effect level from an animal inhalation toxicology study in units of air concentration (mg/L/day, mg/m³/day, ppm/day)
- Human exposure – measured or surrogate in the same concentration units as the animal NOAEL
- D_A – Duration of animal exposure (minutes/day)
- D_H – Duration of human exposure (minutes/day)
- DAF – Dosimetric adjustment factor for respiratory tract region (regional deposited dose ratio (RDDR) for aerosol droplets/particles or a regional gas dose ratio (RGDR) for gases and vapors)
- MV_{actual} – Human minute ventilation (L/min) at actual level of activity
- MV_{rest} – Human minute ventilation (L/min) at rest

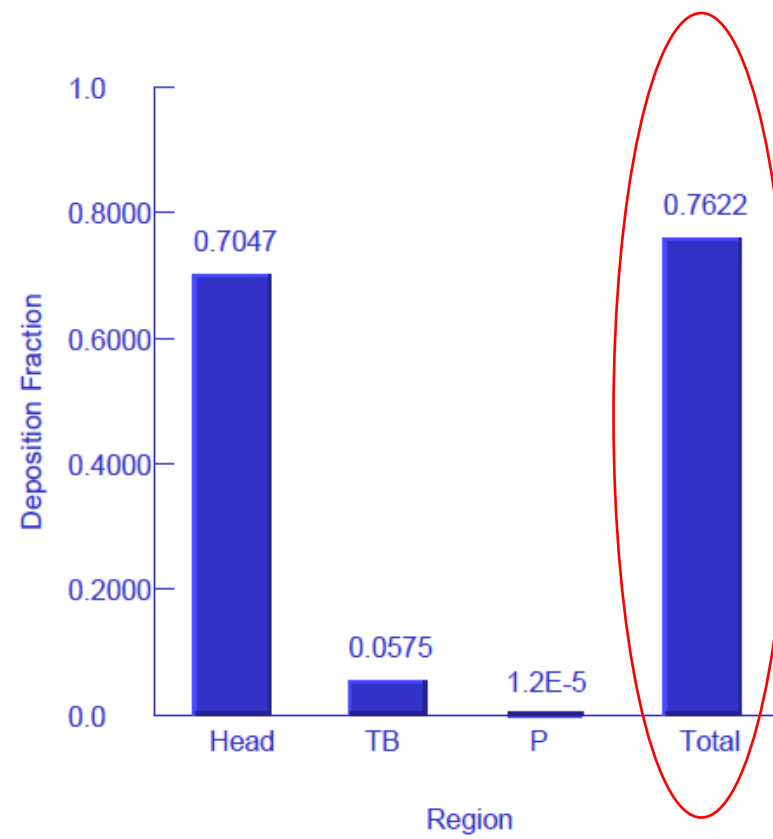


[illegible]

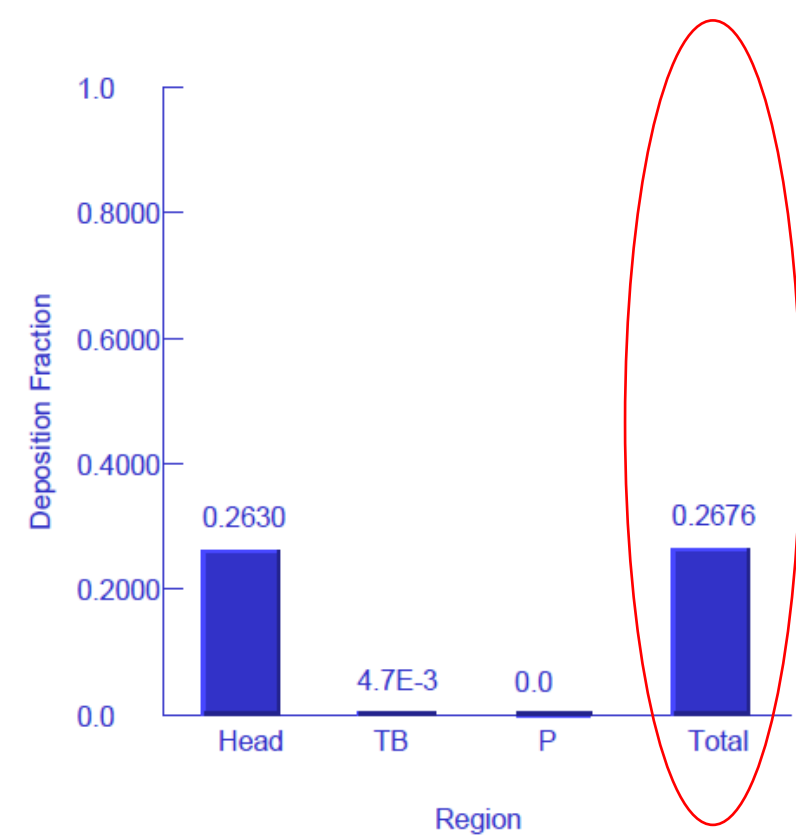
Oronasal Regional Deposition Profile



6 µm droplets



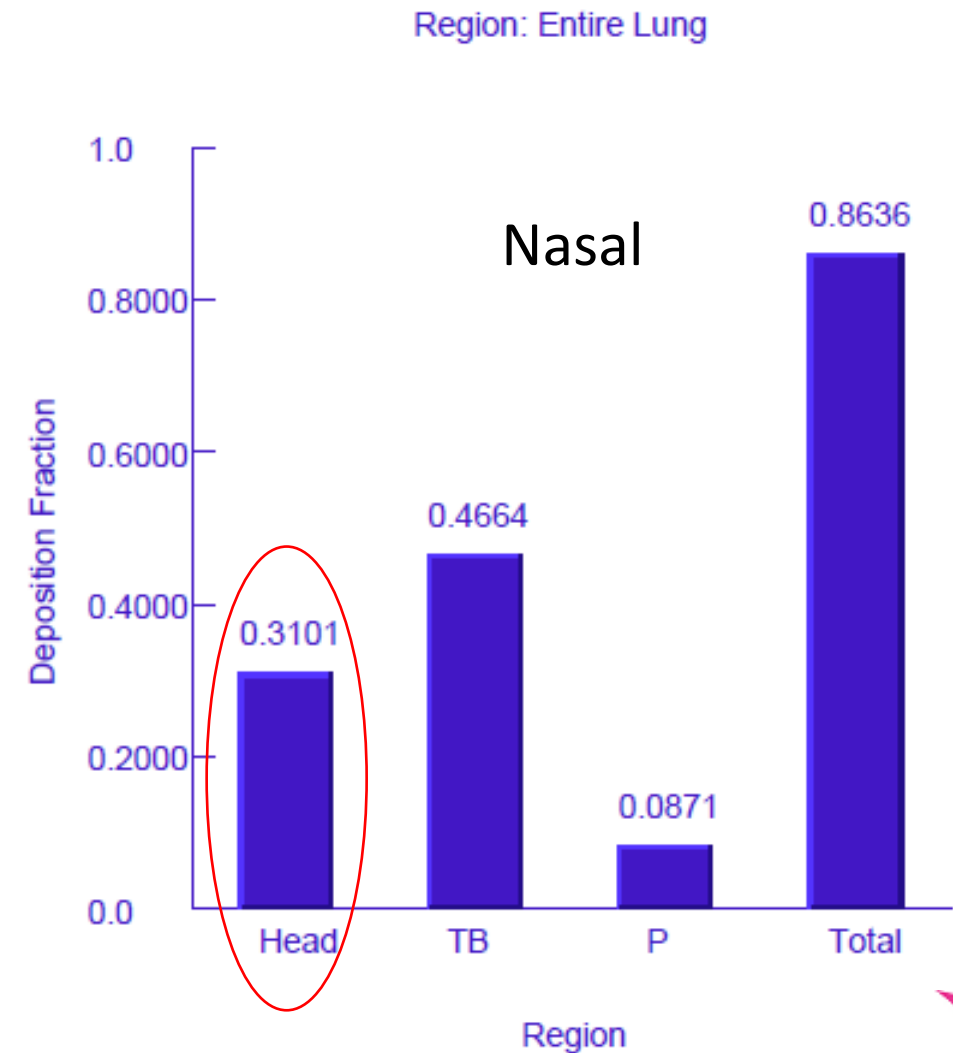
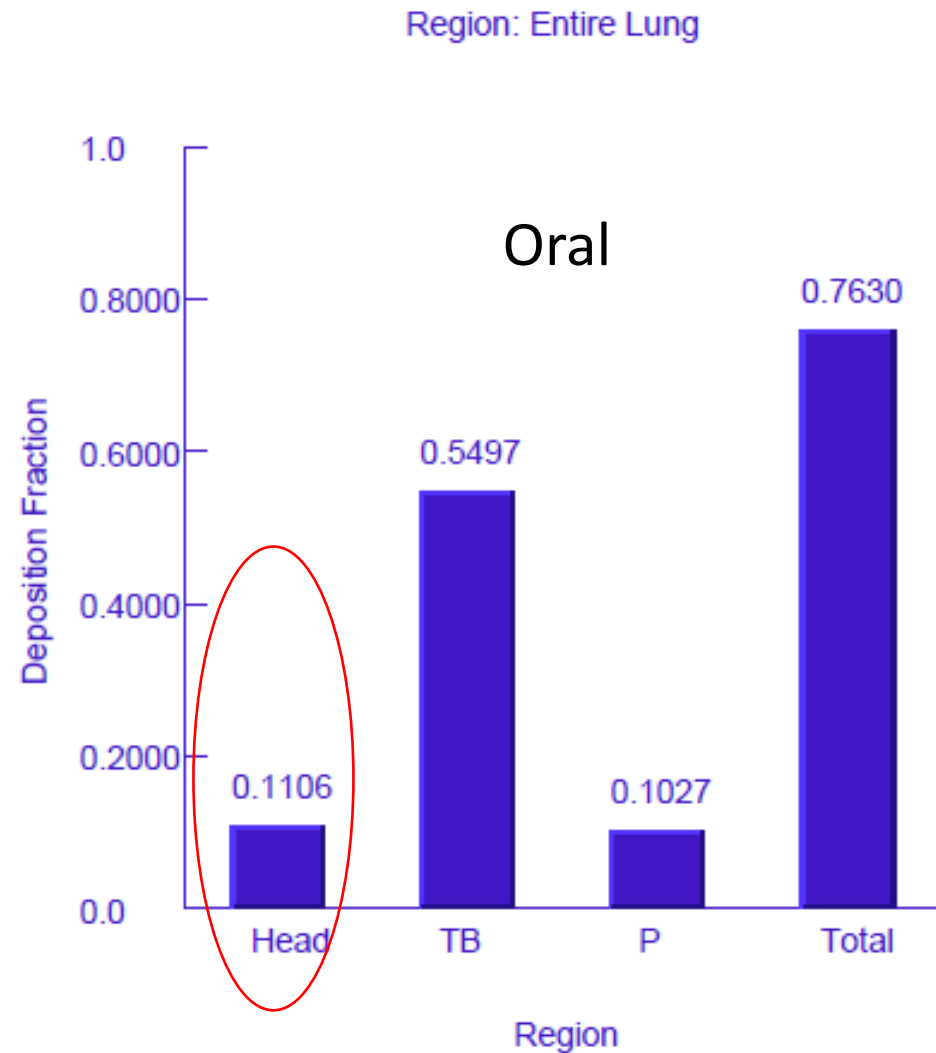
20 µm droplets



50 µm droplets

6 μm Oral vs. Nasal Deposition Profile*

*in 3 Month Old Child



Acknowledgements

- 2-Box Air Dispersion Model
 - Applied Research Associates
 - Owen Price
- Respiratory In Silico Deposition Model (MPPD)
 - The Hamner Institutes for Health Sciences, Applied Research Associates, and University of North Carolina
 - Bahman Asgharian
 - Jeffry Schroeter
 - Julie Kimball
 - Owen Price



Copyright restrictions prevent the distribution of the following items:

Principles for the safety evaluation of cosmetic powders. Steiling W, Almeida JF, Assaf Vandecasteele H. Toxicol Lett. 2018 Nov;297:8-18.

Skin exposure to deodorants/antiperspirants in aerosol form. Steiling W, Buttgereit P, Hall B, Food Chem Toxicol. 2012 Jun;50(6):2206-15.

Principle considerations for the risk assessment of sprayed consumer products. Steiling W, Bascompta M, Carthew P. Toxicol Lett. 2014 May 16;227(1):41-9.



Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: October 30, 2018

SUBJECT: Comments on Draft Revised CIR Precedents – Aerosols Document/Submission of Aerosol Particle Size Data

The CIR Science and Support Committee is pleased to submit comments on the above referenced draft document for consideration by the CIR Expert Panel. While there is general agreement with the content of the current document, the Committee recommends that the delineation of a tiered approach to the evaluation of inhalation safety would add clarity and provide a needed framework.

During the last discussion of the Precedents document, the CIR Expert Panel requested additional information on spray product particle size for hair spray and deodorants. Data have been compiled in response to this request, and are included in this submission. The data are generally consistent with the older data previously reviewed by the Panel. The Committee notes, however, that particle size data are only infrequently needed when conducting inhalation risk assessment for cosmetic spray products due to the tiered approach to risk assessment providing 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.

General Considerations in Assessment of Inhalation Safety

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.¹

A preferred approach for the evaluation of inhalation safety is described in the 2014 publication by Steiling et al.² This publication stresses the critical importance of exposure assessment and describes a tiered approach to the exposure assessment of spray products. The three tiers are briefly described below:

- **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 (for example, see Table 2 in Steiling et al.) and assumes the total amount of sprayed product immediately enters the breathing zone (about 1 to 2 m³ for cosmetics sprayed towards the body). This simple 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.

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.

¹ Behrsing, H et al. (2017) *In vitro* exposure systems and dosimetry assessment tools for inhaled tobacco products: Workshop proceedings, conclusions and paths forward for *in vitro* model use. *Altern Lab Anim.* 45(3):117-158.

² Steiling W et al. (2014) Principle considerations for the risk assessment of sprayed consumer products. *Toxicol Lett.* 227(1):41-9.

Sample Exposure Calculations

Sample exposure calculations using the approach described above are included here for an aerosol hair spray product.

Screening approach: (assumes all ingredient in the product is available for systemic exposure):

Aerosol Hairspray Assumptions:

Amount used per day: 9.89 g (95th percentile from Loretz et al., 2006³)

Ingredient makes up 2% of product

Body weight: 60 kg

Exposure estimate:

$9.89 \text{ g} \times 0.02 \text{ (ingredient)} = 0.198 \text{ g (198 mg)}$

$198 \text{ mg} \div 60 \text{ kg} = 3.3 \text{ mg/kg}$

Refined exposure estimate

There are multiple factors that can be used to refine an exposure estimate. In this example, the following refinements are added:

- 2 box model (Rothe et al., 2011), in which the ingredient distributes in 1,000 L in the first 2 minutes, and distributes in 10,000 L in the next 18 minutes
- Breathing rate 10 L/minute⁴
- 25% exhaled

Exposure estimate:

First 2 minutes: $198 \text{ mg}/1000 \text{ L} \times 10 \text{ L/minute} \times 2 \text{ minutes} = 3.96 \text{ mg}$

Next 18 minutes: $198 \text{ mg}/10,000 \text{ L} \times 10 \text{ L/minute} \times 18 \text{ minutes} = 3.56 \text{ mg}$

Total exposure $3.96 \text{ mg} + 3.56 \text{ mg} = 7.52 \text{ mg}$

25% exhaled (0.75 exchange factor)

$7.52 \times 0.75 = 5.64 \text{ mg}$

$5.64 \text{ mg} \div 60 \text{ kg} = 0.094 \text{ mg/kg}$

Other Refinements:

The simple refined exposure calculation above provides a conservative estimate of inhalation exposure to an ingredient for all regions of the respiratory tract. Other factors can be incorporated to refine the assessment further.

For example, exposure can be further refined to adjust for the amount of material that ends up on skin/hair and is therefore not available for inhalation (see Steiling et al., 2012⁵).

³ Loretz L et al. (2006) Exposure data for personal care products: hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. Food Chem Toxicol. 44(12):2008-18.

⁴ Representative inhalation rate from 2011 EPA Exposure Factors Handbook. Chapter 6 - Inhalation Rates. Accessed at <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?dcid=236252>

Addition of a factor to adjust for respirable fraction (inhaled particles/droplets <10 µm) refines the amount that may reach the deep lung. If, for example, 5% of the distribution is less than 10 µm, the following calculation would apply:

$$0.094 \text{ mg/kg/day} \times 0.05 = \mathbf{0.0047 \text{ mg/kg/day}}$$

Calculations for deodorant would be conducted similarly. Spray deodorant habits and practices data are available⁶.

Use of Advanced Methodology

An example of exposure assessment for antiperspirant spray products, mimicking in-use conditions and incorporating particle/droplet size data, is available in a publication by Schwarz et al. (2018).⁷ Exposure to aluminum from four antiperspirant sprays containing up to 1.5% aluminum is assessed using a simple 2-box model. Exposure of the upper respiratory tract and deep lung deposition were calculated using the Multiple Path Particle Deposition Model. The total systemic exposure via inhalation was found to be less than 0.5 µg per application (less than **0.0084 µg/kg/application** for a 60 kg person). These authors also compared inhalation exposure estimates when the 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 2 boxes result in highly conservative estimates of lung exposure.

Spray Product Particle Size

The CIR Expert Panel has requested that industry provide particle/droplet size data for hairspray and deodorant. In response to that request, a survey was undertaken to collect particle/droplet size information developed by companies marketing these product types. Six companies provided data on aerosol hairspray particle/droplet size, and three companies provided data on deodorant/antiperspirant⁸ particle size. While no pump hairspray data were received, the

⁵ Steiling W et al. (2012) Skin exposure to deodorants/antiperspirants in aerosol form. Food Chem Tox 50: 2206-2215.

⁶ Scientific Committee on Consumer Safety (2016) The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation. 9th Revision. 25 April 2016.
http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_004.pdf

⁷ Schwarz K, et al. (2018) A methodology for the assessment of inhalation exposure to aluminum from antiperspirant sprays. Archives of Toxicology 92: 1383-1392.

⁸ While the original request had been for deodorant data because antiperspirants are OTC products, both deodorant and Ap/Deo data are included in order to have a more robust data set.

particle/droplet size of pump sprays is generally larger than aerosols.⁹ Laser diffraction was the method used to collect data in all cases.

It is important to note that particle/droplet size data under simulated consumer use scenarios are only rarely needed for risk assessment. Particle/droplet 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. While particle/droplet size is an important parameter, other exposure factors are key in assessing inhalation safety, as shown in the preceding exposure calculations. It should also be noted that particle/droplet size data generated under experimental conditions may be different from particle/droplet size in actual consumer exposures. Factors affecting the results include temperature, humidity, spray distance, spray time, container fullness, and the amount of pressure on the actuator.

Detailed information on measuring particle/droplet size from aerosol products is available in a Guidance document published by the European Aerosol Federation¹⁰. In the event that particle/droplet size data are required for risk assessment, there are other methodologies that can be used to further characterize the measurements, such as use of a cascade impactor, particularly for smaller solid particles.¹¹

Results

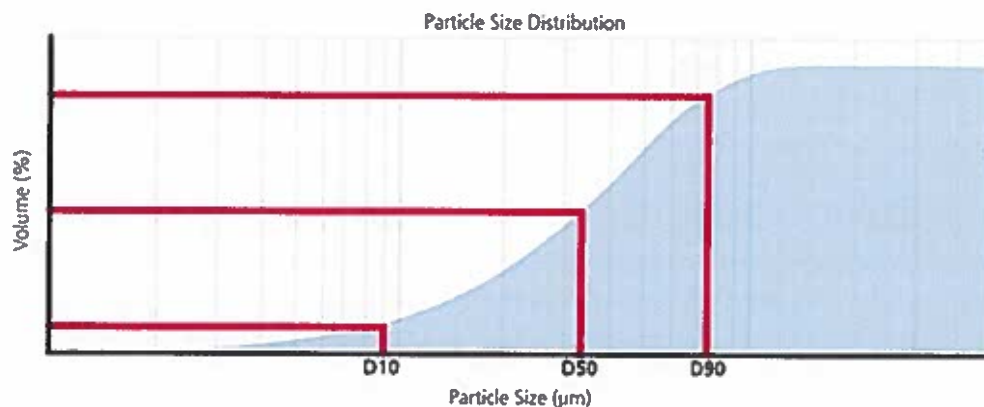
Tables 1 and 2 (attached) provide a compilation of particle size data for aerosol hair spray and aerosol deodorant/antiperspirant, respectively. The data were generated using laser diffraction. Values are presented for DV10, DV50, and DV90, representing the maximum particle/droplet diameter below which 10%, 50%, or 90% of the sample volume exists, respectively. Thus, the DV50 value is the median particle/droplet size by volume, as described in the figure below¹². Also included in the table is the percentage of particles/droplets <10 µm.

⁹ Rothe H et al. (2011) Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett.* 205:97-104.

¹⁰ European Aerosol Federation. (2009) Guide on Particle Size Measurement from Aerosol Products.

¹¹ Steiling et al. (2014) op. cit.

¹² A basic guide to particle characterization. (2015) Malvern Instruments Worldwide.



The data collected using current laser diffraction methodology is generally consistent with the earlier, limited particle/droplet size data available in the literature and included in the draft Precedents document. Particle/droplet size is variable across individual products. Hairsprays have consistently larger median particle/droplet size than deodorant/antiperspirant.

Overall Recommendations/Key Points

The CIR Science and Support Committee respectfully provides the following recommendations:

- Revise the CIR Inhalation Precedents document to clearly outline a tiered approach to assess inhalation exposure and risk assessment.
- Reference the updated particle/droplet size data in the Precedents document. These data are generally consistent with earlier data. Importantly, particle/droplet size data are generally not needed when assessing the inhalation safety of an ingredient in a spray cosmetic product.
- Revise the boilerplate language to reflect less reliance on particle size and more emphasis on exposure levels from spray cosmetic products by the inhalation route. These exposure levels are generally *de minimus*.

Conclusion

The CIR Science and Support Committee appreciates the opportunity to submit comments on the draft revised CIR Precedents – Aerosols Document. The Committee would be pleased to review and provide input on future updated versions.

Table 1 - Aerosol Hair Spray

Company	Product Type	Dv10	Dv50	Dv90	% < 10 μ M
Company A	Hairspray - Aerosol	78.68	89.07	160.6	1.0038
Company A	Hairspray - Aerosol	87.04	96.267	168.1	0.8137
Company A	Hairspray - Aerosol	85.73	95.097	166	0.8567
Company A	Hairspray - Aerosol	45.27	55.01	102.4	1.818
Company A	Hairspray - Aerosol	74.86	85.973	158.6	0.8271
Company A	Hairspray - Aerosol	44.45	53.62	97.44	1.8913
Company A	Hairspray - Aerosol	22.07	48.130	103.500	1.811
Company A	Hairspray - Aerosol	34.17	79.36	162.8	0.8167
Company A	Hairspray - Aerosol	16.53	33.63	64.06	2.231
Company A	Hairspray - Aerosol	29.07	69.657	149.4	1.509
Company A	Hairspray - Aerosol	17.31	40.617	99.4	3.094
Company A	Hairspray - Aerosol	25.99	46.43	90.63	1.929
Company A	Hairspray - Aerosol	32.54	75.387	158.1	1.0194
Company A	Hairspray - Aerosol	40.81	86.04	168.6	0.6928
Company A	Hairspray - Aerosol	25.99	46.43	90.63	1.929
Company A	Hairspray - Aerosol	40.81	86.04	168.6	0.6928
Company A	Hairspray - Aerosol	17.31	40.617	99.4	3.094
Company A	Hairspray - Aerosol	56.41	68.837	140.9	1.22
Company A	Hairspray - Aerosol	40.91	86.74	170.5	0.7047
Company A	Hairspray - Aerosol	37.48	81.35	162.7	0.822
Company A	Hairspray - Aerosol	22.26	53.31	131.7	1.885
Company A	Hairspray - Aerosol	23.12	50.65	95.66	1.58
Company A	Hairspray - Aerosol	22.84	55.853	108	1.732
Company A	Hairspray - Aerosol	24.41	61.65	144.5	1.424
Company A	Hairspray - Aerosol	16.53	33.63	64.06	2.231
Company A	Hairspray - Aerosol	12.76	30.11	61.68	5.8917
Company A	Hairspray - Aerosol	56.41	68.837	140.9	1.22
Company A	Hairspray - Aerosol	17.41	49	112.4	4.1
Company A	Hairspray - Aerosol	32.54	75.387	158.1	1.0194
Company A	Hairspray - Aerosol	71.21	181.83	431	0.262
Company A	Hairspray - Aerosol	43.26	91.08	172.6	0.7154
Company B	Hairspray - Aerosol	18.03	37.12	18.03	2.12
Company B	Hairspray - Aerosol	26.95	49.71	26.95	1.4
Company B	Hairspray - Aerosol	17.26	34.22	17.26	2.32
Company B	Hairspray - Aerosol	15.62	30.66	15.62	2.7
Company B	Hairspray - Aerosol	10.54	23.67	10.54	8.56
Company B	Hairspray - Aerosol	15.05	29.13	15.05	2.86
Company B	Hairspray - Aerosol	11.08	22.54	11.08	7.46
Company B	Hairspray - Aerosol	16	30.42	16	2.5
Company B	Hairspray - Aerosol	16.68	31.46	16.68	2.06
Company B	Hairspray - Aerosol	10.13	19.08	32.98	9.6

Company	Product Type	Dv10	Dv50	Dv90	% < 10 µM
Company C	Hairspray - Aerosol		59.08		3.5
Company C	Hairspray - Aerosol		33.45		6.8
Company C	Hairspray - Aerosol		45.01		3.32
Company C	Hairspray - Aerosol		29.09		6.38
Company C	Hairspray - Aerosol		72.85		2.13
Company D	Hairspray - Aerosol	40.91	86.74	170.5	0.7047
Company D	Hairspray - Aerosol	43.26	91.08	172.6	0.7154
Company D	Hairspray - Aerosol	8.494	16.46	29.563	16.34
Company D	Hairspray - Aerosol	6.955	13.227	23.493	28.477
Company E	Hairspray - Aerosol	30.35	81.92	187.1	
Company E	Hairspray - Aerosol	25.13	50.47	92.73	
Company E	Hairspray - Aerosol	33.59	83.03	175.6	
Company E	Hairspray - Aerosol	20.97	45.65	89.68	
Company E	Hairspray - Aerosol	20.08	44.23	86.84	
Company E	Hairspray - Aerosol	57.61	144.9	359.4	
Company E	Hairspray - Aerosol	35.18	117.1	318.2	
Company E	Hairspray - Aerosol	27.13	89.4	229.8	
Company E	Hairspray - Aerosol	27.29	83.63	215.2	
Company E	Hairspray - Aerosol	26.43	86.22	228.8	
Company E	Hairspray - Aerosol	32.74	110.2	287.9	
Company E	Hairspray - Aerosol	32.63	103.7	270.4	
Company E	Hairspray - Aerosol	30.49	114.4	300.7	
Company E	Hairspray - Aerosol	46.71	163.5	351.2	
Company E	Hairspray - Aerosol	33.39	120.9	307.4	
Company E	Hairspray - Aerosol	30.41	102	274.5	
Company E	Hairspray - Aerosol	32.14	108.2	287.5	
Company E	Hairspray - Aerosol	34.45	112.2	297.2	
Company E	Hairspray - Aerosol	64.73	166.4	409	
Company E	Hairspray - Aerosol	52.04	133.3	341.2	
Company F	Hairspray - Aerosol	25.8	73.1	179.2	4.87
Company F	Hairspray - Aerosol	27.5	72.8	176.7	3.17
Company F	Hairspray - Aerosol	30.1	77.7	184.9	3.01
Company F	Hairspray - Aerosol	25.56	64.17	149.6	3.28

Mean ± Standard Deviation:

Dv10: (n=68) 32.69 ± 18.17; **Dv50:** (n=73) 70.54 ± 36.32; **Dv90:** (n=68) 154.78 ± 102.95;

% < 10 µM: (n=53) 3.24 ± 4.48

Table 2 - Aerosol Deodorant/Antiperspirant Particle Size Data

Company	Product Type	Dv10	Dv50	Dv90	% < 10 μ M
Company A	AP/Deo-Aerosol		19.51		16.98
Company A	AP/Deo-Aerosol		183.63		0.36
Company A	AP/Deo-Aerosol		34.34		4.04
Company A	AP/Deo-Aerosol		24.26		11.34
Company A	AP/Deo-Aerosol		16.98		19.33
Company B	AP/Deo-Aerosol	9.2	25.4	52.2	11.25
Company B	AP/Deo-Aerosol	1.6	13	32.5	37.22
Company B	AP/Deo-Aerosol	3.5	13	37.1	36.18
Company B	AP/Deo-Aerosol	3.1	13.7	51.9	37.13
Company B	AP/Deo-Aerosol	1.4	13.2	27.9	35.41
Company B	AP/Deo-Aerosol	3.1	12.8	29.8	35.81
Company B	AP/Deo-Aerosol	1.2	12.4	30.3	38.97
Company B	AP/Deo-Aerosol	3.7	13.1	33.9	33.81
Company B	AP/Deo-Aerosol	3	17.4	42.5	28.06
Company B	AP/Deo-Aerosol	1.9	15.6	33.5	26.63
Company B	AP/Deo-Aerosol	0.7	8.4	20	60.79
Company B	AP/Deo-Aerosol	4.5	15.8	33.7	24.50
Company B	AP/Deo-Aerosol	4	17.1	43.1	27.55
Company B	AP/Deo-Aerosol	2.3	15.8	39.1	31.18
Company B	AP/Deo-Aerosol	0.8	9.9	27.4	50.34
Company C	AP/Deo-Aerosol	6.74	16.38	32.43	22.13
Company C	AP/Deo-Aerosol	8.10	18.44	37.25	16.73
Company C	AP/Deo-Aerosol	7.06	16.84	34.02	18.74
Company C	AP/Deo-Aerosol	6.46	15.40	31.0	25.06
Company C	AP/Deo-Aerosol	7.87	17.28	33.59	18.13
Company C	AP/Deo-Aerosol	6.22	17.31	37.84	24.61

Mean \pm Standard Deviation:

Dv10: (n= 21) 4.12 \pm 2.63

Dv50: (n=26) 22.96 \pm 33.18

Dv90: (n=21) 35.29 \pm 7.60

%<10 μ M: (n= 26) 26.63 \pm 13.43