

ADMIN

Inhalation

EXPERT PANEL MEETING

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons  
From: Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist  
Date: November 8, 2024  
Subject: Draft Revised Respiratory Exposure to Cosmetic Ingredients Resource Document

Enclosed is an updated draft of the Resource Document – Respiratory Exposure to Cosmetic Ingredients (*report\_InhalationDocument\_122024*), along with the transcripts from previous Panel discussions (*transcripts\_InhalationDocument\_122024*). The Panel last approved the Document at the December 2021 meeting. Subsequent revisions were made at the December 2023 meeting to incorporate additional particle size data in some types of propellant-based sprays, such as dry shampoos in powdered galenic formulations. These findings highlighted the necessity to modify the inhalation boilerplate (BP) to more accurately reflect the Panel's perspective on the associated inhalation risks.

At the September 2024 meeting, the Panel reviewed a Strategy Memo concerning updates to the Inhalation BP and discussed the required context for its application in the report. The Panel then requested updates to both the inhalation BP and the Respiratory Exposure Resource Document, aiming to clarify the rationale behind the changes and to better represent the Panel's understanding of exposure to airborne particles/droplets from various cosmetic sprays, along with the associated health risks.

The updated Document includes additional sample exposure calculations for dry shampoo and propellant deodorant, incorporating the latest particle size distribution data and comparing the results with permissible exposure limits in occupational settings. Additionally, the revisions expand on various aspects including measurement under realistic usage scenarios, the potential use of Threshold of Toxicological Concern (TTC) approaches, tools for assessing regional particle deposition, the examination of inter-species differences in predicting human effects, and concerns about nanoparticle exposures.

The inhalation BP has been revised to accommodate different types of spray products (e.g., pump vs. propellant), and highlights the importance of measuring particle size distribution under realistic usage scenarios for accurate exposure estimate and inhalation risk assessment. Importantly, it emphasizes that the Panel would review all pertinent data and, when necessary, request specific exposure and inhalation toxicity data on a case-by-case basis, especially when existing data are absent or insufficient to ensure the safety of ingredients in aerosolized products. For the Panel's review, the modifications of the Resource Document and Inhalation BP have been highlighted **in yellow**.

Comments provided by the Council on the Inhalation Resource Document (submitted on November 30, 2023) and on the Strategy Memo for the Inhalation BP Revision (submitted on September 24, 2024) have been addressed (identified as *Councilcomment\_inhalationDocument\_122014* and *Councilcomment\_inhalation BP\_122024*, respectively). On October 30, 2018, the CIR Science and Support Committee (CIR SSC) submitted comments proposing a tiered approach for evaluating inhalation safety. The comments also include particle size data for aerosol hair sprays and aerosol deodorants/antiperspirants, which were measured by laser diffraction from companies that market these types of products. These comments are also included in this package for the Panel's consideration (identified as *CIRSSCcomment\_2018\_inhalationDocument\_122024*).

The Panel should review the revised Document to assess the relevance and applicability of the inhalation BP, and update it as necessary to align with their understanding of exposure to airborne particles/droplets from the use of spray products, and issue the document to replace the currently posted version. If there are concerns that are not adequately addressed, the Panel should determine the necessary revisions and the extent to which further modifications are required.

## EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

# Draft Resource Document

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### Respiratory Exposure to Cosmetic Ingredients

12/2024

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume. This resource document was prepared by Jinqiu Zhu, Ph.D., D.A.B.T., E.R.T., D.C.S.T., CIR Toxicologist.

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555 13th Street, NW, Suite 300W, Washington, DC 20004

(email) [cirinfo@cir-safety.org](mailto:cirinfo@cir-safety.org) (CIR website) <https://www.cir-safety.org>

(Panel website) <https://ingredientsafetyexpertpanel.org>

## **BACKGROUND**

Inhalation exposure 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.<sup>1</sup>

The respiratory tract may be identified as both a target organ and an entry point, based on the physical and chemical properties of the ingredient. Understanding the water solubility and reactivity of these substances allows for the prediction of where gases and vapors, and other particles, will be absorbed in the respiratory tract, as well as the potential interactions with respiratory tissue and subsequent absorption into the bloodstream.<sup>2-5</sup> For instance, gases that are water-insoluble and non-reactive tend to have minimal absorption. A moderately-soluble or reactive gas will be deposited throughout the respiratory tract. Gases that are highly soluble or reactive typically deposit or are absorbed predominantly in the nose and upper airways. Furthermore, gases with high reactivity may undergo chemical reactions like hydrolysis, affecting their presence and impact within the respiratory system.<sup>1, 3, 6</sup>

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

Pulmonary overload is a condition in which the accumulation of any inert, poorly soluble particulate material in the lungs overwhelms the capacity of the alveolar macrophages to clear the material from the lungs. Chronic pulmonary overload can cause persistent inflammatory responses, fibrosis and tumors,<sup>7</sup> although the mechanisms of aerodynamic diameter-induced tumor formation are not completely understood.<sup>7-10</sup> The current threshold of the European Union (EU) for protecting workers from pulmonary overload during occupational exposure to respirable dust particles is 1.5 mg/m<sup>3</sup> eight-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).<sup>1, 11</sup>

Droplet/particle size is variable across individual products. Industry can ensure that inhalation exposures to cosmetic sprays and powders are minimized.<sup>11</sup> 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.<sup>12</sup> The binding materials foster the agglomeration of the ingredients and substantially increase their cohesivity. These measures increase the size of the particles in the product.

## **REGIONAL PARTICLE DEPOSITION**

The physical parameter most strongly associated with the deposition pattern of an aerosol in the respiratory tract is the aerodynamic equivalent diameter ( $d_{ae}$ ).<sup>13, 14</sup> The  $d_{ae}$  of a droplet/particle is defined as the diameter of a hypothetical, smooth sphere of unit density (e.g., 1 g/cm<sup>3</sup>) that has the same gravitational settling velocity as the droplet/particle in calm air, regardless of its actual geometric size, shape and density.<sup>6, 15</sup>

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  $d_{ae} \sim 100 \mu\text{m}$ ), which can enter the nasopharyngeal region through the nose or mouth, the bronchial fraction (median  $d_{ae} \sim 10 \mu\text{m}$ ), which can pass through the larynx to enter the trachea, bronchi and bronchioles, and the respirable fraction (median  $d_{ae} \sim 4 \mu\text{m}$ ), which can enter the alveolar region of the lungs.<sup>1, 3, 16</sup> 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.<sup>17</sup> 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, or be absorbed and result in systemic toxicity, depending on their chemical and physical properties.

There is broad scientific consensus that the probability of penetration of droplets/particles with  $d_{ae} > 10 \mu\text{m}$  into the pulmonary region is essentially zero.<sup>1, 6, 18-22</sup> Thus, only droplets/particles with  $d_{ae} \leq 10 \mu\text{m}$  are considered to be respirable. This is a conservative assumption because a  $d_{ae}$  of 5  $\mu\text{m}$  or less is often reported in the scientific literature as the threshold below which droplets/particles can reach the alveoli.<sup>1, 23</sup> In addition, there is consensus that droplets/particles with  $d_{ae} > 15 \mu\text{m}$  are deposited almost exclusively in the nasopharyngeal and bronchial regions of the respiratory tract, and that healthy people will clear particles with  $d_{ae} > 7 \mu\text{m}$  from these regions within 24 hours through mucociliary action.<sup>1</sup>

Various models are available to estimate both total and regional lung deposition of aerosols and particles. Examples include the Multiple-Path Particle Dosimetry (MPPD) model and the Human Respiratory Tract Model (HRTM). The MPPD model provides calculations for the deposition fraction in humans, averaged over the entire lung compartment, allowing for the selection of different particle size ranges and exposure conditions, and it can be applied to different species such as rats, rhesus monkeys, mice, and humans.<sup>24</sup> The HRTM model is a semi-empirical model that relies on experimental data to assess regional particle deposition in humans under well-controlled conditions, particularly adept at calculating specific exposures for each region of the respiratory tract, tailored to the particle size distributions of spray mist.<sup>25</sup>

## **INHALATION EXPOSURE ASSESSMENT**

Particle size distributions are product-specific (i.e., the particle size of a raw material prior to formulation may have little to no impact on the particle size distribution resulting from consumer product use). Numerous factors determine the initial size distribution of droplets or particles released from a spray product, including the product formulation (e.g., volatile or nonvolatile solvent), propellant, can size, differential pressure through the nozzle for

propellant sprays, and formulation and nozzle characteristics for pump sprays.<sup>1, 11</sup> After releasing to the air, the particle size distribution can change rapidly through aggregation, agglomeration, sedimentation, evaporation of volatile components, or hygroscopic absorption of water.<sup>1, 16, 18, 26, 27, 15</sup> For example, all of the water and other volatile solvents and propellants in droplets with  $d_{ac} < 40 \mu\text{m}$  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). Accordingly, a wide spectrum of particle size distributions can be released from cosmetic sprays.<sup>1, 26, 28, 29</sup>

Both pump sprays and propellant sprays (also called “aerosol sprays”) produce aerosols, yet propellant sprays yield a greater proportion of respirable droplets/particles compared to pump sprays. The median  $d_{ac}$  of the airborne droplets/particles of pump hair sprays range from  $60 \mu\text{m}$  to  $80 \mu\text{m}$ .<sup>1, 11, 26</sup> Typically,  $< 1\%$  of the airborne droplets/particles released from pump sprays are in the range considered to be respirable (i.e.,  $d_{ac} < 10 \mu\text{m}$ ).<sup>1, 30</sup> In comparison, propellant sprays can consist of a broad range of particle sizes. Research from past years indicated that the median  $d_{ac}$  of the airborne droplets/particles of propellant hair sprays range from  $25 \mu\text{m}$  to  $50 \mu\text{m}$ ;<sup>1, 11, 26</sup> usually,  $1\%$  to  $2.5\%$  of the droplets/particles emitted from propellant hair sprays are within the respirable range.<sup>11</sup>  
<sup>31</sup>However, a higher proportion of respirable particles could release from propellant-based sprays, as reported by simulated test data, in silico model outputs, and industry survey (e.g., average  $26.6\%$  for propellant deodorant).<sup>26, 32-</sup>  
 35

It's important to recognize that the distribution of droplet/particle size is determined not only by the type of spray dispensing system (pump or propellant-based) but also by the specific product category (e.g., hairspray or dry shampoo) and the galenic form (oil, powder, foam, emulsion, etc.). Also noteworthy is spray systems are rapidly advancing. Consider, for instance, the diverse variations in nozzle characteristics of airbrushes. Cosmetic ingredients can now be dispensed by products with hybrid spraying features, e.g., dry shampoos might be packaged in propellant-based sprays with a galenic form of powder or emulsion.<sup>30</sup> Emerging products such as dry shampoo and airbrush have not yet been clearly defined within the existing regulatory framework, and the currently available data with regard to droplet/particle size distribution and its variability (within and across emerging product types) are limited.

Different types of propellant-spray products may yield substantially different particle size distributions. Estimates based on consumer exposure model ConsExpo 4, developed by the Netherlands' National Institute for Public Health and the Environment (RIVM), indicate that traditional propellant hair spray aerosols have a median  $d_{ac}$  of  $35 \mu\text{m}$  with a coefficient of variation of  $0.3$ .<sup>18, 26</sup> 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  $d_{ac}$  of  $10 \mu\text{m}$  with a coefficient of variation of  $0.3$ , suggesting that approximately half of these particles are within the range considered to be respirable.<sup>18, 26</sup> However, it should note products associated innovative spray formulations and advancing nozzle techniques may release aerosols with a greater proportion of respirable particles. Thus, the Expert Panel for Cosmetic Ingredient Safety (Panel) would closely monitor the new particle size distribution data for these products. The Panel also notes the current data are insufficient to determine median particle sizes (and distributions) resulting from airbrush device use. The fraction of respirable particles that would be emitted by applying cosmetics with airbrush devices remains unknown.

## **Measurement of Particle Size Distribution**

Differences in droplet/particle size distributions between pump and propellant spray products, and between the few hair spray and deodorant spray products tested, are important considerations for evaluating the safety of cosmetic ingredients that may be incidentally respired during intended use. These differences suggest that the safety margin 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<sup>3</sup> space in the breathing zone during the first 2 minutes after spraying, which expands to form a homogenous 10 m<sup>3</sup> cloud over the subsequent 18 minutes.<sup>1, 11</sup> 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.<sup>6, 11, 15, 26, 27</sup> 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.<sup>11</sup> The droplets/particles are likely to be undetectable in the breathing zone within 10 minutes after spraying.

One industry survey provides volume weighted particle size distribution data, measured using laser diffraction, for propellant hair sprays and propellant deodorant/antiperspirant sprays.<sup>35</sup> Six companies provided data on aerosol hair spray particle/droplet size, and three companies provided data on deodorant/antiperspirant particle size. The data collected was generally consistent with the earlier, limited particle/droplet size data available in the literature. Specifically, 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. The 90% particle sizes (Dv90) of droplets/particles released from propellant hair sprays are distributed within the size range of 23.5 – 409 µm, whereas the mean (standard deviation, SD) values of Dv50 and Dv10 are 70.5 (36.3) and 32.7(18.2) µm, respectively. Propellant deodorant/antiperspirant sprays have consistently smaller median particle/droplet size than propellant hair sprays. The mean (SD) values of Dv90, Dv50 and Dv10 of droplets/particles released from propellant deodorant/antiperspirant sprays are 4.1 (2.6), 23 (33.2), and 35.3 (7.6) µm, respectively. In addition, the percentage of respirable particles/droplets (% < 10 µm) is 3.24 ± 4.48 and 26.6 ± 13.4 (mean ± SD) for propellant hair sprays and deodorant/antiperspirant sprays, respectively. Hairsprays have consistently larger median droplet/particle size than deodorant/antiperspirant. It should be noted that droplet/particle size data using laser diffraction measurements of a free spray may be generated for other purposes, such as qualifying packaging, or determining consumer product acceptability. These types of particle/droplet size data, while not equivalent to consumer exposure, can be leveraged in refined exposure assessments with a full understanding of the conservative nature of the exposure estimate.

A 2023 study investigated the droplet/particle size distribution in 78 cosmetic sprays by laser diffraction (this method does not allow for measuring nanoparticles (NPs)), including 63 pump sprays and 15 propellant-based sprays.<sup>30</sup> The findings showed that the level of respirable droplets/particles released by pump sprays averaged 0.5%

of all particles measured (0.0% - 2.2%). Generally, the cosmetic pump sprays released a minimal percentage of respirable droplets/particles, typically less than 1%. Among 15 propellant-based hairsprays currently available on the market, an average of 15.25% of particles measured had an aerodynamic diameter  $< 10 \mu\text{m}$ , with a range between 0.15% and 32.27%; of the thirteen propellant-based hairsprays examined, eleven - comprising three hairsprays and eight dry shampoos - emitted respirable droplets/particles in a range of 6.44% to 32.37%. Specifically, dry shampoos in powder form were found to release the highest percentage of respirable droplets/particles, ranging from 16.66 to 32.27%. (A default value of 25% of respirable droplets/particles was suggested for dry shampoos.) Factors such as the type of spray dispensing system (pump or propellant-based), product type (e.g., hairspray, sunscreen), and the formulation (powder, oil, emulsion) influenced the droplet/particle size distribution.

Due to the compressed format and low usage amounts, inhalation exposure to compact powders is not expected at use conditions.<sup>36, 37</sup> In contrast, loose powders, which lack the particle cohesion, have the potential to generate airborne particles that may carry nanomaterials, with which there is potential for inhalation exposure. Lately, the technique of single-particle inductively coupled plasma tandem mass spectrometry (spICP-MS/MS) has been employed as a screening tool to detect NPs in powder-based facial cosmetics. This technique can further analyze chemical compositions for each NP type, along with respective particle densities and mass fractions. The presence of NPs smaller than 100 nm was observed in all seven powder-based facial products.<sup>38</sup> One study quantified one minute exposure to airborne particles ranging from 14 nm to 20  $\mu\text{m}$  due to the use of three nanotechnology-based, and three regular, cosmetic powders functioning as moisturizer, blusher, blot powder, etc.<sup>39, 40</sup> Results therein illustrated that the coarse aerosol fraction (2.5 – 10  $\mu\text{m}$ ) represented the highest inhaled particle mass, while the minimal inhaled, mass was made by particles  $< 100 \text{ nm}$ . Deposition fractions were calculated based on the International Commission on Radiological Protection (ICRP) model. For all types of powders, 85 – 93% of the particle mass deposited in the head airways, while  $< 5\%$  deposited in the tracheobronchial region and  $< 10\%$  in the alveolar region. The alveolar region was the second most exposed region of the respiratory tract; however, the deposited mass was only  $\sim 1/20$  of that deposited in the head airways. In another study, loose facial and eyeshadow powders were selected to evaluate the quantitative deposition following five minutes of exposure.<sup>41</sup> According to the ICRP model, for all investigated cosmetic powders, 78% of inhalable-sized particles deposited in the head airways, while  $< 2.5\%$  and  $< 1\%$  deposition occurred in the tracheobronchial and alveolar regions, respectively. The estimated dosage in this study was 700  $\mu\text{g}$  for particles with  $d_{ae} \leq 10 \mu\text{m}$  and 200  $\mu\text{g}$  for particles with  $d_{ae} \leq 2.5 \mu\text{m}$ . Another study analyzed the size of particles, shape, accumulation, and distribution of three nanopowders (a moisturizer, a blusher, and a loose powder sunscreen) and three regular cosmetic powders (two blot powders and a finishing powder).<sup>42, 43</sup> The electron microscopy and airborne particle measurements data suggested that airborne concentrations of particles between 100 nm and 20  $\mu\text{m}$  in diameter varied substantially among the different cosmetic powders, e.g., application of nanopowders may result in the release of particles as large as 20  $\mu\text{m}$ , while exposure to nanoparticles was mainly through agglomerates of 5 - 10  $\mu\text{m}$  and larger,<sup>43</sup> and predominant deposition of nanomaterials occur in the tracheobronchial and head airways but not in the alveolar region. A 28-d nose-only inhalation toxicity study was conducted in rats to investigate the toxicokinetic fate of metal oxides post-inhalation in lungs and other organs.<sup>44</sup> This study entailed the use of test powders with primary particle sizes at the nanoscale, specifically including  $\text{TiO}_2$ ,  $\text{ZnO}$ , amorphous silica, and carbon black, with aerosol concentrations set at 3, 12, and 48  $\text{mg}/\text{m}^3$ . These concentrations were chosen to simulate conditions under occupational exposure scenarios. Observations from the study indicated that, within occupational settings, the test nanomaterials tended to form

microscale agglomerates rather than remaining as individual nanoparticles. Notably, the nanomaterials did not display potential to translocate beyond the lung into the blood compartment. Besides lungs, very small particulate amounts were detected only in the lung-associated lymph nodes (LALN). The authors concluded that evidence was lacking to suggest the nanomaterials could move beyond the pulmonary region following simulated occupational exposure.

The current weight-of-evidence suggests that particles from cosmetic powders are predominately large, and only small portion of inhalable fraction deposit in the lower regions of the respiratory system (pulmonary region). Further reduction of incidental inhalation exposures to respirable particles from cosmetic products can be accomplished by utilizing use devices, ingredients, and formulations that enable minimized aerosol generation, and/or skew the size distributions of the particles released from these products outside of the respirable range.<sup>11,12,34</sup> However, application of a nanomaterial in loose powder or sprayable products may pose a risk of inhalation of airborne particles into the consumer's lung airways.<sup>45,46</sup> During consumer use, nanomaterials can be released and enter the respiratory system as free nano-sized particles, agglomerates, and nanoparticles attached to larger particles. Additionally, other substances present in the nano-enabled products could be physically transported on the nanoparticles themselves.<sup>42,47</sup> When there is evidence of systemic exposure to nanomaterials, absorption, distribution, metabolism, and excretion parameters should be considered in safety assessments of the nanomaterial in cosmetic products.<sup>48</sup>

Additional analysis using photon correlation spectroscopy indicated the presence of particles < 100 nm in both regular and nanotechnology-based cosmetic spray products (e.g., regular hair spray and hair nanospray, as well as regular facial spray and facial nanospray).<sup>49</sup> During the application of all investigated sprays, particles ranging from 13 nm to 20  $\mu$ m were released. Further quantitative assessment of inhalation exposure and deposited dose of aerosol were performed in these cosmetics and several other consumer spray products, such as silver nanospray and disinfectant nanospray.<sup>50</sup> During realistic usage simulation of one minute exposure, similar deposition profiles were shown in regular hair spray, hair nanospray, regular facial spray, facial nanospray, regular skin hydrating mist, and skin hydrating nanomist. The highest deposited dose for the head airways was ~ 1171 ng/kg body weight (bw) per application (hair spray), and the head airways deposited doses from the remaining products were in the range ~ 205 to ~ 785 ng/kg bw per application. The tracheobronchial region deposited doses for the examined sprays were between ~ 1 and ~ 63 ng/kg bw per application, while those for the alveolar region were between ~ 1.4 and ~ 101 ng/kg bw per application. In addition, all investigated sprays demonstrated similar proportional distributions of deposited doses in the respiratory system: ~ 85 – 88% of the total respiratory system deposition occurred in the head airways, ~ 4.6 – 5.2% in the tracheobronchial region, and ~ 7.0 – 9.5% in the alveolar region.

Some liquid powder consumer products are specially designed to be dispersed through low pressure aerosol technologies such as airbrush devices or aerosol canisters, which nebulize liquid cosmetics into a fine mist or spray.<sup>51,52</sup> Engineered metal nanoparticles (ENPs) are frequently incorporated into such aerosolized cosmetics and may be emitted into the consumer breathing zone. Mounting evidence suggests the application of nano-enabled consumer spray products can cause pulmonary exposures to pressurized aerosols and metal nanoparticles, which raises potential public health concerns.<sup>41,42,51-53</sup> For instance, the aerosol properties of four airbrush consumer products, including a light and dark shade of foundation from each expensive or inexpensive product line respectively, have been examined during simulated realistic makeup application utilizing a fully automated aerosol generation system.<sup>51,52</sup> Aerosols were monitored using both a scanning mobility particle sizer (SMPS) that

measured particle size distributions between  $\sim 10 - 435$  nm and an optical particle sizer (OPS) that measured size distributions between  $0.3 - 10$   $\mu\text{m}$ . A spray duration/aerosol generation of 20 minutes represented a worst-case scenario of application with 8–12 drops ( $\sim 400 - 600$   $\text{cm}^3$ ) of liquid powder cosmetics placed in the reservoir of the nebulizer as per airbrush manufacturer's instructions.<sup>1,49,50</sup> Results indicated peak emissions of particles were color shade dependent and varied between 12,000–22,000 particles/ $\text{cm}^3$  with modal diameters ranging from 36 nm–1.3  $\mu\text{m}$ , and the majority of monitored mean particle diameters were  $\leq 100$  nm for all products. Peaks of larger particles with a mean diameter sized  $0.3 - 2$   $\mu\text{m}$  were also observed, indicating agglomeration during consumer application. While these larger particles were fewer ( $\leq 5000$  particles/ $\text{cm}^3$ ), these constituted the majority of the mass concentration, e.g., for particles with count mean diameter of 1255 nm, 82% mass fraction primarily deposited within the head airways, and  $< 10\%$  deposited within both the tracheobronchial and pulmonary regions. In addition, analysis of the elemental composition by scanning electron microscopy (SEM) demonstrated the existence of metal oxides ENPs in both the original products and collected aerosols, such as titanium dioxide ( $\text{TiO}_2$ ) and iron oxide ( $\text{Fe}_2\text{O}_3$ ), which are commonly found in powder-based makeup, functioning as pigmentation to produce various shades of cosmetics.<sup>54-57</sup> These findings showed that a fraction of airborne particles released from airbrush devices could be inhaled, and consequently deposited, in all regions of the respiratory system, which may cause unintentional adverse health effects. Aerosol monitoring data were also utilized to determine potential inhaled dose in human lungs as well as in vitro concentrations for epithelial cell treatment, using MPPD model.<sup>52</sup> For nano-sized particles, the entire exposure duration of 20 minutes could cause lung surface loading of  $60$   $\mu\text{g}/\text{m}^2$  based on the peak deposition mass flux of  $3$   $\mu\text{g}/\text{min}/\text{m}^2$ , and for micro-sized particles, an inhaled dose within 20 minutes of exposure was estimated to be  $1.1$   $\text{mg}/\text{m}^2$ , based on the peak deposition mass flux of  $55$   $\mu\text{g}/\text{min}/\text{m}^2$ . Further toxicity testing revealed significant increases in oxidative stress, single-stranded DNA damage, and 8-oxoguanine levels were identified post-exposure to collected aerosol suspensions versus pristine ENPs ( $\text{TiO}_2$  and  $\text{Fe}_2\text{O}_3$ ).<sup>52</sup> However, the current study did not assess whether the oxidative stress could be reversed with *N*-acetyl cysteine rescue, which may function as a fast-acting antioxidant in vivo and thus can provide valuable information on severity of toxicity. In addition, the authors also noted the limitations of using a glove box chamber versus a cleanroom to test exposures to particles, such as the ability to simulate exposure in a similar room size as the products that are used by consumers, more control of airflow and air ventilation systems, and control of other parameters, such as particle movement and deposition.<sup>51</sup>

The application of regular eyebrow powders may result in user exposure to respirable particles.<sup>58</sup> The concentration of  $\text{TiO}_2$  in airborne particle fractions (particles with  $d_{ac} \leq 10$   $\mu\text{m}$  or  $\leq 4$   $\mu\text{m}$ ) was proportional to the presence of  $\text{TiO}_2$  in the bulk powder. However, on the basis of the currently available data, it is not clear whether the nanoparticles released during the product use include additional nanosized ingredients other than the engineered nanoparticles that were incorporated into the product (e.g., whether the released nanoparticles include derivatives from natural product ingredients, or particles from product carrier liquid).<sup>49, 51, 52, 58</sup>

### **Inhalation Exposure of Nanoparticles from Aerosolized Consumer Products**

Nanoparticles with diameters in the range of 10 - 100 nm preferentially enter the alveolar areas, but will also be partly exhaled as they remain dispersed in the inhaled air.<sup>59</sup> For particles or agglomerates larger than 100 nm, diffusion becomes less likely, and the density increasingly plays a key role in determining the location and extent of deposition.<sup>60</sup> Observations from rat studies suggest that when nanomaterials accumulate in large quantities in the alveoli, they may no longer be cleared by macrophages. This excessive accumulation can result in chronic irritation,

inflammation, and cytokines release, leading to local toxic effects. For instance, the carcinogenic potential associated with TiO<sub>2</sub> nanoparticles has been noted in rats when dust is inhaled in large quantities that impair the normal particle clearance mechanisms in the lung. However, it should also be noted that nanoparticles have unique properties that make them more susceptible to influence from species-specific differences in lung geometries. Considerable differences in regional particle deposition patterns and clearance rates for nanoparticles were observed in simulated studies parameterized using experimental data and the unique lung geometries for rats and humans.<sup>61, 62</sup> The ConsExpo nano tool can be used to estimate the alveolar load from the use of ENP-containing spray products.<sup>63</sup> It integrates models that calculate the external aerosol concentration in indoor air with models that predict the deposition and clearance of inhaled aerosol from the alveolar region, providing the mass-based inhalation exposure as well as offering alternative dose metrics, such as the total number or total surface area of the inhaled nanoparticles.

Due to insoluble/poorly-soluble, biologically-persistent, and surface-reactive nature, the interaction of nanoparticles with biological entities may occur at the near-molecular level.<sup>48, 19, 64</sup> Studies have revealed that exposure to airborne nanosized particles can cause potential adverse effects not only in the respiratory tract, but also in the heart, brain and the immune system.<sup>39, 65-67, 59</sup> While the toxicity of pure nanomaterials is described by a considerable amount of research, there is limited information on exposure to nanomaterials combined with other ingredients in cosmetic formulation, that is, little is known about how chemical components of varying physicochemical characteristics, contained in liquid powder cosmetics, may alter the physicochemical and toxicological properties of incorporated metal nanoparticles.<sup>43, 51, 68</sup> Studies demonstrated certain chemicals, such as organic solvents and volatile organic compounds within the complex mixture, may transform constituent nanoparticles by modifying particle surfaces.<sup>64-67</sup> Surface modification may further cause profound changes in a nanomaterial with regard to certain physicochemical properties and potentially the altered toxic effects.<sup>64</sup> The mobility of nanoparticles in aqueous solutions may be increased by a wide range of stabilizers, including thiols, carboxylic acids, surfactants and polymers, which can enhance the dispersion of ENPs.<sup>51, 69</sup> For example, addition of surfactants can cause a more stable nanoparticle suspension as a whole by creating micelles.<sup>68</sup> When aerosolized liquid powder consumer products are realistically applied via a commercial airbrush/nebulizer, chemically modified nanoparticles of unknown physicochemical properties and biological activity may be emitted into the consumer breathing zone, and impact respiratory health differently than that of pristine nanoparticle exposures.<sup>51, 68</sup> In addition, nanoparticle agglomerates can exhibit different biological effects compared with uniform particles of similar size, and thus pose different health hazards than solid particles, potentially due to interactions of product matrices and format, as well as a combined surface area greater than that of solid particles of the same size.<sup>42, 52, 70</sup> Therefore, the use of airbrush devices would result in inhalation exposure to single nanosized particles and multi-sized agglomerates, including complex nanoparticle-containing composites, which may present unknown health risks.

Characteristics of nanoparticles, such as size distribution, shape, and surface area, are unique to each aerosol and can affect their regional deposition in the lung airways, as well as their interactions with biological organisms. To better understand aerosolized ENP exposures and their potential implications on human health, a novel aerosol generation system coupled with individual animal exposure pods, for measuring particle concentration, has been developed to monitor and sample aerosols from various type of nano-enabled consumer products, and to mimic real-world consumer exposures to liquid powder consumer sprays.<sup>51, 52</sup> Such an exposure platform provides reproducible

aerosol generation and can be used for in vivo toxicological assessments to determine toxicological profiles of aerosol fractions, as well as potential respiratory hazards for realistic application.

The Panel considered that currently available data suggest that a fraction of airborne particles/agglomerates resulting from airbrush delivery are respirable (i.e., the majority of particles with diameters  $\leq 100$  nm, and the majority of the collected aerosols contained agglomerates sized  $< 2$   $\mu\text{m}$ ), and all of the four investigated products may have similar size distributions.<sup>51, 52</sup> The Panel also noted that the spray device and liquid carrier have shown significant effects on aerosol particle size and size distributions in multiple studies.<sup>71-74</sup> As more nanotechnology-based consumer products are being formulated and released into the market, in order to determine safety for the discrete ingredient used in aerosolized consumer products that are specially delivered through airbrush systems or other nano-enabled aerosol canisters, data requirements for inhalation risk evaluation would include characteristics of airborne particles, such as the final particle size (and size distribution) of a spray product, the maximum use concentration of ingredient, and information on methods of use and spray characteristics (e.g., exposure duration and frequency, and technical details of spray equipment), as well as inhalation toxicity testing data, if necessary.

As airbrush technologies have become increasingly popular for consumer product use, however, little guidance has been developed by regulatory authorities across the world to address safety concerns relating to potential exposure of the consumer via the inhalation route. A generic airbrush set typically consists of a trigger-controlled spray painting gun, an air compressor to create airflow, and a hose connector.<sup>75</sup> The airbrush pressure can be adjusted to apply various types of makeup products, such as lighter, heavier, or more detailed styles. As a result, spray parameters resulting from airbrush use are triggered by individual habits and are highly sensitive to the exposure situation (e.g., particle/droplet size distribution at spraying, ventilation rate, room volume, frequency and duration, etc.). To build realistic exposure scenarios, it is therefore important to understand how each type of nano-enabled spray is realistically applied.

While the regulations enforced by the Food and Drug Administration (FDA) do not define airbrush devices by their intended use in cosmetics (i.e., the FDA only classifies airbrush as a medical device, which is applied in dental restorations by using air-driven particles to roughen the tooth surface),<sup>76</sup> the Panel noted some negative health effects associated with usage of airbrush consumer products and sunless tan have been reported to the FDA Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS),<sup>77</sup> including eye swelling and irritation, skin irritation, erythema, pyrexia, necrotizing fasciitis, pain, angioedema, pruritus, etc. The Panel recognized nano-enabled consumer products have a complex mixture that contains many elements, and airbrush applications might result in inhalation exposure to nanosized metal oxides, such as  $\text{TiO}_2$  and  $\text{Fe}_2\text{O}_3$ , which poses public health risks.<sup>41, 51, 52, 55</sup> For instance,  $\text{TiO}_2$  is classified as a “Carcinogen Category 2 (inhalation)” by the European Commission,<sup>78</sup> and in the EU, several nanomaterials (e.g., nano form of  $\text{TiO}_2$ ,  $\text{ZnO}$  and carbon black) are not allowed to be used in applications that may lead to exposure of the end-user's lungs by inhalation.<sup>45, 79</sup> Based on this evidence, to be determined safe, application of cosmetics via airbrush technologies warrants further, extensive evaluation. Such evaluation of device use is outside the purview of the Panel review process.

However, the Panel also noted a case wherein a color additive, i.e., dihydroxyacetone (DHA), is used in spray-tan booths (i.e., airbrushing it onto consumers). Therein, the FDA issued an advisory, warning individuals against unwanted exposure and suggesting that customers request measures to shield their eyes, lips, nostrils, and mucous membranes, to avoid ingestion and inhalation of this color additive. Use of DHA in this manner is an unapproved use. Though DHA is currently regulated and allowed by the FDA for use in externally applied

cosmetics, such as sunless spray tanning products (i.e., DHA is only approved for external application, which means that it should not be used around the eyes, on the lips, or on any body-surface covered by mucous membranes), the safety of its use in a mist or in a spray-on tanning booth has not been assessed.<sup>80-82</sup> In addition, the majority of seventeen surveyed tanning booth locations simply suggested the customers hold their breath through spray tanning.<sup>83</sup> Furthermore, unlike airbrushed tans that involve trained technicians, home airbrush systems are widely used by consumers; to achieve even and full coverage, the airbrush nebulizer is aimed at the face and rotated in a constant application pattern, potentially resulting in prolonged inhalation exposure to micro-to-nanosized particles. Similar precautions and protection measures are thus advised to refrain from aerosol inhalation during applying spray-on liquid powders through low-pressure airbrush technologies.

### **Measurement of Exposure Under In-Use Conditions**

Characterizing the particle size distributions released from finished powder products under use conditions is difficult. This is because the methods used to measure the particle sizes of powder products involve dispersing the powder in a solvent or applying a pressure differential to break up the agglomerated particles.<sup>12</sup> 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 SMPS and aerodynamic particle sizer (APS). These sampling devices provide airborne particle concentrations and size distributions in the range of 14.1 nm and 20  $\mu\text{m}$ ,<sup>42, 50</sup> which does not cover the full spectrum of particle sizes typically released from cosmetic sprays (with the largest portion being in the 50 – 300  $\mu\text{m}$  range). In comparison, particle/droplet size data measurements of a free spray may be generated using laser diffraction analyzers, which typically cover a particle size range of 10 nm to 4 mm (i.e., particle sizes larger or smaller than this range cannot be detected by this method). In addition, SMPS requires at least 3 minutes of application to scan the entire particle size, which represents an exaggerated estimate of duration per aerosol spray application compared to customary cosmetic use conditions.<sup>36</sup> Organic particles or a more complex mixture are hard to detect using electron microscopy.<sup>40</sup> 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 consideration.<sup>40</sup> 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.<sup>40, 84, 85</sup>

Data obtained from RIVM ConsExpo spray model, as well as an industry survey, demonstrated pump sprays tend to produce larger aerosols that are non-respirable, whereas propellant deodorant sprays may generate respirable particles/droplets sized < 10  $\mu\text{m}$ .<sup>1, 18, 27, 35</sup> As for cosmetic products in spray form, the major targets are the skin and hair, but spraying causes the partitioning of the product between the target and the surrounding air. For the risk assessment purpose, the use of spray products should be quantified not only in terms of the amount of product dispensed from the spray can, but also the product fraction reaching the skin and deep lung regions during application.<sup>1, 86, 87</sup> 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.<sup>36, 40, 85, 87</sup>

Therefore, in most cases, a refinement of spray characteristics is required to achieve realistic consumer exposure measurements, which will provide a clear insight into the inhalable and respirable fractions that might be expected. One study, which performed exposure measurements with deodorants/antiperspirants in aerosol form, indicated that experimentally measured exposure is generally many times lower than the that derived from the in silico models after inhaled doses are refined to adjust for the amount of material that ends up on skin/hair (and is therefore not available for respiration)<sup>86</sup> In another study, inhalation exposure to aluminum from four antiperspirant sprays was estimated when the product was sprayed against a skin surrogate, as opposed to spraying in the air (“free spraying”).<sup>88</sup> Findings suggests free spraying overestimated uptake by more than a factor of two (i.e., calculating the systemic uptake using release data obtained for the free spray operation results is an overestimation of the uptake by more than a factor of two).<sup>35, 88</sup> Thus, a safety assessor may expect that unintentional exposure by inhalation during usage of some types of cosmetic sprays, under realistic exposure conditions, can be very low to negligible.<sup>36</sup>

### **Tiered Approach for Inhalation Safety Evaluation**

The Panel noted that particle/droplet size data under simulated consumer use scenarios are generally not needed when conducting inhalation risk assessment due to the tiered approach to risk assessment, which provides an adequate margin of safety at the screening and modeling tiers. This is consistent with the very low product and ingredient exposures based on short exposure durations, ingredient content of product, and total amount of product used.<sup>35</sup> 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 exposure includes three tiers:<sup>87</sup>

- Tier I is a screening approach that employs worst case default assumptions, assuming all product leaving the container is potentially respirable and likely to become systemically available. This approach uses existing habits and practices data, and assumes the total amount of sprayed product immediately enters the breathing zone (about 1 to 2 m<sup>3</sup> 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 utilizes additional factors in determining exposure such as room volume, room ventilation rate, discharge rates, spray times, and particle/droplet size. Computational models of varying complexity have been developed (e.g., 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 aerosolized cosmetic ingredients 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.

It is important to note that particle/droplet size data obtained under simulated consumer use conditions are seldom required for risk assessment. Particle/droplet size data obtained from laser diffraction measurements of a free spray can be utilized for various purposes, such as qualifying packaging or assessing the acceptability of consumer products.<sup>35</sup> Although these data are not directly comparable to consumer exposure, they 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 subsequent sample exposure calculations. It is also important to recognize that particle/droplet sizes measured in experimental settings may differ from those during actual consumer use. Various factors, such as temperature, humidity, spray distance, duration of spray, container fullness, and actuator pressure, can influence the results.

### Sample Exposure Calculations

Sample exposure calculations utilizing the approach described above are presented here for an aerosol hair spray product.<sup>35</sup>

- Screening Approach:  
(assumes all ingredient in the product is available for systemic exposure)

Aerosol hairspray assumptions:

Amount used per day: 9.89 g (95<sup>th</sup> percentile)<sup>89</sup>

Ingredient makes up 2% of product

Body weight: 60 kg

Exposure estimate:

$9.89 \text{ g} \times 0.02 \text{ (ingredient)} = 0.198 \text{ g (198 mg)}$

$198 \text{ mg} \div 60 \text{ kg} = \mathbf{3.3 \text{ mg/kg}}$

- Refined Exposure Estimate:

There are multiple factors that can be used to refine an exposure estimate. In this example, the following refinements are added:

- Two-box model,<sup>1</sup> in which the ingredient distributes in 1000 L in the first 2 minutes, and distributes in 10,000 L in the next 18 minutes
- Breathing rate 10 L/minute<sup>90</sup>
- 25% exhaled

Exposure estimate:

First 2 minutes:  $198 \text{ mg}/1000 \text{ L} \times 10 \text{ L}/\text{minute} \times 2 \text{ minutes} = 3.96 \text{ mg}$

Next 18 minutes:  $198 \text{ mg}/10,000 \text{ L} \times 10 \text{ L}/\text{minute} \times 18 \text{ minutes} = 3.56 \text{ mg}$

Total exposure  $3.96 \text{ mg} + 3.56 \text{ mg} = 7.52 \text{ mg}$

25% exhaled (0.75 exchange factor)

$7.52 \times 0.75 = 5.64 \text{ mg}$

$5.64 \text{ mg} \div 60 \text{ kg} = \mathbf{0.094 \text{ mg/kg}}$

- 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 (i.e., the amount of material that adheres to skin and hair is unavailable for inhalation).<sup>86</sup>

Addition of a factor to adjust for respirable fraction (inhaled particles/droplets  $<10 \mu\text{m}$ ) refines the amount that may reach the deep lung. If, for example, 5% of the distribution is less than  $10 \mu\text{m}$ , the following calculation would apply:

$0.094 \text{ mg/kg/day} \times 0.05 = \mathbf{0.0047 \text{ mg/kg/day}}$

Calculations for dry shampoo and propellant deodorant are carried out in a similar manner, as detailed in Appendix I. The results show that using the highest percentages of respirable droplets/particles as inputs - 32.3% for dry shampoo (powder)<sup>30</sup> and 40% ( $26.63 + 13.43\%$ , mean + 1SD)<sup>35</sup> for propellant deodorant – yields exposure levels of  $0.0075 \text{ mg/kg/d}$  and  $0.062 \text{ mg/kg/d}$ , respectively. It is important to note that these calculations are based on a worst-case scenarios wherein dry shampoo and propellant deodorant release their maximum possible percentage of respirable droplets/particles. In comparison, the Occupational Safety and Health Administration (OSHA) sets a general concentration limit of  $5 \text{ mg}/\text{m}^3$  for an 8-h workplace [time-weighted average (TWA) permissible exposure limit (PEL)] for respirable, poorly soluble low toxicity particles ( $5 \text{ mg}/\text{m}^3$  is equivalent to  $0.67 \text{ mg/kg/d}$ , assuming inhalation rate of a 60 kg person is  $1 \text{ m}^3/\text{h}$ ).<sup>91</sup> Lists of maximum air levels for a variety of substances have also been established by OSHA and/or American Conference of Governmental Industrial Hygienists (ACGIH).

### Realistic Exposure Measurements under Simulated Use Conditions

An example of exposure assessment for propellant-based antiperspirant spray products, mimicking in-use conditions and incorporating particle/droplet size data, has been reported.<sup>88</sup> Exposure to aluminum from four antiperspirant sprays containing up to 1.5% aluminum is assessed using a two-box exposure model. Realistic exposure measurements of released fractions under simulated use conditions are used to refine the input data of the two-box model. The simulation involved a spray application within a  $10 \text{ m}^3$  bathroom, featuring a residence time of 12 min. Systemic exposure of the upper respiratory tract and deep lung deposition were calculated using MPPD Model. The total systemic exposure via inhalation was found to be **less than  $0.5 \mu\text{g}$  per application** (i.e., less than  **$0.000084 \text{ mg/kg/application}$**  for a 60 kg person). In this study, the inhalation exposure estimates for when the product was sprayed onto a skin surrogate were compared to estimates for spraying it in the air ("free spraying").

Free spraying overestimated the uptake by more than twice. The findings suggest that, to reduce conservatism in exposure assessments of antiperspirant sprays, it is essential to determine the airborne release fractions of aluminum; this can be achieved by spraying onto a surrogate surface that mimics particle size-dependent skin deposition. Additionally, this observation demonstrates that employing a tiered approach and refined exposure modeling leads to a more accurate estimation of the amount of aluminum potentially inhaled and systemically absorbed, which is not respirable to any significant extent. Thus, gathering data from measurements under simulated usage conditions is vital to improve the accuracy of exposure estimates.

### **OTHER CONSIDERATIONS OF SPRAYED PRODUCT**

While there may be some unique considerations (e.g., specific considerations applicable to a particular product type) in the evaluation of safety following exposure by the inhalation route, the basic framework for risk assessment – consisting of hazard identification, exposure assessment, and risk characterization – is fully applicable. Both local (lung) effects and systemic effects are considered in the evaluation of hazard and risk. 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.<sup>92</sup>

The Panel recognized that aerosols from propellant deodorant sprays or airbrush devices 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 airbrush delivery. Identifying the use of ingredients in deodorant spray and airbrush products may be especially important, because they potentially release the largest quantity of respirable droplets/ particulates among the products evaluated. However, better information about particle size distributions and their variability (within and across product types) that can be reasonably expected, generally, from a broad range of products (e.g., hair, sunscreen, indoor suntanning, foot and deodorant sprays, and loose powders), would substantially increase confidence in safety assessments of ingredients in products that may be aerosolized.

The Panel notes the particle inhalation risks associated with the applications of airbrush technologies and propellant deodorant sprays. The final particle size distribution of a spray product is the result of the composition of the formula, the concentration of individual ingredients, and other relevant spray parameters (e.g., spray nozzle, can size, propellant type and pressure). When considered necessary, risk characterization for spray products can be carried out to assess the risk to human health at certain levels of exposure under real-use conditions (e.g., Risk Characterization Ratio (RCR) can be derived by comparison of the calculated exposure with the relevant derived no-effect level (DNEL) for an ingredient).<sup>93</sup> The Panel also recognizes currently available data suggest the use of airbrush delivery of consumer products might lead to inhalation exposure to ingredients such as TiO<sub>2</sub> and Fe<sub>2</sub>O<sub>3</sub>, which may pose a risk to public health if respirable. The Panel thus considers the data to be insufficient to assess the safety of airbrush delivered cosmetics.

Additionally, the purview of the Panel is exclusive to assessing the safety of ingredients as used in cosmetics. Assessing the safety of devices, such as airbrush delivery systems, is obviously outside of that purview. The only

approved use of airbrush systems is as a medical device. Clarification is needed as to the regulatory purview of using airbrush devices to deliver consumer products (e.g., certain contact lens solutions are considered to be devices in the US [21CFR886.5928]). Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Surveying the cosmetic market reveals that the airbrush applications may be used for temporary tattoo including face and body painting. Some airbrush devices, equipped with an airbrush gun/needle and compressor and utilizing AC powder-driven technology, are marketed for a wide range of applications. These include art painting (on canvas or graffiti), as well as painting toys, shoes, and cars, in addition to makeup and nail applications.

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. 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.

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  $d_{ac}$  ranging from 1 to 4  $\mu\text{m}$ , which is well within the range considered to be respirable. However, this ingredient, as supplied to formulators, has an average  $d_{ac}$  of about 20  $\mu\text{m}$ , and the ingredient aggregates and agglomerates to form clusters and chains with  $d_{ac} > 125 \mu\text{m}$ , 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.

Additionally, questions are raised regarding the impact of interspecies differences on the predictability of human effects.<sup>94</sup> Disparities in macroscopic anatomy, microscopic anatomy, and physiology between rats and humans can impact the results of inhalation toxicity tests. The key influencing factors include breathing mode (e.g., nose-only versus oronasal breathing), airway structure (e.g., complexity of the nasal turbinates), cell types and location within the respiratory tract, and local metabolism. For instance, certain effects observed in rats, such as irritation of the larynx and ventral pouch, are identified as having little or no relevance to humans. Therefore, there

is a need for testing approaches that align more closely with human biology and mechanisms of toxicity, e.g., designing test systems that more closely model the human respiratory tract and are scientifically appropriate to predict effects in humans, such as reconstructed human lung models, precision-cut lung slices, or certain microphysiological systems/(multi) organs-on-chip.<sup>95</sup>

In the development of inhalation thresholds of Toxicological Concern (TTC) by building upon repeat dose toxicity (RDT) database (particularly in cases where exposure via the inhalation route is sufficiently low), it is suggested to consider the duration of toxicity studies and consumer exposure in relation to dose metrics.<sup>96,97</sup> For instance, while rodent inhalation RDT studies typically test 6-h exposures, the goal is to extrapolate these exposures for cosmetic products in applying an inhalation TTC; cosmetics generally involve a significantly shorter inhalation exposure times, ranging from 5 to 12 min, a variable that is accounted for in exposure models, such as the Creme model.<sup>95</sup> On the other hand, developing inhalation Thresholds of Toxicological Concern (TTC) still presents many challenges, with significant variations observed between values derived from different datasets.<sup>96</sup> For instance, inhalation TTC values range from 8.27 µg/d to 1400 µg/d for Cramer Class I, which includes simple chemical structures with low potential toxicity.<sup>96,98</sup> And for Cramer Class III, which contains structural features indicative of significant toxicity, inhalation TTC varies from 4 µg/d to 470 µg/d.<sup>98,99</sup> Regarding fragrance materials, the Research Institute for Fragrance Materials (RIFM) enforces a local respiratory TTC limit of 1400 µg/day for Cramer Class I and 470 µg/day for Cramer Class III, while materials in Cramer Class II are subject to the Cramer Class III threshold.<sup>100</sup>

The Panel notes emerging data suggest that propellant-based hairsprays dry shampoos or deodorants emit substantially larger fractions of particulates with aerodynamic equivalent diameters within the range considered to be respirable, e.g., an average of 25 and 26.63% for propellant dry shampoos or propellant deodorants, respectively.<sup>30</sup> However, the Panel also notes that when measured data from simulated applications are available and applied in refined inhalation modelling, the estimated systemic exposure doses may be significantly decreased.<sup>88</sup> Therefore, a more appropriate and accurate exposure characterization is crucial for a robust and reliable risk assessment.

The Panel also noted data are currently insufficient to assess the inhalation exposure of each ingredient in relation to the unintended exposure resulting from the intended use of the finished products delivered by airbrush system. If substances are meant to be included in sprays or aerosols, evaluation of consumer exposure via inhalation is paramount in the overall safety assessment. 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.

The Panel is aware of the FDA has proposed changes cosmetic product categories and codes under the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), which covers airbrush applications associated with

makeup and suntan preparations.<sup>101</sup> Nonetheless, there are still significant opportunities to increase category specificity, for current and future products, that could better inform initial analyses of risk and safety. **Currently, the FDA has “other” categories to allow for innovative products.** Some products have not yet been clearly defined within the existing regulatory framework. Take, for example, the diverse products formulated and delivered by dry shampoos. Surveying the cosmetic market reveals that dry shampoo may come in various forms, including aerosol sprays, foams, and powders. Foam-based dry shampoos may be associated with fewer inhalation safety concerns, while research has also looked into particle size distribution in dry shampoo powder products that are packaged in propellant-based sprays.<sup>30</sup> Hence, a more specific classification/subcategorization is proposed for cosmetic aerosol sprays (pump-based vs propellant-based) and powders (pressed vs loose), along with rapidly emerging airbrush technologies that could pose potential incidental inhalation risks.

## **Appendix I: Sample Exposure Calculations for Dry Shampoo and Propellant deodorant**

### **Exposure Calculations for Dry Shampoo**

Sample exposure calculations utilizing a tiered approach are presented below for dry shampoo.

- **Screening Level:**

(assumes all ingredient in the product is available for systemic exposure)

Dry shampoo assumptions:

Amount used per day: 2.4 g<sup>102, 103</sup>

Ingredient makes up 2% of product

Body weight: 60 kg

Exposure estimate:

$2.4 \text{ g} \times 0.02 \text{ (ingredient)} = 0.048 \text{ g (48 mg)}$

$48 \text{ mg} \div 60 \text{ kg} = \mathbf{0.8 \text{ mg/kg}}$

- **Refined Exposure Estimate:**

There are multiple factors that can be used to refine an exposure estimate. In this example, the following refinements are added:

- Two-box model,<sup>11</sup> in which the ingredient distributes in 1000 L in the first 2 min, and distributes in 10,000 L in the next 18 min

- Breathing rate 10 L/min<sup>104</sup>
- 25% exhaled<sup>104</sup>

**Exposure estimate:**

First 2 min: 48 mg/1000 L x 10 L/min x 2 min = 0.96 mg

Next 18 min: 48 mg/10,000 L x 10 L/min x 18 min = 0.864 mg

Total exposure 0.96 mg + 0.864 mg = 1.824 mg

25% exhaled (0.75 exchange factor)

1.824 x 0.75 = 1.368 mg

1.368 mg ÷ 60 kg = **0.0228 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, addition of a factor to adjust for respirable fraction (inhaled particles/droplets <10 µm) refines the amount that may reach the deep lung. If conservatively assuming that 32.3% of the dry shampoo particles are less than 10 µm, based on the data from a 2023 study,<sup>30</sup> the following calculation would apply:

0.0228 mg/kg/d x 32.3% = **0.0075 mg/kg/d**

**Exposure Calculations for Propellant Deodorant**

Sample exposure calculations utilizing a tiered approach are presented below for dry shampoo.

- **Screening Level:**

(assumes all ingredient in the product is available for systemic exposure)

Propellant deodorant assumptions:

Amount used per day: 6.54 g<sup>105</sup>

Ingredient makes up 2% of product

Body weight: 60 kg

Exposure estimate:

6.54 g x 0.02 (ingredient) = 0.131 g (131 mg)

131 mg ÷ 60 kg = **2.18 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:

- Two-box model,<sup>11</sup> in which the ingredient distributes in 1000 L in the first 2 min, and distributes in 10,000 L in the next 18 min
- Breathing rate 10 L/minute<sup>104</sup>
- 25% exhaled<sup>104</sup>

Exposure estimate:

First 2 min:  $131 \text{ mg}/1000 \text{ L} \times 10 \text{ L}/\text{min} \times 2 \text{ mins} = 2.62 \text{ mg}$

Next 18 min:  $131 \text{ mg}/10,000 \text{ L} \times 10 \text{ L}/\text{min} \times 18 \text{ min} = 2.36 \text{ mg}$

Total exposure  $2.62 \text{ mg} + 2.36 \text{ mg} = 4.98 \text{ mg}$

25% exhaled (0.75 exchange factor)

$4.98 \times 0.75 = 3.73 \text{ mg}$

$3.73 \text{ mg} \div 60 \text{ kg} = \mathbf{0.062 \text{ mg/kg}}$

- Other Refinements:

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.<sup>86</sup> For deodorant spray, at the screening level, the exposure values were obtained by measuring the product emitted from the can, which accounts for both dermal deposition and the inhaled amount. One study<sup>86</sup> provided estimates for maximum potential dermal exposure from sprays: 23.5% for ethanol-based sprays and 11.4% for non-ethanol-based sprays, respectively. Using these figures, the estimated inhaled fractions are calculated to be 76.5% for ethanol-based sprays and 88.6% for non-ethanol-based sprays, according to the most conservative estimates.

Therefore, the inhalable fraction:  $0.062 \text{ mg/kg} \times 0.886 = 0.055 \text{ mg/kg}$

Addition of a factor to adjust for respirable fraction (inhaled particles/droplets  $<10 \mu\text{m}$ ) refines the amount that may reach the deep lung. If conservatively assuming that 40% ( $26.63 \pm 13.43\%$ ) of the dry shampoo particles are less than  $10 \mu\text{m}$ , based on the data submitted from industry,<sup>35</sup> the following calculation would apply:

$0.055 \text{ mg/kg/day} \times 40\% = \mathbf{0.022 \text{ mg/kg/d}}$

## Appendix II: Revised Inhalation BP

### COSMETIC USE section –inhalation bp language

in all documents – first paragraph of Use section

The safety of the cosmetic **[ingredient(s)]** addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of **[this**

**ingredient/these ingredients]** in cosmetics and does not cover **[its/their]** use in airbrush delivery systems. Data included herein were obtained from the FDA's Registration and Listing Data (RLD) database (previously from the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use)) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based at that time on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

route of exposure type paragraph, when exposure via inhalation is known

In practice, as stated in the Panel's respiratory exposure resource document (<https://www.cir-safety.org/cir-findings>), most droplets/particles incidentally inhaled from **cosmetic pump sprays [if there are only powders, and no sprays, change to incidentally inhaled from cosmetics]** would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable to any appreciable amount, meaning they do not significantly enter the deep lung. **[if there are known propellant-based deodorant or dry shampoo uses: There is some evidence indicating that aerosol deodorant spray and dry shampoo products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable. The proportion of respirable droplets/particles released depend on the product characteristics and formulation. However, in the absence of measured data on airborne substances released under simulated in-use conditions, the information is not sufficient to determine whether lung exposures from the use of propellant-based sprays, compared to other cosmetic sprays, result in greater lung exposures and pose significantly higher inhalation risks. For instance, a case study suggests that when measured data on particle size distribution under simulated use conditions are available, refining input data in exposure modeling approaches can significantly reduce the estimate of inhalational uptake.] [if there are known powder uses: 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.] The Panel notes the risk from inhalation to cosmetic spray products is not only related to the exposure but also to the level of toxicity of the individual ingredients. The Panel will review all relevant data and, when necessary, request specific exposure and inhalation toxicity data on a case-by-case basis, particularly when existing data are absent or insufficient to ensure the safety of ingredients as used in aerosolized products. To perform a reliable inhalation risk assessment, the Panel would request robust data on spray characterization such as measurements of particle size distribution under realistic use exposure scenarios, alongside consumer use habits and practices data for specific types of sprays.**

**DISCUSSION – standard inhalation bp (modify as necessary)**

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., ...). Inhalation toxicity data were not available. **[modify previous sentence, as appropriate]** However, the Panel noted

that in **cosmetic pump spray** products, the majority of droplets/particles would not be respirable to any appreciable amount. **[if there are powders, in addition to or instead of sprays, change to, “However, the Panel noted that the majority of droplets/particles would not be respirable to any appreciable amount.”]** **For other propellant-based sprays, there is some evidence suggesting that aerosols released from these products may release larger fractions of particles with aerodynamic equivalent diameters within the respirable range. However, due to the lack of measured data of particle size distribution under realistic application conditions, it is unclear whether these products lead to significantly increased lung exposure. [If the chemical and biological properties of the ingredients indicate no toxicological concerns]** Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the physical and biological properties of these ingredients. **[If the ingredients are used in cosmetic pump sprays only]** Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. *[modify previous sentence, if appropriate.]* **[If the ingredients are also used in propellant-based sprays]** Refined exposure models that incorporate particle/droplet size measurement under in-use scenarios and consumer habits and practices data allow for a more accurate estimation of lung deposition of aerosols and particles. 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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**APRIL 10-11 2017 EXPERT PANEL MEETING****Marks Team Meeting – April 10, 2017**

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...

### **Belsito Team Meeting - April 10, 2017**

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

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

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

DR. BOYER: Correct.

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

DR. KLAASSEN: I don't have any solid statements either, other than this 10 microns has been around in the scientific community for at least 35 years. Maybe much longer than that, but that's kind of what it takes to get it down. And I don't know how good the data was, but everybody's kind of used that. And it's probably not that great. So I think you could kind of reply, this time be a little soft and say that traditionally toxicologists have used this but if there are these later papers with deodorants showing a smaller median mass diameter, maybe we need to

reconsider this and make it a little smaller. Although we'd sure like to see more data on this area. You know, kind of half-way answer it. And then we can think about what we want to put in our new boilerplate, want to be more general. I guess I would like to know what goes on back in the toxicology data 35 years ago that everybody said 10 microns. I know I summarized that data 35 years ago and it was 10 microns. What I reviewed and what I remember from then it does not exist here anymore. But I think there are more than just a couple three studies that have kind of concluded this 10 microns. And it would be nice to see all of the papers that have done this before we change our boilerplate.

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

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

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

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

DR. KLAASSEN: No kidding?

DR. BOYER: Yeah.

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

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

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

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

DR. BOYER: We didn't reference those.

DR. BELSITO: For powders.

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

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

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

value of what you're trying to measure.

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

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

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

DR. LIEBLER: PM 2.5.

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

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

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

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

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

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

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

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

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

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

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

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

DR. BOYER: No.

DR. KLAASSEN: Maybe it should be something.

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

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

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

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

DR. LIEBLER: Which would bother me.

DR. BELSITO: Right.

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

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

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

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

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

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

And relook at it more than just in terms of yes. We need a response to her now, and I agree with what Curt said. It should be thanks for bringing this to our attention. We are looking into it. We don't have all the answers. And I

think we need to begin to look into some of those. Perhaps grab 10, since the weakest link seems to be underarm deodorants, grab ten off the shelf and look at the range of --

DR. SYNDER: Worst case scenario.

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

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

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

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

DR. ANSELL: It dropped to zero in minutes.

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

DR. SYNDER: Not anymore.

MR. 8: Oh yeah?

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

MR. 8: Who is doing inhalation?

DR. SYNDER: I don't know.

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

MR. 8: In Rochester.

DR. LIEBLER: The end of an era.

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

DR. LIEBLER: Greg [inaudible]

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

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

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

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

DR. BELSITO: Okay.

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

DR. ANSELL: It's classic analytical methodology.

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

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

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

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

allows us to make a decision other than don't worry about it.

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

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

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

DR. LIEBLER: She says it's not.

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

DR. LIEBLER: She uses some of our numbers.

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

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

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

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

DR. LIEBLER: That's correct.

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

DR. LIEBLER: What's the distribution like.

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

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

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

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

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

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

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

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

DR. BELSITO: But I don't, I think we are assuming the data's old and unreliable. I think that the issue is that she's

right. We only looked at a couple of products and I don't even know that we looked at underarm deodorants and these sprays as opposed to pumps.

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

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

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

DR. LIEBLER: Nazarenko?

DR. BELSITO: Yeah.

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

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

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

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

DR. LIEBLER: Who's presenting on this?

DR. BELSITO: Ivan.

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

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

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

#### **Full Panel - April 11, 2017**

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...

**SEPTEMBER 10-11, 2017 EXPERT PANEL MEETING**

**Marks Team Meeting - September 10, 2017**

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.

DR. 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.

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

DR. MARKS: Okay.

MS. 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.

### **Belsito Team Meeting – September 10, 2017**

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 diameter of 35 microns, whereas the deodorant propellant sprays are 10. And they have the same coefficient 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 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 area? 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 nanoparticle 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.

### Full Panel - September 11, 2017

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.

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

#### **Belsito Team Meeting – December 3, 2018**

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

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

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

To say that we don't give a darn about particle size, I think, is really overstepping what we really mean. I mean, I agree with this tiered approach, but we want to know particle size as well. That was my biggest issue with this whole report. And that language occurs several times throughout the report. It's on PDF 103, PDF 104.

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

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

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

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

If we make that the introductory comment, as opposed to we don't need to know particle size. It's a little bit different. Instead of saying, we don't need to know, say, we often won't have that information. Therefore, a tiered

approach allows us to begin with a most conservative assessment. But if we have additional information, we can go on to these tiers, two and three, to incorporate the additional information into our assessment.

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

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

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

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

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

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

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

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

DR. BELSITO: We did not.

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

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

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

DR. EISENMANN: Right.

DR. BELSITO: Okay.

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

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

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

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

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

DR. EISENMANN: Correct.

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

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

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

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

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

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

DR. ZHU: Publication?

DR. BERGFELD: Yes.

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

DR. BERGFELD: Danish?

DR. ZHU: Yeah, Danish.

MS. FIUME: 2015?

DR. ZHU: 2015.

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

DR. ZHU: I think she saw this documents.

DR. BERGFELD: I think we've had a policy to get back to her every time there's been a letter, and go through the itemized list. Yes. We can look at that.

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

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

MS. FIUME: Yeah, the 2015.

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

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

DR. KLAASSEN: I have a general question to my colleagues. If you have a one-fold increase, what does that mean? You double it, right? What's a 400 fold decrease? Can you have more than a one-fold decrease? We keep

using, like, he just read, and we use in these documents; they might have said that, but I don't think we should continue to say -- how about 1/400th the amount if that's what's meant.

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

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

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

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

DR. ZHU: I see.

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

DR. LIEBLER: Or 0.25 percent.

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

DR. ZHU: Sure.

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

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

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

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

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

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

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

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

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

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

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

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

the powder language.

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

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

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

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

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

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

MS. FIUME: Right.

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

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

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

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

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

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

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

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

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

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

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

DR. SNYDER: To be honest, when I read this, I thought we could no longer use a boilerplate statement. That I think that we're almost obligated, depending upon the use conditions, and taking into consideration particle size

distribution, the formulation of the product -- because the formulation can also impact the absorption and other issues.

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

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

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

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

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

DR. SNYDER: Under that one heading.

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

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

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

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

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

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

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

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

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

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

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

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

DR. BELSITO: Okay.

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

when the survey gets returned.

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

MS. FIUME: Are those separated out, Carol?

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

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

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

DR. BELSITO: Right.

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

DR. KLAASSEN: Does she have any health problems?

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

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

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

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

DR. BELSITO: Right.

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

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

MS. FIUME: Which was why I was --

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

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

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

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

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

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

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

MR. GREMILLION: Okay.

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

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

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

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

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

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

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

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

DR. LIEBLER: No, I don't think so. Because I don't think we could provide useful enough guidance in a boilerplate anyway.

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

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

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

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

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

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

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

MS. KOWCZ: It's a forced air. It's a forced pressure, basically. Because you're trying to keep two types of ingredients separated. So, one ingredient needs to be protected from the rest of the formula. And the bag-on-valve

is just keeping one type -- let's say the DHA is very reactive with the rest of the formula. So, DHA is in one part, the formula's in the other, and it's a forced airbag, and it forces it through the nozzle.

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

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

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

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

MS. KOWCZ: A talk.

DR. BELSITO: A talk, yeah.

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

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

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

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

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

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

DR. BELSITO: Yes.

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

DR. BELSITO: Exactly. Right.

MS. FIUME: Okay.

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

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

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

MS. FIUME: Okay.

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

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

DR. BERGFELD: Who's reporting on this?

DR. SNYDER: Dr. Marks.

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

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

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

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

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

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

DR. LIEBLER: Say that again, Paul.

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

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

DR. SNYDER: Okay.

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

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

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

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

And secondly, if you look at Table 2, again, the exposure amount of face powder range from 73 milligram to 85 milligram. The data is coming from Danish EPA's report. And, actually, this data also coming from review paper. So, if you look at the table in the review paper, it shows that the face powder, the dose at 85 milligram, is coming from Loretz paper; 2008 paper. After carefully checking the original paper article, we found that this kind of data is actually from another paper. So this citation we will correct that.

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

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

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

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

And I guess Paul's point is, how does this work as a boilerplate? Are we not going to -- because up until now we've

simply been using it in the cosmetic use section. Is this just going to be like we'll refer to it, like we do for hair dye epi, and then look at it case by case within the report itself, based upon what it's used? How do we use this boilerplate?

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

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

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

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

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

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

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

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

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

MS. KOWCZ: Okay, that's a whole packaging issue, also, as well. So, it's not just the particle size that's distributed. And the end result will be an entire -- it does depend on the type of packaging, the nozzle, the diameter. There's a whole physics to the packaging mechanisms as well.

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

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

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

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

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

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

DR. KLAASSEN: And what we would really like to know is, with those various systems, what percentage of the

product is less than 10 microns? Because we kind of use as a cutoff if things are less than -- they aren't going to get down into the respirable track if they're not less than 10 microns. So, that's the part that we're really interested in.

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

DR. KLAASSEN: Yes.

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

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

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

DR. LIEBLER: No, airbrush is an airbrush.

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

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

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

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

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

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

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

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

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

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

DR. BELSITO: Right.

DR. SNYDER: Worst-case scenario.

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

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

DR. BELSITO: Where are you, Paul?

DR. SNYDER: Let me find it here.

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

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

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

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

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

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

DR. BELSITO: On page PDF 100 --

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

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

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

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

DR. ZHU: We actually discussed that already.

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

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

MR. GREMILLION: I was looking at the response to comment three. In the first, second, third, fourth paragraph. "In addition, recent studies indicated that most of the mass, 85 percent to 93 percent of inhaled airborne particles released from cosmetic powders is deposited in the head airway, not the pulmonary region."

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

DR. BELSITO: Which point are you on?

MR. GREMILLION: Number three.

MS. FIUME: Powders are different than the sprays.

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

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

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

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

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

**Marks Team Meeting – December 3, 2018**

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

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

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

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

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

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

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

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

So, I think we need to decide what is the purpose of the document. Because everybody's having different suggestions, at different levels, and it becomes a very mixed bag as far as the science of respiration of chemicals. So, Council wants to tell us or --

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

DR. SHANK: Right.

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

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

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

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

DR. HILL: I think part of it is, is that if you got something like the silica we were talking about earlier, and particles

are the problem, potentially, in developing something like silicosis, that's a very different toxicology scenario than something like the polyaminopropyl biguanide that we were discussing. Where there's clearly that communitive exposure, but it's really things that get in there as a liquid, not particles that matter. But what size of the droplets and how deep in the lungs can they get.

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

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

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

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

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

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

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

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

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

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

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

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

DR. HILL: And I guess the other part of it is, if we want something to use as a boilerplate per se, then we might need to have 16 different scenarios where under this circumstance you use this. Because I'm, all the time, finding

myself, I get to the end and we have this bit of discussion which we can't put in the discussion, because we can't put references there.

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

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

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

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

DR. MARKS: The factual?

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

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

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

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

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

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

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

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

DR. MARKS: Right.

DR. HILL: Right.

DR. SHANK: This isn't the boilerplate.

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

DR. SHANK: In here.

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

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

DR. SHANK: Particle size.

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

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

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

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

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

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

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

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

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

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

DR. MARKS: Yeah, okay.

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

DR. MARKS: Aerosol.

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

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

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

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

DR. MARKS: Yeah. Analysis of particle size.

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

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

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

DR. HILL: Distribution?

DR. MARKS: Analysis of particle --

DR. SHANK: Particle Aerodynamic Properties on Exposure.

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

DR. SHANK: Sure.

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

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

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

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

DR. SHANK: Properties.

DR. MARKS: Properties.

DR. SHANK: On Exposure.

DR. MARKS: Respiratory --

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

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

DR. HILL: Nasopharyngeal.

DR. SLAGA: Nasopharyngeal, all the way down.

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

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

DR. MARKS: Well, Respiratory Exposure.

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

DR. ANSELL: Yeah, Respiratory Exposure.

DR. MARKS: Get rid of that?

DR. HILL: Incidental Respiratory Exposure.

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

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

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

DR. SHANK: Oh.

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

DR. SHANK: I think so.

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

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

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

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

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

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

DR. SHANK: I see.

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

DR. SHANK: Okay.

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

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

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

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

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

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

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

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

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

DR. SHANK: Right.

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

DR. SLAGA: To me it does --

DR. HILL: It should.

DR. SHANK: Respiratory would include nose to alveoli.

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

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

DR. SHANK: Respiratory system.

DR. HILL: The entire -- okay.

DR. SHANK: Thing.

DR. SLAGA: Yeah.

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

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

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

DR. SLAGA: Yeah.

DR. MARKS: Yeah.

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

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

DR. ANSELL: Assessment of?

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

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

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

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

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

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

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

DR. MARKS: Yeah.

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

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

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

DR. SLAGA: Right.

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

DR. SLAGA: No.

MS. FIUME: No.

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

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

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

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

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

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

That should be internal because it's coming into the documents in the proper context, as opposed to potentially taken

out of context if somebody else sees it. That's how I view it.

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

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

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

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

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

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

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

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

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

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

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

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

DR. ZHU: The broad assumption?

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

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

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

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

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

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

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

DR. SHANK: I like the latter. I like the precedent document as you've written it. And I like your response to the

Women's Voices for the Earth, as you've written it. There're separate.

DR. SLAGA: Yeah.

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

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

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

DR. SHANK: Correct.

DR. MARKS: Only change the title.

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

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

DR. HILL: That isn't already?

DR. MARKS: Yeah.

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

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

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

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

DR. SLAGA: Sounds good.

DR. MARKS: Does that capture --

DR. SHANK: Yes, it does.

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

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

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

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

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

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

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

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

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

DR. SHANK: Yeah.

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

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

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

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

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

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

DR. SHANK: Right.

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

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

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

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

DR. SHANK: Tomorrow.

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

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

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

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

So, if you're trying to assert that somehow an aerosol propellant spray for a suntan is different than a hairspray, bologna. It depends on how the nozzle is designed, and it could not necessarily be the same for this ingredient in a

hairspray from manufacture A, versus B, versus C, versus Q, right? It depends on what device they're using to do the delivery, not that it's a suntan product, or a hairspray, or deodorant.

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

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

DR. HILL: Show me your evidence.

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

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

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

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

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

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

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

MS. FIUME: And it is.

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

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

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

DR. HILL: Exactly. Exactly.

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

DR. ANSELL: Not at tier 1.

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

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

DR. HILL: You're right.

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

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

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

DR. LORETZ: Right.

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

that information.

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

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

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

DR. HILL: And that's tier 1.

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

DR. ZHU: Yeah.

MS. FIUME: So, can you state that?

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

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

DR. ZHU: Okay, sure.

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

DR. HILL: Yes.

DR. SLAGA: Yeah.

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

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

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

DR. SHANK: This is the response.

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

DR. SLAGA: Yeah.

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

#### **Full Panel – December 4, 2018**

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

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

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

DR. BERGFELD: Ron.

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

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

DR. BERGFELD: Don.

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

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

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

DR. BERGFELD: Paul.

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

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

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

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

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

DR. BERGFELD: Headed that way. Okay.

DR. SNYDER: Headed that way. I'm still a believer -- again, I'm not an inhalation toxicologist. But for respiratory exposure, for the lower levels of the lung, it's driven by physical properties. The toxicity may be influenced by other properties of those particles that reach the lungs, but the reaching of the lungs is just purely a physical property. So, the larger particles are picked up by the mucociliary apparatus, and coughed up, and swallowed and eliminated.

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

DR. SHANK: And chemical.

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

DR. HILL: It's physical until --

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

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

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

want to lose that perspective.

DR. BERGFELD: Ron Hill.

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

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

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

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

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

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

DR. BERGFELD: But it will be a guide.

DR. BELSITO: It'll tell people how we look at a respiratory tox endpoint. But in the actual documents, we will need to put in a little bit more data sometimes. Sometimes it'll be sufficient, sometimes it may not be. But it will be a case by case basis, as opposed to hair dye epidemiology that we just throw in every hair dye.

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

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

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

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

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

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

DR. BERGFELD: Dan?

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

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

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

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

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

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

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

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

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

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

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

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

DR. BERGFELD: Any comments?

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

DR. BERGFELD: The title?

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

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

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

## **SEPTEMBER 16-17, 2019 EXPERT PANEL MEETING**

### **Marks Team Meeting - September 16, 2019**

DR. MARKS: We're back to the administrative folder and on page -- we're now with the inhalation resource document as we're now referring to them. Let's see. I have page 24. Was that the minutes? That's Jinqiu's memo dated August 22nd, the revised respiratory exposure from cosmetic ingredients precedents document. So now we have precedents, which were we calling these resources or precedents?

And the Panel requests the collection analysis of particle size distribution consumer use of such sprays. To date, the CIR has not received such relevant information. That's on paragraph three of Jinqiu's memo. And then let me go back. Ron, I think you were the one suggested the title change.

DR. SHANK: Yes. My fault.

DR. MARKS: Now, in fact, I may differ. My summary was there's toxicity local and systemic. There was this tiered approach in the document which we liked, that looking at inhalation toxicity is more complex than just the particle size. And I think Paul summarized the best; we would have the ideal, which we often don't have, is prefer to have the actual respiratory toxicology data. Ron, Tom, comments?

DR. SHANK: I liked the --

DR. MARKS: And, Ron, I may have you comment after. Is that summary -- I know it's succinct and brief, but did that capture at least part of all this? This is a complex and actually extensive document that Jinqiu has put together, which I felt was quite nice. But, Ron, go ahead and comment.

DR. SHANK: I'm trying to find --

DR. SLAGA: I agree with you. I think it's pretty good.

DR. BERGFELD: It's on page 78, I think, of the administrative --

DR. SHANK: Seventy-eight.

DR. BERGFELD: Yeah, I think so.

DR. SHANK: Thank you.

DR. MARKS: Yes. That's the beginning of the document.

DR. SHANK: Thank you. Okay.

DR. MARKS: Dated 9/2019.

DR. SHANK: I think it clearly states the complexity of the inhalation toxicity tests and toxicology. And, yes, there's a lot of emphasis on particle size, but there's also a clear discussion of other parameters that affect the toxicity of inhaled material. And I like that. I wouldn't make any changes.

DR. MARKS: Oh, no, that's fine. What's the response to Jinqiu? He says, the Panel requested collection and analysis of particle size distributions consumer use data of such spray products. Do we still need that, or you think the resource or precedent document covers that in terms of --

DR. SHANK: I think it's covered.

DR. MARKS: Okay. Good.

DR. SHANK: You can go into a lot of detail on just particle size, but I think the purpose of this is to get a broad picture of inhalation toxicology. And it does that.

MR. GREMILLION: So, in the Women's Voices letters, she suggested that the technology for characterizing particle size distributions is better than how it's characterized in this document.

DR. HELDRETH: Yeah, Jinqiu read through those comments. And his response was that it is an interesting technology, but it is quite new and not commonly used to address particle size in cosmetic materials. While it will likely be a relevant tool in years to come, it's not quite vetted and useful for these purposes at the moment.

DR. ANSELL: And precedent talking, it wouldn't be so prescriptive as to define exactly what instruments should be used.

DR. HELDRETH: Indeed --

DR. ANSELL: I mean, it's interesting, but I think we agree with Ron. That it outlines in a precedent level, at a high enough level, exactly how we do inhalation toxicology. Our only comment is then the last half where you try to force it into specific sentences and that it's really going to need it to be crafted.

So we find that we like the document, and we think it's a good job in capturing how this is done. But we're uncertain of the value of now trying to take those concepts and try to generate a boilerplate which was the historical thing to capture --

DR. HELDRETH: In conversation with Jinqiu, the true intention here is for the document up to, but not including, the sample calculations and all of the prescriptive language for the staff to follow. It would be a useful white paper, a precedents document, that could be finalized and posted on the CIR website. Whereas, the rest of the material, we

certainly wanted Panel input and approval on; for the staff to use as a resource when they're drafting a draft conclusion for the Panel or taking those steps forward.

While they're all arranged here in one piece which is historically how CIR did this in the past, we propose that only the first half, as Jay was pointing out, really be the public publicized piece that the Panel could point to in the report to say, if we get to a report and we're using Tier 2 as part of the assessment, here's a reference what we think what Tier 2 means and why it's appropriate here. And then the prescriptive language and the way that say Jinqiu will do a calculation when requested, we have that material in house to provide the panel with things in the same way in each report.

DR. ANSELL: You would propose not to go so far as to exclude the sample exposure calculations?

DR. HELDRETH: I mean, that's up to the panel if they want to draw the line somewhere else.

DR. MARKS: What page were you going to draw the line on, Bart?

DR. ANSELL: Eighty-six? 84.

DR. HELDRETH: So middle of the page on PDF page 84, there's a sample exposure calculations section. Our proposal was to draw it just above that, but if you feel that those sample calculations are applicable across the board, then, by all means, we could draw the line right before precedent language.

DR. ANSELL: We would recommend the Panel keep that. I think that's illustrative. It's a nice example. It's not specific to any particular case, but it shows in a very practical way the types of calculations that would be done. But I think you're right that somewhere in there would be where we would draw the line.

DR. HELDRETH: Mm-hmm.

DR. MARKS: Ron, do you like the sample calculations? And then just in the document where we get the prescriptive -- and that's --

DR. SHANK: I didn't feel that part was necessary. I don't object to it, but it got to -- it's a detail that I didn't think was necessary in this kind of a document.

DR. MARKS: So you would end it at sample exposure and exposure calculations?

DR. SHANK: Yes. But I don't object to the inclusion. The wording at the very end, I felt, was mostly for staff.

DR. MARKS: Right.

DR. SHANK: Precedent language, et cetera.

DR. MARKS: Right.

DR. SHANK: That would not be in the final document.

DR. MARKS: And, Jay, you said from an industry point of view, you felt the sample exposure calculations would be helpful in the document?

DR. ANSELL: I think our position is that everything up to 84 was just what we thought it should be. I personally thought the sample exposure was helpful, but I'm completely open on it. It's up to you guys.

DR. MARKS: So we all agree that precedent language would be an internal use and that wouldn't be in the public document. Normally, when we have a decision which could -- perhaps the sample calculations increase the safety, it might be worthwhile leaving it in. I don't know.

DR. SHANK: I don't see that it's --

DR. MARKS: It's necessary?

DR. SHANK: -- it's helpful.

DR. MARKS: And then would you have the sample exposure calculations again in internal or --

DR. SHANK: No, to me, that's strictly an in-house.

DR. MARKS: In-house, yes.

DR. SHANK: For CIR staff.

DR. MARKS: Okay. So we would end it at page 84 sample exposure calculations. Okay. Very helpful. Excellent

discussion ends page 84 for public use calculations and prescriptive language for internal use; so after that. Okay. Any other comments?

Should I do that mini preamble like the toxicity is local and systemic -- because the local is in the pharynx and such. And you've mentioned that many times that it's not just the lungs we're concerned about, but it's the whole respiratory passage.

The tiered approach we liked. Ron reinforcing more complex than just particle size. And I'll acknowledge Paul's comment that we prefer to have the actual respiratory tox data, but this is a -- how do we want to call it now? Is this going to be resource or -- what term do we want to use for these what used to be called boilerplates?

DR. HELDRETH: So, since this doesn't provide the prescriptive "boilerplate" language, we're calling these types of white paper -- we're calling it precedents. And then the title for this one is specifically Respiratory Exposure to Cosmetic Ingredients.

DR. MARKS: So you're referring to this as a white paper?

DR. HELDRETH: Well, that's just a --

DR. MARKS: How about resource document?

DR. HELDRETH: I think resource document or -- CIR Precedents is the title we have for this and some of the other findings documents that you'll find on our website.

DR. BERGFELD: That leaves me cold. Precedents for what? I mean, it's a CIR -- if you say precedents.

DR. ANSELL: Yeah, I think resource -- the term from the thesaurus should be more along resource as opposed to precedent which suggests that it's something that will be built upon or is -- I don't know.

DR. MARKS: Well, I'm going to refer to it as a resource document tomorrow whatever the final.

DR. BERGFELD: Okay.

DR. HELDRETH: And we can make that change. Precedents is what it was called in the past, but looking at the findings page, some of our newer similar documents like hair dye epidemiology or infant skin, you're right, we did call it resource document. So we can make that change as well.

DR. MARKS: Yeah, Bart, you weren't here for the discussion of the parabens. We were talking about generating a resource document for that also to keep up with the almost weekly new epidemiology studies.

DR. HELDRETH: Okay.

DR. MARKS: Okay. That was the last agenda item for our team today. Any other comments? Did I overlook anything, team members?

DR. BERGFELD: You did well.

DR. MARKS: Okay. Good. See you later on today, and I look forward to tomorrow's full panel meeting.

### **Belsito Team Meeting - September 16, 2019**

DR. SNYDER: Admin page 79.

DR. BELSITO: Inhalation. Page 79. So just a few comments in the background section in the third paragraph. It says, while particles/droplet size is an important parameter, the physical/chemical properties in ingredients in a spray formulation as well as realistic da da da da, but it seems like we're ignoring powders. So shouldn't that be in the spray formulation or a powder? It's the third paragraph -- the third sentence of the third paragraph. Where you just sort of say while particle/droplet size is an important parameter, the physical properties of ingredients in a spray formulation or a powder now.

DR. HELDRETH: Yes.

DR. SNYDER: So who's taking the lead on this document now?

DR. HELDRETH: Jinqiu is still working on this.

DR. SNYDER: Oh, is he? Okay. So he's getting the information? Okay. Thanks.

DR. LIEBLER: So, if we do that, I mean, that's fine with me too. But, if we do that, we should probably say

particle and droplet size, or particle or droplet size.

DR. BELSITO: Right.

DR. LIEBLER: Because powder doesn't go with droplets.

DR. HELDRETH: But droplets can be particles.

DR. LIEBLER: Droplets are particles, but powders don't give droplets, right? That implies moisture.

DR. HELDRETH: But you could say particles and it covers a dust and a -- I mean, we don't have to do that. I'm just saying that.

DR. LIEBLER: You don't have to have droplet in there. You could just say particle size. It's an important parameter of physical/chemical properties of ingredients in the powder or spray formulation.

DR. HELDRETH: Whatever way, that's fine.

DR. SNYDER: So I had a kind of a -- from the presentation which we had, I had kind of a different take on it. So it's droplet/particle size distributions that's important. And it's product specifics. And then it's also based upon the type of spray. So, if we use those three that captures -- encompasses everything.

DR. HELDRETH: Okay.

DR. SNYDER: So I think that's probably the easiest way to do it; to say that the particle size distributions -- the product's type and then the type of spray that it's used in -- formulated to be used in. Something along that line.

And, on the background, the first sentence, it's not inhalation toxicity, it's actually inhalation exposure. Incidental inhalation exposure is an important consideration for the sprays and powder. Because, if there's no exposure, we're not worried about anything. If there's exposure, then we want to know if there's any toxicity associated with exposure. So that's the first sentence there.

DR. BELSITO: So what are you saying?

DR. SNYDER: So there I said, it's really inhalation exposure is an important consideration for sprays and loose powders.

DR. LIEBLER: I did that, added on particle. I just did the added-on particle/droplet powder.

DR. HELDRETH: Okay. I'll find it in there. Thank you.

DR. KLAASSEN: The second paragraph, the third line; when we say in here, insoluble. What's the word insoluble, insoluble in what?

DR. LIEBLER: I think the implication is aqueous.

DR. KLAASSEN: Okay, yeah.

DR. LIEBLER: So we could add aqueous.

DR. KLAASSEN: I would like that better.

DR. LIEBLER: Got it.

DR. BELSITO: So insoluble. This is the third paragraph.

DR. KLAASSEN: In fact, what inhalation toxicologists in the SAB meeting do, we all know about --

DR. BELSITO: Where is this?

DR. KLAASSEN: The third line of the second paragraph. We all know about octanol-water coefficients. Okay, which is kind of important for absorption from the gut. But what inhalation toxicologist will do is to take blood and gas and do the blood/gas, which really tells you what -- if there's a good correlation then. But I don't think we need to say -- I think water -- or aqueous is a better word.

DR. LIEBLER: I just put water in.

DR. BELSITO: So absorption of a water insoluble?

DR. LIEBLER: That's what I added.

DR. BELSITO: Then PDF page 80. The end of that first paragraph, it says, inhaled droplet 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. I added, or that in these regions -- or be absorbed and cause systemic toxicity depending upon their chemical and physical properties. Because that's actually what we've been talking about with wheat, right?

DR. SNYDER: Yeah. But, I mean, it's actually local and systemic.

DR. BELSITO: Right.

DR. SNYDER: So it should always say local and systemic because there could be pulmonary toxicity.

DR. BELSITO: Or it could be absorbed and cause systemic toxicity.

DR. SNYDER: Exactly right. And cause liver toxicity. Correct. That's why I say local and systemic toxicity.

DR. BELSITO: Yeah, but here we're talking specifically about nasopharyngeal and bronchial.

DR. SNYDER: Oh, okay. I didn't catch that part.

DR. BELSITO: They could still be absorbed systemically from the nasopharyngeal and bronchial.

DR. SNYDER: Well, more likely they're going to be absorbed because they're going to be swallowed, because of the mucociliary.

DR. BELSITO: Right.

DR. SNYDER: So there could still be exposure. Yeah.

DR. BELSITO: But absorbed in some fashion.

DR. LIEBLER: So what do you want to do, Don? Do you want to add to the very end of the sentence?

DR. BELSITO: Yeah. Well I thought, "in these regions" -- "cause toxic effects in these regions, or be absorbed and cause systemic toxicity, depending upon their chemical and physical properties."

DR. LIEBLER: Okay. Yeah.

DR. BELSITO: And then again on page 80, the next to the last paragraph, the last sentence; it says, "Usually 1 percent to 2.5, but no more than 5, of droplet/particles emitted from propellant hair sprays are within the respirable range." I'd say you'd need to define that. You mean less than 10 microns? We don't define what we consider the respirable range.

DR. HELDRETH: Yes. The two sentences before that. "Are in the range considered to be respirable, i.e. less than 10 micrometers."

DR. LIEBLER: Right.

DR. BELSITO: Okay.

DR. LIEBLER: I think it's clear.

DR. BELSITO: Okay. I'll delete that comment.

DR. KLAASSEN: I had a little question about the last sentence of this page. "In contrast, analogous estimates indicate that the tested deodorant spray aerosols have a median diameter of 10 microns with a coefficient of .3, suggesting that half of these particles are within the range considered to be respirable." I guess, I am thinking that we're giving a little bit too much mathematical accuracy to this 10 micros. But I don't feel tremendously strong about this, but I'm a little nervous about it. In other places -- anyway.

DR. HELDRETH: I think Jinqiu was trying to find a way here to give some sort of boilerplate language to the fact that we don't have that consumer use data for those types of sprays.

DR. LIEBLER: Would you rather say, suggesting that up to half of these particle? So half seems precise, you know, 50 percent. If the median is the borderline of respirable, not respirable; if we're treating it that way then it's very precise. But we know that both of those numbers have some play in them. You could say up to half, approximately half, less than half.

DR. BELSITO: Less than or equal to.

DR. LIEBLER: Less than or equal to half. Thank you, Don. Do we have any other hands?

DR. KLAASSEN: Okay.

DR. BELSITO: So what are we changing and where exactly are we?

DR. KLAASSEN: I just think this is way, way, way, way too quantitative for the softness of the data, and especially this 10 microns. We're not saying that something of 10 microns is zero percent absorbed and something that's 5 percent is 50 percent absorbed.

DR. LIEBLER: We're not saying that 10 microns is a hundred percent respirable and -- that nine is a hundred percent and 11 is not at all.

DR. KLAASSEN: You're right. It's just getting too quantitative.

DR. LIEBLER: And that's why I suggested saying that approximately half of these particles are within the range.

DR. KLAASSEN: I even think that's too strong. I would like to have it even more vague than that, because I'm not convinced that that's true.

DR. BELSITO: Vague scientist?

DR. SNYDER: I think that one of the things that we --

DR. KLAASSEN: We don't know that slope.

DR. BELSITO: Slippery.

DR. SNYDER: One of the things that I had -- and I made several comments about this. This document somewhat confuses the potential for inhalation exposure from a cosmetic use, versus inhalation toxicity and safety. So really the only thing we want to talk about is potential for inhalation exposure from cosmetic use. And if your tiers to do that, okay, I think it works.

But I think where we get in a slippery slope is when we drift into the toxicity issues. And that's a whole different mindset and a whole different set of data that we need. If we have inhalation exposure, then we're going to default to we need inhalation toxicity data, we need an OECD inhalation study or something like that.

But this data is just the document that's going to help us bridge when we have aerosol uses and we don't have any exposure. Because the aerosol uses don't -- either the particle size, the product type, or the spray pump that you use or whatever. So, to me, we've got to -- I think that this document is trying to blend in too much safety data on inhalation and that's not what this is about, to me. This is about whether or not there's inhalation exposure from cosmetic use.

And, if you look at the tiers, that's what you've done in the tiers. And so, if you go to page 82 on the tiered approach, the last sentence before the bullets, it says, "a preferred approach for the evaluation inhalation safety includes..." -- to me, it's not inhalation safety, it's inhalation exposure -- "includes three tiers." The first one is related to whether or not it's respirable or not. And that's based upon the physical and chemical characteristics of the product -- of the ingredient.

And then the second tier refines the above estimate to arrive at a -- not a more realistic, though still conservative. I'd say it utilizes additional factors in determining exposure. Because that's all we're talking about here, is exposure. So if we have exposure, then we've got to have the data to say that there is no.

And the third one does deal with measurements of exposure in a simulated conditions. So I think if we keep that exposure premise, the document becomes much easier -- does that make sense?

DR. HELDRETH: I think so.

DR. BELSITO: So how do you want to do this here, Paul? A preferred approach for the evaluation of the inhalation exposure.

DR. SNYDER: Exposure. It includes three tiers: tier one's a worst-case scenario. All the product leaving containers potentially respirable -- not inhalable, respirable. And becomes systemically available. Okay, that's fine because that's assuming -- and then the next tier is we utilize additional factors in determining exposure. And we take into account factors like the room volume, ventilation, blah, blah, blah.

DR. BELSITO: Tier 2 refines the above estimate to arrive at a more realistic --

DR. SNYDER: Well, Tier 2 utilizes additional factors in determining exposure.

DR. BELSITO: So you want to get rid of “refined the above estimate?”

DR. SNYDER: Yeah, I don't like the refined or all that -- more realistic, I don't like that term anyway.

DR. BELSITO: You want that all struck through?

DR. SNYDER: Utilizes additional factors in determining exposure. This is all about exposure. So it utilizes additional factors in determining exposure.

DR. BELSITO: In or to?

DR. SNYDER: Utilizes additional factors “in” determining exposure potential is what I've got written. Tier 2 utilizes additional factors in determining exposure potential. Because that's really what we're talking about here, is exposure. We're working through different levels to say whether or not there's any exposure through cosmetic use.

DR. BELSITO: So you're changing the entire first sentence?

DR. SNYDER: Yes. And then, Tier 3 is fine because it requires actual measurements of exposure under simulated conditions of use. So I think that keeps them all in parallel if you keep the exposure approach. Because that's all -- if we have exposure, then we have to have some safety data. So we don't need safety data if we don't have exposure.

Because then in your summary statement down below, it's all exposure. In practice, exposure to cosmetic sprays is very low. I'd probably say, exposure to aerosolized cosmetic product. Will get you to capture all of the different types of spray products or whatever.

DR. BELSITO: And Tier 3, you make no changes to?

DR. SNYDER: No, I think it's fine. And then that's all in sequence with that last paragraph, in practice. Except for I would -- exposure to aerosolized cosmetic ingredients or something like that.

DR. BELSITO: Okay. And then, I guess, other considerations of spray products, the second paragraph. It says, “the Panel would like to know whether the current practice of use, propellant sprays, pump sprays, or both, when appropriate and the information is available.” But, if the information is not available, then we're going to ask for it, right?

DR. SNYDER: Right.

DR. BELSITO: So I don't know -- I'm not sure why we have that sentence.

DR. KLAASSEN: Which sentence are we on now?

DR. BELSITO: PDF 83, Other Considerations of a Sprayed Product. It says that, “aerosols from propellant sprays are distinct from those from pump. For each ingredient or ingredient group, 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.”

But it's not available, aren't we going to ask for it? So, I mean, simply say that we want to know whether the current practices of use include propellant sprays, pump sprays, or both, period. Because won't that always be appropriate as we get a sense of particle size from the different types of sprays?

DR. SNYDER: Yeah, and it's all very specific to the product type; whether it's a pump, a propellant, a powder --

DR. LIEBLER: So you can just delete that clause?

DR. BELSITO: Right.

DR. SNYDER: Yeah. I inserted in the opening sentence that there was specific considerations applicable to a particular product type. Because it's all driven by the ingredient and the product type.

DR. BELSITO: Mm-hmm.

DR. EISENMANN: Well, it's a lot more factor in that, but that's --

DR. LIEBLER: Yeah.

DR. BELSITO: Right. So then you get --

DR. SNYDER: Well, and there are other considerations, yeah.

DR. BELSITO: When you get into -- go ahead, Curt.

DR. KLAASSEN: In this document, there's a fair amount about the difference between hairspray and deodorant. But there's not -- at least I don't recall -- anything in here about really the difference between pump and aerosol or what -- you know, spray --

DR. SNYDER: Propellant -- there's pump spray and propellant spray.

DR. KLAASSEN: But is there "data"?

DR. SNYDER: We got it. What's his name gave us good data on that. Because he said the propellant is made to be broken into smaller particles, given an increased surface area which you don't get with the pump spray. So those are the other considerations we take when we see what the use is; and particle size distribution really matters on a propellant, to me.

DR. KLAASSEN: I guess what I'm saying, shouldn't that be in here?

DR. SNYDER: Well, I think it is in the --

DR. LIEBLER: It's cited.

DR. SNYDER: Isn't it in the beginning?

DR. KLAASSEN: Yeah, but -- okay, where? Is there --

DR. EISENMANN: I know we provided some data just for hairsprays, propellant versus --

DR. LIEBLER: Page 80, second paragraph from the bottom and third paragraph from the bottom, are the citations for the pump versus propellant spray particle size distributions.

DR. KLAASSEN: Which page?

DR. LIEBLER: Page 80.

DR. KLAASSEN: Eighty. Where at?

DR. LIEBLER: Second paragraph from the bottom.

DR. KLAASSEN: Oh, both sprays, okay.

DR. SNYDER: Because I remember he said that there was -- propellants were a mean size of 14 to 15 microns and the pumps were much larger, 50 to 80 in diameter in mean size.

DR. KLAASSEN: Sixty to 80.

DR. BELSITO: But that's just for hairsprays which are designed to aggregate, right? I mean, a deodorant is probably going to have an even smaller particle size from a propellant, right?

DR. EISENMANN: Well, we've got a little of that information too. That's in there.

DR. SNYDER: Yeah, I thought all that data up to the tier thing was pretty good. I thought just a little bit change in the background. I thought this was really good. I mean, there was a lot of good data in here that then made the tiered approach seem very logical.

DR. LIEBLER: I actually had no problem with this.

DR. BELSITO: But then when we get to exposure calculations, I mean --

DR. SNYDER: I don't know if that needs to be in our document. I mean that maybe something as a sample for us to how we might approach it to calculate. But I don't know that -- because this is just all a bunch of assumptions. I'm not certain it's applicable to all products -- ingredients and product type, even within the subtype of --

DR. BELSITO: But we're putting together a boilerplate, and we're going to have inhaled products or respirable products. And then we will need to assess the potential for toxicologic concern, right?

DR. LIEBLER: Yes.

DR. BELSITO: So we're going to need exposure calculations, right?

DR. LIEBLER: That's true. I don't know that this example provided is necessarily going to serve as a template for -  
-

DR. SNYDER: It's a read-across. It's a read-across for all of them.

DR. LIEBLER: Well, read-across maybe not be the right word. But as a template for how we would do all of the calculations. I would say it looks like one possible example, but not the template.

DR. BELSITO: Well, I just -- and I don't know that this would cover everything that we do. But it may be of interest to have either Danielle Botelho or Alison Fryer from RIFM come and speak to us about respiratory TTC, the Threshold of Toxicologic Concern. Which I don't completely understand, but I can tell you clear as almost all of RIFM's materials. And may be of help to us as we look at materials that could be respirable, what this threshold of toxicologic concern for inhalation is, what it's based on, what the levels are.

DR. KLAASSEN: If you look at that paragraph where we're comparing the pump sprays and the propellant sprays, at the end it says usually one to two and a half percent is within the respirable range. I mean, that's telling us very little. I guess this gives me much more confidence, even more confidence, than I had before in regard to respiration.

DR. LIEBLER: Do you mean to say this doesn't tell us much? Or you mean to say, this tells us that the answer is very little?

DR. KLAASSEN: Very little.

DR. LIEBLER: Okay. I understand what's your saying now.

DR. KLAASSEN: Sorry.

DR. BELSITO: But the exposure -- the respirable amount would be minute?

DR. SNYDER: The exposure potential is very minor for all cosmetics.

DR. KLAASSEN: That's what this is saying. Very minor. I'm not saying it's --

DR. BELSITO: And, therefore, I think that we could probably -- if we understood what the threshold of toxicologic concern for inhalation is if we had, as a Panel, a better sense.

DR. SNYDER: I think a threshold of toxicologic concern would say where's the safety for toxicity, right? Isn't that what the threshold toxicological concern is?

DR. BELSITO: No, but it's basically a level at which you don't need to worry about it.

DR. KLAASSEN: You don't need to worry about it.

DR. BELSITO: And it's --

DR. SNYDER: You don't need to worry about it as in there's a toxicity, a systemic toxicity?

DR. BELSITO: Yes, even if there's a toxicity --

DR. SNYDER: But that's not what we're talking about here. We're not talking about that here. We're talking about exposure.

DR. BELSITO: Yeah, but it's all based off of -- I don't completely understand it. It's different for skin than it is for other endpoints.

DR. SNYDER: Yes. Right.

DR. BELSITO: There's a threshold for -- it's not called the threshold -- it's not called the TTC for sensitization; it's called a sensitization threshold. But, for all the other endpoints that RIFM looks at, there's a TTC and it's based off of Cramer classification. And it's accepted apparently by the EU authorities and other authorities as EU goes through REACH. And a million different chemicals have to be cleared that materials with -- I don't know. Again, Dan, do you completely understand the TTCs for all endpoints other than skin, which are based off of Cramer classification that we deal with all the time?

DR. LIEBLER: Right.

DR. BELSITO: Most of the endpoints aren't necessarily TTCs. But I can tell you inhalation is almost always based off of -- below the Threshold of Toxicologic Concern.

DR. LIEBLER: Well, for many ingredients we can clear developmental and reproductive and also chronic toxicity based on TTC.

DR. BELSITO: Right.

DR. LIEBLER: I think that the TTC argument -- I agree with Paul the TTC argument is important for us to consider

but probably not in this document at all.

DR. SNYDER: No. No. I don't think so.

DR. LIEBLER: This is really about exposure, at least the way it's framed at this point.

DR. SNYDER: We cleared most of it. We clear most cosmetics because there's no exposure.

DR. LIEBLER: I think that it might be a good idea for us to consider another document or another CIR document on the concept of TTC and how we apply it across multiple endpoints -- the TTC family of reasoning if you will.

DR. SNYDER: That's essentially what we do. We say that, yes, there's some toxicity but the doses that occurred in the animal studies were milligram quantities, and we're talking picograms. So it's essentially what we do. It's just another name for what we do.

DR. LIEBLER: What we normally do is we don't have a formal policy; we simply state in the discussion, the Panel felt that the exposures were below the level needed of concern. But we don't have any kind of framework to say how we got there.

DR. SNYDER: Right.

DR. LIEBLER: We don't calculate Cramer class values for any of the ingredients.

DR. SNYDER: I think that TTC was hot a number of years ago and then it kind of went away, didn't it? As I recall?

DR. KLAASSEN: Let me say, I'm not aware of the Cramer values nor the TTC. What does the TTC do? Do they take the most potent -- let's say for teratology, they take the most potent teratogen ever discovered and then say if you're exposed to less than that?

DR. LIEBLER: No.

DR. KLAASSEN: So what's it based on? I don't know.

DR. LIEBLER: So the Cramer classifications are essentially a stepwise evaluation of the features of a chemical, the structural features of a chemical. And it's informed by a body of knowledge about -- not red flags -- about structure alerts for different types of toxicities; and other properties of the chemical that it would influence metabolism, the likelihood of being persistent versus rapidly excreted, et cetera.

These are all calculated into a parameter that allows a chemical to be classified into either of three Cramer classes. The ones that are most likely to present some significant hazard are in one classification; and the ones that have feature that are least likely to produce any hazard are in the opposite classification. There's a middle classification that doesn't have many chemicals in it.

So, based on the Cramer classification and the exposure level, a decision can be made if whether or not a Cramer class C -- Class 1 are the ones that are considered the most hazardous.

DR. BELSITO: No.

DR. LIEBLER: I got it backwards.

DR. BELSITO: Three is the most hazardous.

DR. LIEBLER: Three is more hazardous. So one you would have essentially less of a margin of exposure. One demands a much greater margin of exposure. But, if you calculate the exposure based on usage and amount that's used in the product, you can calculate that margin of exposure. And, if it's below that threshold, we feel it's not of toxicological concern. I think, for very good reasons that are enumerated in the paradigm of the Cramer classification used to calculate the TTC.

And the thing is for RIFM, that's in our procedures document. It's laid out in detail with supporting literature. And I think none of our peer reviewers have ever quibbled with it.

DR. BELSITO: It seems that it's what's commonly accepted by toxicologists now when you're looking at materials for which there's little --

DR. SNYDER: Data.

DR. BELSITO: -- data. I think it's largely been driven by Europe with the REACH program, and the need to classify materials.

DR. LIEBLER: Right.

DR. BELSITO: But it may -- I mean, again, I'm just throwing that out because it seems that we're struggling with the respiratory issues; at the same time that RIFM's not struggling with them at all because almost everything -- and I mean fragrances are de facto inhaled because otherwise you wouldn't smell them, right. Whether they're pumped or just put on the skin.

It might be interesting to get Danielle down here since she's just up in New Jersey -- and it's a train ride or a short flight for her -- to explain to us Cramer classification and TTCs for inhalation and what they're doing. Because it may be an approach that we may be able to use if we understood it.

DR. LIEBLER: Yeah. I mean, the whole logic for using the TTC is enumerated in our procedures document, which is already published. And the extension to respiratory TTC is relatively recent, but very useful. I will say that with RIFM, many of the materials we review in RIFM are used at lower concentrations than many of the materials we review in CIR -- or the ingredients we use in CIR. It's just a little bit of a fragrant ingredient is all it takes for most of those products.

DR. KLAASSEN: Right.

DR. LIEBLER: So we may find that TTC is actually less useful in CIR overall.

DR. BELSITO: Not helpful.

DR. SNYDER: I think that's what I was alluding to. I think for risk assessment they were pushing that years ago for risk assessment for drugs. And they found it to be of limited use. That's what I was getting at.

DR. BELSITO: Okay.

DR. SNYDER: For impurities and things at very low levels, which has no tox data, then it can be useful.

DR. LIEBLER: Yes. I think that's exactly what it's for. I mean, basically, it's the --

DR. BELSITO: So then it may not help us?

DR. SNYDER: Well, it may for like respiratory with exposures. So you're talking low levels and very low exposure potential, so, therefore, it may. I don't know. It would be interesting to look into it.

DR. KLAASSEN: Yeah. I think I would like to learn more about it.

DR. BELSITO: So, even though it's higher volume we have an estimate of what would get down into the alveoli; we can reduce that to a number and then at those exposure levels it's below the TTC.

DR. LIEBLER: Yes.

DR. SNYDER: What the actual exposure would be. Do you get into new exposure?

DR. KLAASSEN: The way that all of this structural activity data started to be used is we got a million chemicals and we don't know which ones we should look at and which ones we shouldn't. So let's do some of these things and see which ones are potentially the worst, and then we'll study those in detail. And I think going too far in this extrapolation to real data we have to be a little careful.

DR. LIEBLER: Well, that's why we have rules. That's why that procedure is quantitative. I mean, at least it has well-defined, scorable parameters for the chemicals to evaluate for what Cramer class they fall into. And then there are supporting data for toxicity thresholds for representative chemicals in the classification.

It is the answer to the problem; you don't have any data on this, exposure is low, we look at the structure and we go, that doesn't have anything that's going to be toxic in it, but where's the proof? And that's why that whole framework was introduced, essentially, to deal with that situation.

DR. KLAASSEN: Right. But it doesn't mean it's right.

DR. LIEBLER: Okay.

DR. KLAASSEN: You have to admit, there are chemicals that surprise us once in a while.

DR. LIEBLER: This is true.

DR. KLAASSEN: But I still like -- before I put it on my great grandchild's skin, I would still like to have it be tested on one other person -- or one other animal first.

DR. LIEBLER: You have no business putting anything on your great grandchildren's skin. That's for your children to do, they're the grandparents.

DR. KLAASSEN: Yeah, but sometimes we babysit.

DR. LIEBLER: You still have no business.

DR. KLAASSEN: So the EPA has also suggested that after 19' -- or 2035, there will be no more animal testing. You know, it probably is coming, but I think we have to be cautious. That's all I'm saying. I think it's good for our first estimate.

DR. HELDRETH: So I think what I'm hearing is that much of the inhalation exposure assessment, and certainly all of the safety assessments when it comes to inhalation, is case by case.

DR. KLAASSEN: Yes.

DR. HELDRETH: And not really something that can be done in a boilerplate per se. So would it be amenable to the Panel to think of this more of a white paper precedence document, and basically come to a full stop right before the sample exposure calculations?

DR. BELSITO: Yeah.

DR. HELDRETH: That would be the general principles of what the Panel feels. Is that's something we could publish. All this other information in here is certainly useful for the Panel, for the CIR staff.

DR. LIEBLER: Right.

DR. HELDRETH: And then maybe this will help inform some other white paper or a boilerplate document, when we have experts come in and talk about TTC or give you other things that may be informative to that.

DR. KLAASSEN: I'd like to say that this document is much, much better than anyone I've seen previously on respiration; and I thought it was quite good.

DR. HELDRETH: It was all Jinqiu.

DR. LIEBLER: Yeah, he did a great job on this. I do agree with the suggestion of just deleting the sample exposure calculations from this document. And we can keep the precedent language to use. I looked through that and I didn't have any problem with any of it.

DR. EISENMANN: In the cosmetic use section, in the precedent language itself where it says, particle size --

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

DR. LIEBLER: Eighty-six.

DR. EISENMANN: It's in the blue part. "Particle/droplet size distribution as well as regional deposition data under consumer use conditions are generally considered but rarely needed when assessing the inhalation safety of an ingredient in a spray cosmetic product. A tiered approach to the exposure assessment of spray products requires actual exposure measurements and more refined modeling." I don't think that belongs in this.

I mean, the cosmetics use section should just be discussing how the ingredient is used in the products and focus on that. And this more general information which is already -- you've already discussed it doesn't belong in a CIR report, it belongs in your document.

And then the airbrush makeup thing. I'm not sure that that's relevant for every product -- every ingredient. And then the fact that you're calling loose powders. We never know if a powder is a loose powder. We just don't know. So I don't like that word there.

DR. KLAASSEN: So what are you suggesting, Carol?

DR. EISENMANN: That that statement not be included. That the general information about how the tiered approach doesn't need to be in every report. You'd use that approach, but it doesn't necessarily need to be written up in the cosmetic use section of every report. So that should not be language that's added to the report.

DR. HELDRETH: Sure. We could just point to this white paper once it's published.

DR. EISENMANN: Mm-hmm.

DR. LIEBLER: Okay. But that language -- so what you're talking about, Carol, is under cosmetic use section, that

heading, on page 86, if you go down to the first big section of blue type. That's the part that you're suggesting does not need to be there?

DR. EISENMANN: Right.

DR. LIEBLER: The thing is that follows the statement, "therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable to any appreciable amount." Well, that is what we currently have in our Use section. But we do know that there's an exception to that; and the exception is deodorant spray products.

DR. EISENMANN: Right. And I didn't say that to be out, it's after that.

DR. LIEBLER: And it says, if products include deodorant sprays add -- and then this section. So I think that if we do have deodorant sprays as part of the -- or if the ingredients are used in deodorant sprays that this ought to be there. This blue section ought to be there.

DR. EISENMANN: I agree up to the next part of it, "particle/droplet size distribution as well as regional deposition data under consumer conditions are generally considered but rarely needed when assessing the inhalation safety of an ingredient in a spray cosmetic product." The rest of it.

DR. SNYDER: I see. You weren't proposing nixing all the blue section, just the second half?

DR. EISENMANN: No, not all the blue, the last part of it.

DR. SNYDER: I modified that. But I probably should have just nixed it, just eliminated it. I tried to modify it to make it work but it --

DR. EISENMANN: Especially a tiered approach to the exposure requires actual -- if you come out fine on first tier, you don't need that additional information.

DR. SNYDER: Right.

DR. BELSITO: Okay. So where are you eliminating the blue from, Carol, after 2006?

DR. SNYDER: Where it says you don't need data on particle size distribution, generally don't need data.

DR. EISENMANN: Right. The sentence that starts, "particle/droplet size distribution as well as regional deposition data."

DR. BELSITO: I don't see it. Oh, okay. "Particle/droplet size..." Okay. You want all of that eliminated? It's in blue.

DR. EISENMANN: Right.

DR. LIEBLER: From there to the end of the blue font.

DR. BELSITO: Right. And we don't need that because we'll be --

DR. EISENMANN: You'll be actually describing how it's used; and then, if necessary doing a -- at least you could probably do the first tier of an assessment to see if somebody needs to do a further tiered approach. I'm not saying it's wrong; it's just not the place for it in the cosmetic use section.

DR. BELSITO: Okay. Any other comments on this? As long as we've looked at it. So none of this language will - I mean, this is just for us to think about as we approach and put in. This is not boilerplate; this is not part of the white paper, but we might as well hear it since we've reviewed it. Any other comments on these scenarios, the discussion? I didn't have any others.

DR. LIEBLER: Nope.

DR. BELSITO: Okay.

DR. LIEBLER: Much improved. Good progress.

DR. BELSITO: So we're suggesting we go ahead with this white paper on how we approach respiration -- or products that could be inhaled. And then in terms of what we actually put into the reports will depend upon how it's used.

DR. SNYDER: Case by case.

DR. BELSITO: Yeah. Case by case. Okay. Wow.

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DR. MARKS: Right, so these won't be quite as quick as the re-review summary. So we'll refer to this as a resources document, on Page 78 of the Admin. We felt it was an excellent document. The toxicity, local and systemic, the tiered approach, more complex than particle size, and preferring to have actual respiratory tox data is the gold standard as Paul elucidated the last meeting.

The only change that we felt should be made in the document is that it ends at Page 84 for public use. The pages subsequent that, with calculations and prescriptive language, be for internal use. And they were the only comments we had concerning changing the document, making it somewhat shorter.

DR. BERGFELD: Dr. Belsito? Comments?

DR. BELSITO: Yeah, so we thought that we should end the document before we get into how we're going to use the discussion sections and sort of make this a boilerplate, because it's going to be very case-by-case. So, we felt that --

DR. LIEBLER: I think we wanted to cut it right where Jim just said, right before the sample exposure calculations.

DR. BELSITO: Right. I think we agree with you. Right.

DR. MARKS: Yes.

DR. LIEBLER: So the prior material all stands on its own very nicely.

DR. MARKS: Yes. That cutoff is on Page 84.

DR. BERGFELD: There was a discussion on how to name it or call it, would it be a resource document or be a precedent document. Is there a comment on that? I think the Marks Team want it to be a resource document.

DR. LIEBLER: I'm fine with that.

DR. BERGFELD: Okay.

DR. LIEBLER: With resource document or something like that.

DR. BERGFELD: Yeah, it seems there is agreement that the cutoff will be at Page 84, and we can proceed. This is a document that's floating and being adapted each time we have to use it. And so we'll be doing that. Is that correct?

DR. HELDRETH: Yes, at this point if it's the consensus with the panel the point up, but not including the sample exposure calculation, will be finalized and posted on the CIR website, underneath the Findings section along with the other resource documents. However, if any further information were to come to light, and the panel wanted to make changes, we can always reopen it.

DR. BERGFELD: And, could I just ask a question since we all agreed with our inhalation resource document. We'll be looking at that each time we come in to look at inhalation, making sure that it adapts to the ingredient or chemical we're reviewing?

DR. HELDRETH: My understanding is that the public piece of this will be something that the panel can point to in the reports; to explain why it's reasonable to use a Tier 1 or Tier 2, for example. Or of why the data that they have overrules those types of approaches.

And then, the pieces that we're cutting off are usual tools for the staff when we are, say, making a draft discussion to propose for the panel. But, as Dr. Marks suggested, there are very much a case-by-case basis and the panel will have the opportunity to adapt it to the data that's before them.

DR. BERGFELD: All right. Then the last question I have regarding this. If the panel member wants to look at the whole document where will it be? Will they be able to access what the scientific writers have?

DR. HELDRETH: We can certainly make that available to anyone.

DR. BERGFELD: I think that would be good. Okay, well we've come to the end of the meet --

MR. GREMILLION: Sorry --

DR. BERGFELD: Yes?

MR. GREMILLION: Sorry to make your repeat this. But I wonder what's the benefit of cutting off the sample calculations? I mean, why not just leave it in there instead?

DR. HELDRETH: From that point forward it's really just standard operating procedures for the staff to follow. It's really not a resource document like many of the other resource documents on our website are, that are something we can cite to the panel's thinking.

MR. GREMILLION: It seems like it would be helpful to the public to know this is kind of what you're calculating. And, I mean, these are --

DR. MARKS: I think when we use the calculations that will be in the final report. So if the panel decides we would like to have calculations, this is the guideline for the staff to use. The same with the wording in the prescriptive language. Again, this is guidelines for the staff, but the panel will ultimately concur as to whether the wording.

I think that it could be confusing to have those sample calculations in prescriptive language for public reading. It's really for our internal use and we'll use them appropriately.

DR. HELDRETH: Yeah, for some other document types where it's very clear that we're going to use the same language in each and every case, then we have a true boilerplate. And that certainly is something worth publishing. But here in this case with inhalation it seems to have become quite apparent over the last few years that these are case-by-case and there really is no true boilerplate.

And so putting this language out there as if it were boilerplate, I think, that's contradictory to what's actually is going to happen with the panel. So I think instead of it providing information for the public I think it's confusing to publish that information.

MR. GREMILLION: Okay.

DR. BERGFELD: So, we have generally agreed that the public should have an overview of what we're doing, but not the intimate details that needs to go into the report. They'll have the report to read at the end. So, we have come to the end of the -- yeah?

DR. SNYDER: One comment on Page 86, under the Cosmetic Use section, if you go down to the middle of that section there's a large blue area. And about the middle of it, it starts with "particle droplet size distribution as well as regional deposition data," we deleted those five lines out of that section.

So I just want to have that reflected in the minutes that our team wanted to delete that because we thought that wasn't relevant to the cosmetic section for individual reports.

DR. BERGFELD: Marks Team?

DR. MARKS: That's fine.

DR. BERGFELD: That's fine. All right, any other comments before we come to saying goodbye?

MR. GREMILLION: In practice, 95 to 99 percent of the droplet particles --

DR. HELDRETH: No, it actually starts with --

DR. BELSITO: "Particle droplet size distribution as well as regional deposition."

DR. BERGFELD: Any other statements or comments? Our next meeting is December 9th and 10th here at The Westin. And if no one has anything else to say, have a good fall, we'll see you then. We are adjourned.

## **DECEMBER 6-7, 2021 EXPERT PANEL MEETING**

### **Belsito Team Meeting - December 6, 2021**

DR. BELSITO: This is not my area of expertise, obviously, so I will open it up. We had some Wave 2 data, but I'll open it up to other Panel members who are perhaps a little bit more familiar with this, Paul, Dan, and when Curt gets on, Curt.

DR. LIEBLER: Sure, I have plenty of comments and thoughts. I don't know if Paul is -- would you rather go first, or can I go ahead?

DR. SNYDER: Yeah, that's fine. I have a lot of comments, not so many about the document but about how we utilize the document I guess would be my comment.

DR. LIEBLER: Okay. Well, that's good. That'll complement what I have to focus on because I'm more focused on some of the particle size measurements and things like that. First of all, Jinqiu, I just want to compliment you on a really superb job on this revision of the document and your careful responses to the letters from Alexandra Scranton. I think the exchange with her and your input has certainly strengthened the document, and we're a lot closer to where we want to be. I don't want to go through this in great detail, but I'd like to make a couple of observations and suggestions.

First of all, I went through the entire thing, and then I got the Wave 2 and then I went through it again. So I've gotten at least two good looks at it and I went through it one more time yesterday. I think that one of the issues recently has been the question of whether we've really misread the particle size of distributions for ingredients that could be aerosolized. Part of this, I think, has been driven by the fact that there's no single technology platform that covers the full span of particle sizes.

Much of the data that we use to generate our previous estimates of particle size distributions and the attending boilerplate in the previous resource document was based on laser diffraction, I think, which covers the larger end of the particle size, which is the majority of the particles in these distributions.

Then, as I see it, a couple of things happened. One is that there was introduction of nanoparticles as cosmetic ingredients and an interest in measuring the size distributions incorporating these nanoparticles. Secondly, the introduction of other technologies that could get down to assess the smaller particles, and these are the SMPS, I think, and the APS platforms.

These generated measurements below our threshold of interest, which is ten microns which is thought to be the largest respirable particle size, down into actually much smaller particles than that. Some of these distributions were reported in more recent literature, some of which has been cited in letters to us by Ms. Scranton. I think that one of the things that got in the sauce of looking at these new data is that focus on these small particle size distributions tends to ignore the majority of the particles in an aerosol, which are much larger and were already the sizes that we were thinking about previously.

In one of the presentations to us from a couple of years ago, I guess Dr. Rothe pointed this out. I think this point has not been clear enough, and I'm glad that Jinqiu Zhu has put this into our document very clearly that the majority of the particles are in these larger size ranges of 50 microns and higher. We have, in the past, been unable to reliably measure. We'd have good data. We were unable to reliably measure the very small particles below ten microns. I think we fell back on a formulation in largely dismissing their possible existence, and our boilerplate was built around that.

I think that was a mistake to do. In retrospect now, that's not an accurate way to handle it. I think what we have is -- we do have data on the smaller bins of particle size from these other techniques. And I think we need to acknowledge that, as Ms. Scranton has pointed out, I think as Jinqiu Zhu has also acknowledged in our draft document. I think what we still need to do is modify our boilerplate enough to indicate to not dismiss the existence of the smaller particles but to point out correctly that, for most products that could be aerosolized and inhaled, they're a very small fraction.

The one exception that we have good data on are propellant-spray deodorants. This sets aside the entire issue of airbrushes. Those were my general comments on the document. I mean the approach taken in what I think has been the most difficult issue which is this particle size distribution problem. I'm going to pause there and see if anybody else has any comments or questions. Jinqiu, have I characterized that correctly in your view? Are we in sync?

DR. ZHU: Yes, I think so. We discussed that issue specifically on PDF page 81 and PDF page 87, about the particle size measurement by the current available equipment.

DR. LIEBLER: Right. I have a few comments; mostly they're grammar usage. I do have a couple of other suggestions. One is that on PDF page 88 where you talk about the three-tiered approach to exposure assessment from inhalable particles, the council memo from, I think it was, the October 2018 memo, it suggested -- oh, I'm sorry. No, I mixed that up a second. The recent council memo that's given to us in Wave 2 suggested adding sample calculations to these descriptions. I guess it was Tier I and Tier II. I thought that was a good idea, and I would support that suggestion.

DR. ZHU: What?

DR. HELDRETH: I see that Tom Gremillion has his hand up.

MR. GREMILLION: Thanks, Bart. I guess I wanted to ask about -- my understanding from reading Ms. Scranton's letter is that some of the technology that previously had been assumed to not generate smaller particles is actually capable of generating particles in this respirable range. Does the Panel or maybe the council has a reaction to this? It seems like there should be a burden on the manufacturers or the manufacturers should be thinking about the particle size that's coming out and aware that they can design these products in a way that makes them respirable, if there's a respiration, inhalation risk.

I guess I just wanted to check my understanding there. There's kind of disclaimers now about the airbrush technology, but it sounded like, when reading the letter and even looking at it with the comments as well, even some of the pump sprays can generate these smaller particles.

MS. KOWCZ: I have my hand up. This is Alex, and I just want to address what Tom is saying. The council agrees with the CIR comments. Jinqiu, I think you also did a great job on commenting on Alexandra Scranton's letter. Thank you, Dan, for agreeing that our suggestions might be a good one. I do think that the manufacturers take into consideration all of this. They do their safety risk assessments on every product and product form. I just wanted to make sure that I address Tom's question.

DR. LIEBLER: If we're going to take it, I would like to make and -- I'm getting feedback from somebody. Whoever's not talking, if you can mute for a second. All right.

DR. KLAASSEN: Can you hear me now?

DR. LIEBLER: Oh, Curt, hi. We hear you.

DR. KLAASSEN: Okay. I'm getting feedback here also, so it's difficult to talk, but for some reason, I can see you and hear you. I guess you can't see or hear me through the computer.

DR. LIEBLER: That's correct.

DR. KLAASSEN: Maybe (audio skip).

DR. BELSITO: We're now having problems, Curt, hearing you on your phone as well.

DR. KLAASSEN: Okay. Hang up on my phone, and I'll try to talk to Bart or somebody and see if we can get this straightened out.

DR. LIEBLER: Okay.

DR. BELSITO: The other option, Curt, is simply to do it on your phone and not do the video at all. You don't need to see our faces.

DR. KLAASSEN: Okay. It still doesn't work right. Okay. I'll get in contact with Bart and see what we can do.

DR. BELSITO: Okay. Great. Paul, you have some comments on the paper? Then, I had some questions about the written document.

DR. SNYDER: Yeah, sure. Can you hear me okay?

DR. BELSITO: Yes.

DR. SNYDER: I echo the same as -- this is a very well-crafted document, very thorough. I like the edits and the things that are written in yellow. I think that there's some things, probably the responses to the -- if we're going to share this with the Women's Voice of the Earth, then we probably should tone down a little bit, maybe a little less abrasive. Rather than "not correct," just say "don't support" or something like that. Then, I couldn't edit this document. Every time I went to edit it, like I put in sticky notes or something, it would really do this weird thing.

I would like to have a different version sent to me that I could actually edit because I've taken a lot of notes, handwritten notes, of some editing that I'd like to propose. I can certainly show that as just a note to Jinqiu too.

I didn't have that many issues with the actual document. I guess what became apparent to me in this document is that we probably can no longer default to these broad assumptions regarding particle size, broad assumptions regarding exposures, broad assumptions regarding potential toxicities.

My preference would be, moving forward, that we actually have ingredient-specific statements because, if there's no deodorant spray use, which is the highest particle size distribution in the respirable range, then we really don't need to have that much documentation to support safety. I think that we need to -- the particle size distribution is

important information. I think we should almost always ask for that. If we don't get it, then we can default to an ingredient-specific statement regarding what we know based upon this resource document about particle size distribution.

We should always give them an out for either particle size distribution data or for inhalation toxicity data. I'm not proposing that we need to ask for inhalation toxicity data, certainly, unless -- going to my second point, is the root of exposure. And so the root of exposure, if we have good systemic exposure data, oral studies, toxicity studies show that there is no potential for systemic toxicity, then the systemic toxicity through the lung exposure is mitigated.

That doesn't mitigate local toxicity from lung exposure, but that could be mitigated by the particle size distribution, known chemistry, known physical properties of the ingredients. That's why I kept coming back around to it's really driven by specifics related to the ingredient, whether we have tox data, whether we have particle size distribution data, whether we have exposure data regarding potential for exposure, either systemically or locally, through respiration of respirable particles.

That was kind of a synopsis, a quick and dirty synopsis, of mine. I liked the document a lot. However, I think going forward -- in those old reports when we made those broad assumptions, I don't think we can do that anymore. I don't think we make broad assumptions regarding particle size distributions. I don't think we can make broad assumptions about exposures and things like that. I think we probably need to really craft a statement for each individual ingredient that's specific to the ingredient that's on your purview. That's where I was headed with this.

Certainly, the tiered approach helps with that. I don't think we can just say, oh, see our resource document. Here's our boilerplate. I'll just leave it at that.

DR. LIEBLER: Paul, I agree with you on the need to frame these in the context of the ingredients. I think that's a key point here. If we have safety data that tends to indicate that, even if there is some respirable fraction of an aerosolized ingredient, it doesn't pose a concern, then I think that makes it relatively easy to deal with, if I'm paraphrasing you correctly.

DR. SNYDER: Yes, that's exactly what I'm saying. I just think that we -- I'm a little bit worried that we're -- I don't want to overemphasize this because I don't feel that -- the potential for respiratory exposure is very low. In the absence of any other physical or chemical properties of the ingredient, in the absence of any systemic toxicity data or anything that would -- obviously, crystalline silica was a totally different bag of worms. That cannot get down into respirable range.

DR. LIEBLER: Right.

DR. SNYDER: Most of what we deal with, there is very, very -- the risk just doesn't exist. I don't want to drive these companies crazy with all these hurdles. I think we can go through a due diligence. We can ask for particle size distribution if there's something unique about it, like with the airbrushes. That's part of the reason why I said, "Ask for the particle size distribution." If they don't give it to us, well, it's insufficient because we don't know.

DR. LIEBLER: We would do that in a case where there's a concern about systemic or local toxicity based on other data that we have, right?

DR. SNYDER: Correct. It's a weight of evidence.

DR. LIEBLER: Yeah.

DR. SNYDER: It's basically a weight of evidence approach. I don't think that we can throw the baby out with the wash just because we have this detailed inhalation document. It's very useful to us and to the writers. I don't think it should be shared. I think it should be an internally utilized document. We can go back and refresh ourselves when we're reviewing an ingredient. We can update it as we get new information as people do some of the things you were talking about, newer methodologies for particle size distribution, et cetera, et cetera.

DR. BELSITO: Yeah. I guess the only issue that I have is, first, Linda Katz's response that airbrush technology in cosmetics is not being regulated, that, if it's not a drug, the FDA has not looked at it. We don't know anything about that technology that's being used or potentially being used. We've seen examples where it is used in cosmetic products.

The other issue that I have that I don't feel that I have a good handle on is, if I understand correctly, the particle size for spray deodorants is smaller than the particle size for other types of sprays. Is that correct, Jinqiu?

DR. ZHU: Smaller than pump sprays. We don't have much data for airbrush devices. But so far, the current data

suggested that the particle size distribution here is more than are for deodorant sprays.

DR. SNYDER: Don, if you look on page 9 of the resource document, if you look those particle size distribution charts, the one for deodorant spray cans, if you look, that curve is really, really tight down under the ten microns. Thus, the data suggests less than 50 percent of the particle sizes in those aerosolized deodorants are less than 10 microns, which is very, very different than particle size distribution in all the rest of those there.

That's where I'm saying we have good data on some of these aerosolized products, deodorants in particular. We should be very concerned about deodorant sprays because, also, it's sprayed up around the face. Now a powder that you use down around the feet or whatever or products you have powder on the face would be also a concern. That's why I was thinking that we need to take more of an ingredient and a use and a potential for exposure rather than just broad assumptions that we've been making previously.

DR. BELSITO: I agree. My second point is that when we are getting cosmetic use, very frequently you get possibly a spray, possibly a powder. We certainly don't get, is it used in a deodorant spray? We don't have a separate category for that.

The other thing that I've become very sensitive to is, do we know whether that ingredient is used in a product that's being applied by airbrush technology? We don't have that data. When the CIR staff and Carol, PCPC, goes out, we're not getting specific information on use of that ingredient in a deodorant spray or whether there's any airbrush technology. And so, how do we make our decisions when we don't know that for certain?

DR. SNYDER: Well, that goes to the old saying, absence of data is not a support of safety. So, if it has a spray and non-specified, then we say it's insufficient because we don't have data into what the classification is because we can't -- again, that's ingredient specific because the Panel cannot mitigate toxicity in the absence of data on particle size distribution or for potential for exposure.

DR. BELSITO: Then that's going to be the case for every spray.

DR. SNYDER: Well, not if we know that it's a deodorant propellant or if we know that it's a powder or we know that it's -- you know what I'm saying?

DR. BELSITO: Yeah. But oftentimes, we just know that it's possibly a powder or definitely a powder, definitely a spray, but we don't know what kind of spray products. Is it a deodorant spray, or is it a hairspray? Is it a foot powder spray? We don't have any information as to whether this particular ingredient is used in a product that's currently available by airbrush technology.

I think, quite honestly, in the absence of the FDA or some other regulatory body telling us anything about airbrush technology, we need to create almost a boilerplate for respiratory that we haven't been able, in most cases, in almost all cases, to assess the safety for this ingredient for use in airbrush technology.

DR. SNYDER: For airbrush, I totally agree. There is no data. We have no data. We cannot support safety for airbrushes. I'm speaking more for the other, the propellants in the deodorants and things like that. I think airbrush is way off on the right where we don't have any data.

DR. BELSITO: I understand, but we also have no information as to what ingredients are being used in these airbrush technologies. Literally, for almost everything we review that potentially has an inhalation exposure, we have to have a boilerplate to say we can't assess the safety for airbrush use. Is that not the case?

DR. LIEBLER: That is the case because we don't have the information. You've succinctly stated what our problem is. I think this goes beyond the inhalation specifics, per se. We have a method of application and a technology used to apply certain cosmetic ingredients that is just falling outside of the reporting system. It's outside of the sort of the set of tools that council uses to gather information that they provide to us.

Therefore, we don't really have a way to handle it. Our information about these things has come largely from memos from Alexandra Scranton, which we really appreciate her contributions to our process. But on the other hand, that can't be the way that we capture this stuff. And so I think this is a problem with the system as it is currently configured. I realize that many of these providers of these products are probably not even members of the trade association and have no motivation to play ball with the system. I noticed Carol has her hand up.

DR. EISENMANN: I just wanted to clarify that, in the surveys for quite a while now. I have been separating the deodorant category to aerosol and pump and non-spray. For that, I do get information. I have been including in the last several surveys that they should identify whether or not an ingredient is used in an airbrush product.

So far, nobody has put any of their -- have said that they're using anything in an airbrush. Where I did want a specific ingredient, most of our members are not doing airbrush, as far as I know. Some of them are using the term "airbrush" on their products as a marketing term. We have other spray products, and they say it looks like airbrush, but they're not actually using airbrush.

DR. BELSITO: Okay. If you're inputting that information, then, Bart, if you're still on this call, I think that we need to be splitting out in our use categories. We talk about propellant sprays, whether they're deodorant or other would be very helpful. I think then what we also have to do, is we have to have a category saying, "airbrush technology" or "airbrush application" with a "none reported." Because otherwise we really can't say, "safe as used" because we didn't specify that we were told that there was no -- or we had no information about airbrush technology.

I think we still need to create a boilerplate that says that we just simply don't have the data if we don't. There may be certain ingredients where we do have chronic respiratory, and it's not an issue, so we have the data that that could be supported. But in most cases, we don't have that. I think we need to craft a boilerplate when we don't have negative, chronic inhalation that states that we don't have data to support use of this -- if this material were to be used in airbrush technology, the data is insufficient to support safety or something like that.

I think we need, in the cosmetic use typically Table 3 section, a specific row that says, "deodorant aerosols and airbrush technology" and at least a "none reported" or whatever so we're showing that we're doing due diligence. Tom, you've had your hand up for a long time.

MR. GREMILLION: Thank you, Dr. Belsito. I wanted to ask, on page 26 of the Wave 2 file in Alexandra Scranton's letter, she cites this pump spray that emits maximum particles of a maximum four microns in size. So is the distinction between a product like that and airbrush technology just based on the exposure? I read that, and I thought, okay, so you've got small particles coming out of pump sprays too. How does --

DR. LIEBLER: Tom, this is Dan. This is a good example of the problem with the different measurement platforms. The platform that the authors of this Laycock, et al., paper that Ms. Scranton cites in her letter, that's one of our papers that we also cite. I went and read through that paper. That paper is noted by the desire to measure droplets or particle sizes from nanoparticle-containing products, broadly speaking, not just cosmetics but various consumer products as well.

They went and bought this one, I guess, off the shelf from a store and analyzed it. They used a technology platform that measures in this very small particle range below ten microns, below our typical threshold for what's respirable. Indeed, they got signal from this product that indicates there are particles in that size range, but they did not attempt to measure the larger particles that are typically produced from pump sprays. That was just not measured. In other words, they were measuring the tail of the distribution on the low-particle-size end of the distribution.

I think Ms. Scranton's letter suggests that virtually all the particles that were measured from this product were in that range, and that gives the erroneous impression that all the particles from that product are in that range. That's not likely the case at all. It's a pump spray. I mean it's not capable of producing entirely such small particles. The thing that's new is these platforms that can measure the very small particles are capable of making measurements where people couldn't people previously measure. They do get a signal. They do get data there.

So they're adding definition to, essentially, the low end of the distribution, but the high end didn't go away. It's just not reported in this paper because that wasn't the point of the investigators who did this study, they wanted to look at the low end. There's no platform that covers it all, and that's the problem here.

MR. GREMILLION: Yes. That's helpful because she says virtually all the particles measured from this pump spray were smaller than ten microns, and that's not correct.

DR. LIEBLER: Well, the way she wrote it, "all the particles measured," (inaudible).

MR. GREMILLION: Yes. Okay. Thank you. That's all.

DR. BELSITO: Yeah, you need to go back to that presentation that we had many years ago where they showed sort of the overall distribution, and then they pointed out that these papers were focusing on less than 20 microns and so you get this distortion.

DR. LIEBLER: I think this teaches us that there are always going to be very small particles, and the reason we ignored them in the past is because we couldn't or didn't measure them or the people who did these studies weren't measuring them. There's still a very small percentage of most aerosolized cosmetic products that we've ever seen data on with the exception of the propellant deodorant sprays. Propellant deodorant sprays versus propellant

hairsprays, the same kind of propellant device gives you very different particle size distributions. That has to do with the chemistry of the ingredients that are coming out of the nozzle.

I think that Paul has a really good point, that these assessments should be ingredient-specific or ingredient-family-specific. I think that we can't completely get rid of boilerplate here, though. I'm not sure if I'm misinterpreting Paul's suggestion. I don't want to completely get rid of boilerplate, but I think we've been using it in a very imprecise way. It's been probably correct most of the time when we've used it, but sometimes it's not correct. I think the thing that has sort of stirred up this field again is nanoparticles, airbrushes, and the ability to measure small ends of the particle size distribution.

The solution for us probably is a boilerplate that's adjusted case by case, depending on the characteristics of the ingredient family, including the other data for safety.

DR. SNYDER: Yeah. That's more of what I was saying. I was thinking that we would have a boilerplate statement regarding sprays, but it would have to be ingredient-family-specific. It could also be then supported in the discussion by, no, there are good toxicity data saying that, even if there is systemic exposure, there's no chemical or physical properties that would give concern for respirable toxicity, things like that.

Also, Don, to go to your point, I think that we need to push back to council and that Carol needs to ask for more details. There needs to be, okay, is it a spray use? If the answer back is yes, then there has to be some very, very specific questions asked. Otherwise, we're going to require -- like I said before, we've got to have -- we should always have some particle distribution data for that reason because, some of these broad assumptions, I don't feel comfortable making anymore. Because there's such a wide range of these propellants and these products and things, I just don't think that we can -- those broad assumptions are out the window with today's technology. I think it's being driven a little bit by marketing, as Carol stated, that they're trying to give this impression that, even if they don't have nanoparticles, they give you the same look because they have all these small particles.

That's probably the reason why this study was done more as a marketing ploy than anything so they can make a statement and support it with data. But then when Dan looks at the data and says, "Well, they didn't even measure 80 percent of the particles because they're way above the range of what's looked at."

So I think we're all on the same page. I think as we go through the reports today, I think it's going to be a little bit painful. But we're going to have to think about how we would craft the boiler statement for these families of ingredients.

DR. LIEBLER: I think that this isn't Carol's fault, or this is no fault of Carol's. She's listened to all of our discussions. She's on the leading edge of the questions that we were considering. She's getting everything she can squeeze out of industry. The problem is, I think, that, particularly in the airbrush space, it sounds like most of the members are not using airbrush technology platforms to deliver their products. They're outside of the system.

The problem is we have things that are perceived as cosmetics that are outside of our review or data capture system, and we are simply hearing anecdotal reports about these that make us wonder if we're capturing everything. We're obviously not. So I think the only choice we have right now with this situation as it is, is to routinely put in insufficiencies for airbrush technology for ingredients for delivery by airbrush technology. It's the only way we can handle it because we just don't have the data to deal with it any better way.

DR. BELSITO: Yeah. That was exactly my point, Dan. We need to create that boilerplate because we're not going to get the data. The other thing that I wonder is, should CIR send a letter back to Linda stating that this technology is being used in cosmetics, and we urge the FDA to look further into the use of this technology since it can deliver respirable particles or it may deliver? We just don't have the data, right? So I guess "may" would be the correct way of addressing it.

I think this is not going to go away. In New York, I'm seeing more and more women bringing in products that look like it's airbrushed when I'm doing patch testing. I think it's something that FDA really needs to look at.

DR. HELDRETH: Don, we have Dr. Manga on the line here, who is our FDA liaison. I don't know if she wants to comment on that or not.

DR. MANGA: Hi, everyone. Can you hear me?

DR. BELSITO: Yes.

DR. MANGA: Hi, this is Prashiela. I stand by what Linda said, which is we don't really regulate the technology itself. That would probably fall under the Consumer Product Safety Commission. We're definitely aware, now that

it's been brought up to us of the products. Certainly, the actual cosmetic product itself would be under our purview, and we would look at those. I think the airbrush technology itself is not something that falls under our purview.

DR. LIEBLER: Right. That's true, but, of course, it doesn't really solve the problem, does it? I understand it's not a device in the context of what the FDA's authorized to regulate medical devices. So we understand that limitation. But this is a device that's used to deliver a product that may be entirely safe and not respirable if it's delivered in some other way other than an airbrush. We can review the ingredients and say safe.

I guess, with sort of everybody following off the pitch here about airbrushes, all we can do is say its data are not sufficient to assess the safety when it's delivered by an airbrush because nobody's going to pick up the ball and run with it here.

DR. BELSITO: I guess I heard that it's not FDA, but it goes to another component, regulatory authority. I missed what that component was.

DR. LIEBLER: Consumer Product Safety Commission.

DR. BELSITO: Okay. So should we draft a letter to them?

DR. SNYDER: That was going to my question. Should Bart, on behalf of the CIR Panel, query them as to where are they at with these technologies and methodologies for delivering these small particles?

DR. HELDRETH: I absolutely will.

DR. BELSITO: All right. Okay. I would just like to go back to just a couple of -- I'm sorry.

DR. KLAASSEN: This is Curt. Can I ask something?

DR. BELSITO: Sure.

DR. KLAASSEN: I'm on the telephone right now listening to you. I think that the main problem here that Dan has suggested is really the percent of what you spray, first of all, that gets to the nose. The first thing one really needs to know is the inhalable fraction, which we really have zero data on it, except there are some indications that it's extremely small. So, if you're spraying your hair, what percentage of that, if you spray your hair for a minute, actually gets into your nose? That's the inhalable fraction. Then, it can deposit extra thoracically, then thoracically, and then down into the alveoli.

We have been emphasizing all along that that goes down into the alveoli, which we call the respirable fraction, which is okay. But as some of you have been noting, it's not only the size of some of these things; it is the chemical. For example, as we all know, formaldehyde can be in a small particle, but all of the damage is done in the extra thoracic, thoracic fraction. That has to do with its chemical properties. Whereas, if one has something like ozone or nitric oxide, it goes all the way down into the alveoli, and that has to do with the chemistry and not so much with the particle size.

Now, I think there's a beautiful figure that got first sent to us by the lady in Wyoming or what have you. There's this picture on page 4 of this document of this graph of a pump spray and an aerosol spray. If you look at that pump spray and see how much of it is less than ten microns, it's almost nothing. One normally in science would determine the area under the curve of those larger particles and then the small particles. So it looks like, with the pump spray, it's less than one-tenth of one percent that even gets to the nose is small enough to enter the nose.

Where I think the emphasis should be here, rather than getting into all of this particle size, is really the dose. In essence, the dose that gets into the lung by inhalation is close to zero.

DR. LIEBLER: Curt, I think your point is well taken. The dose is, obviously at the end of the day, the most important thing to determine the likelihood of toxicity is something that has a potential toxicity.

The figure you point to is from Dr. Rothe's presentation. Actually, it's on PDF 6 of the inhalation document that we're reviewing. It's a nice example of an aerosol versus a pump. You can see the tail for the aerosol extending below ten microns.

With the other figures that Paul was pointing out to us -- and I lost the page for those -- those distributions can shift quite a bit one way or the other.

They're mostly like the aerosol spray here, but they can be significantly shifted, depending on the nature of the ingredient that's being sprayed. The deodorants shift over to the right. I'm sorry, to the left. So you got more under-ten microns. This is the part that is really confounding for us is -- depending on the chemical nature of this

substance being sprayed, those distributions can give you a significant number of particles that are below. Still, the majority is above ten microns. I will agree with you about that.

The question is, is there some -- well, I should say I agree with Paul as saying that we can't just put an arbitrary number on it and say greater than X percent is greater in particle diameter than ten microns and not respirable. It just depends on the ingredient. That's the problem that we -- our current boilerplate is too clumsy to deal with that.

DR. KLAASSEN: Yeah. While this is an over-exaggeration, what I'm going to say, but not much of an over-exaggeration, I guess my gut feeling is that inhalation of these cosmetic products from a toxicity standpoint is essentially nil. Do we have one example where this has ever been a problem?

DR. LIEBLER: Curt, I agree with you about the gut feeling and the sense from the totality of the data that we've seen that that's the case. I can't give you a quick example. I certainly can't. But I think the issue is what are the criteria that we say we can apply to make that assertion with confidence in our reports to credibly back it up?

DR. SNYDER: I think this is a little akin to what I've learned from you over the years about sensitization data, that in order for you to have confidence for an absence of sensitization, you would need to see data. I always look for the sensitization studies to have upwards of a hundred subjects in the studies, down at the maximum concentration in use and those kinds of things to give us confidence that the statements that we're making about absence of sensitization is appropriate. If we don't have that data, then we ask for it. I think this is kind of a little bit like that.

I think that on the individual ingredient basis, some of them -- well, this one's used in a lot of sprays. This is used in deodorants. So we need to see some particle size distribution. Otherwise, we're going to default to our boilerplate and say that the assumption is based upon a resource document that around 50 percent of the particle size in a spray can deodorant are less than ten microns, unless they show a different particle size distribution or they provide us with inhalation studies that suggest a safety or other safety data and chemical and physical properties.

So the bar just moves. That's why I think it has to be tailored to each individual ingredient family. I just think that these broad assumptions are out the window for me.

DR. KLAASSEN: We're never going to get that data. It's one thing to get sensitization data. And there's a reason for sensitization. There are hundreds of compounds in cosmetics that cause an allergic response. But I think we're in a different ballpark here. We've never had an example of anything causing -- a cosmetic causing inhalation toxicity. I mean, you know, why don't we (audio skip) determine (audio skip) because it's cosmetic (audio skip) makes your toenail fall off.

DR. BELSITO: The only problem I have with that argument --

DR. KLAASSEN: No cosmetic (audio skip) so we don't look for that.

DR. BELSITO: Yeah. I guess the only problem that I have with that argument is, so we don't have any examples in the literature of a cosmetic creating a lung issue. I think, in part, that could be due to the fact that there are many other confounders out there to determine to what percentage this use of a cosmetic product may have caused the lung issue at hand is sort of hard to know. Was the individual a smoker? Were they a mortician? Were they a beautician? What else were they exposed to? Can we blame it on some other chemical?

Again, inhalation is not my area of expertise. It's probably my weakest area. Maybe Dan can comment. RIFM has this two-box model for inhalation of products. Certainly, when you're using pumps and propellant sprays, there is a proportion that is inhaled, at least based on these models that they use.

DR. LIEBLER: Don, this two-box model that RIFM uses would correspond to what is our Tier 2 classification in the document that Jinqui has put together for us.

DR. BELSITO: Okay.

DR. LIEBLER: We feel that Tier 1 will handle most of the situations we have to evaluate. In the case where we need a little bit more careful modeling to make an assessment because it may be a close call, then we can employ Tier 2, which would involve additional assumptions about the situation and additional modeling capabilities like the two-box model. I'd like to zoom out if I may, Don, to say, where do we go from here? I think we've got a good resource document now.

It's been updated with respect to a lot of the points that have been raised by Ms. Scranton, by additional literature. Now I think we should probably finalize this version of the resource document and then move on to the question of boilerplates and how we handle the respiratory issue. There's the incidental inhalation issue in our reports. We do

need a revised boilerplate that utilize information from this resource document. I think the next phase for us is to update those boilerplates or update the boilerplate that we use.

Then we can customize that boilerplate framework on a report-by-report basis, as Paul suggested. This way, I think we can move forward. We've done our diligence on this. We've identified things we can address. We've identified other things we simply cannot address. That's how we move forward. That's my suggestion.

DR. SNYDER: I concur with that suggestion.

DR. LIEBLER: Tom's suggested it. I thought that's a leftover hand from your previous comments.

MR. GREMILLION: No. I'm sorry. I didn't want to interrupt. Maybe this is obvious, but I just want to check my understanding because I'm a little confused about the emphasis on the airbrush technology because I'm seeing these references to nano-enabled chemistry that seems to affect the particle size of other delivery devices. From what I understand, the airbrush technology poses a problem because it's particularly good at getting the particle sizes down to the respirable level.

Maybe it's also because of the exposure. You're using the airbrushes longer. I wanted to check my understanding of why would -- this special treatment of airbrushes.

DR. BELSITO: Tom, I think it's because we don't understand the full range. But also, airbrushes are primarily used by women to apply makeup to the face, so they're pointing it directly at their nose. When airbrush is used for (audio skip) it comes with the recommendation -- I don't know if it's recommendations or guidelines -- that the nose be plugged and the eyes be shielded and the mouth covered, the mouth closed and the nose plugged. The airbrush used by consumers doesn't come with those recommendations, and it's being directly applied, in almost all instances that I'm aware of, to the face.

DR. LIEBLER: Thomas, can I maybe chime in with a little bit different way to address your question? With airbrushes, there are basically two issues. One is that it's true that airbrushes make a finer mist than a propellant spray can, the classic spray can-type product. They make smaller particles, but the distribution of those particles depends on the chemical nature of the ingredients that are being sprayed out of the airbrush.

It's not a fixed distribution with airbrushes that we can say X percent is less than ten microns and get into the deepest part of the lung. But we don't have hardly any data on airbrush use. That's the first thing. The second thing is we have almost no documentation of usage in the consumer space. We just have a lot of anecdotal evidence that certain products are being sold to be used with airbrushes. That's about it.

MR. GREMILLION: Okay. All right. Thank you. That's helpful.

DR. ZHU: One thing I want to add is that current information suggests that the airbrushing's always associated with nanometer particles exposure. That's always the issue.

DR. LIEBLER: Are we looking at Curt's screen here? Ah.

MS. KOWCZ: Looks like it, Dan.

DR. BELSITO: Curt, your shared your screen.

DR. LIEBLER: That may be part of the troubleshooting process here.

DR. BELSITO: Okay. Oh, maybe Bart is working with him. Okay. To go into the document, I guess, let me summarize where I think we are at this point. I think we like your document, Jinqiu. I have one or maybe a couple of comments or questions, but we also need to be a little bit more particular in just knee jerking to the respiratory boilerplate and that we're going to craft some type of language as a boilerplate that will state that the safety of the ingredient for use in airbrush technology is not known.

Then, I guess the question becomes where do we put that in the discussion? If we don't have data that shows in the report that in fact it is used, then do we put that language in the discussion?

DR. LIEBLER: Seems to me that's the place for it (audio skip) use.

DR. ZHU: Actually, I draft a boilerplate language. I wonder if I can present it to the Panel right now.

DR. BELSITO: Sure.

DR. ZHU: Okay. Let me try to share. Can you see?

DR. BELSITO: Yes.

MS. KOWCZ: Yes, we do.

DR. ZHU: Okay. Is that clear?

DR. LIEBLER: You unshared your screen, or somebody unshared your screen before I finished reading it.

DR. BELSITO: Yeah.

DR. ZHU: Oh, I'm sorry. Just do it again?

DR. LIEBLER: Yes.

DR. ZHU: Okay.

DR. LIEBLER: I think this is a good start, and it states the problem. The question I would have is in what part of the report is this intended to be used? Is this intended to be in the discussion, Jinqiu?

DR. ZHU: Maybe used in like in the report (audio skip) medical report discussion part to discuss potential inhalation risk.

DR. LIEBLER: Yes. I think that we could use something along these lines. It would probably need to be condensed considerably. We can start with something like this. I think there's a couple of places where we have inhalation boilerplate in our reports. One is the discussion, and one is in the uses section.

DR. BELSITO: Right.

DR. LIEBLER: Those are the two areas where we need different versions of the boilerplate. I would suggest that the one that's in the uses section start as a template, and then we can edit that rather than do it from scratch. My suggestion is that this be a next step for the Panel after having assessed this resource document.

I think you've done a great job on the resource document. I don't think it makes sense to refine it any further. I personally feel that way. Then we need to think about how we take the information we've gathered and put that into our reports in a practical way. I think the resource documents are always available publicly. Aren't they?

DR. BELSITO: Yes.

DR. LIEBLER: I think Paul mentioned that we shouldn't be sharing this, but I think we need to. This is a basis for our understanding of the issue. We're going to have to have a resource document that's publicly accessible.

DR. SNYDER: My only question about publicly sharing it was that I don't think -- I was trying to prevent the CIR staff from having an inefficient use of their time to constantly be bombarded with these studies that, as you pointed out and it's been discussed, are not valid or that the data -- I just was worried that there's going to be a lot of additional comments. Obviously, some good comes out of those comments, but I think a lot of those are not valid.

As long as we have a SOP where every 18 months or something that you search for these different technologies and see if there's new data that can change the particle size that technology (audio skip). I just didn't want the staff to be overwhelmed with -- because, if this sitting out there, people can nitpick at it. If they don't understand the science, they don't understand the technologies used to make some of these measurements. That was my only comment. I don't have a problem sharing it publicly, but I was just trying to save the staff some issues.

DR. BELSITO: Yeah, but I think it needs to be public because we really rely on people, quote/unquote, nitpicking. We would not have been aware of this whole airbrush issue if it had not been brought to us by Women's Voices of the Earth. I think that keeps us on our toes and keeps us in tune with what's going on that we might not be picking up. We also rely on it in our assessments, and we don't go into great detail. The detail needs to be there someplace.

DR. SNYDER: Don, as an aside query here, where did the patch testing come on hair dye on the label? Where did that come from, that query?

DR. BELSITO: I think it came from back in the '30s. Someone dyed their eyelashes or eyebrows and got blinded, and there was a whole issue about restricting hair dyes and this whole sensitization thing. That whole language about coal tar exemption came into being. Bart, isn't the regulation going back to the 1930s?

DR. HELDRETH: Yes, that sounds right to me. There really hasn't been much of a change for cosmetic regulations since that time period.

DR. SNYDER: Because I really like the way that you stated that there should be a statement on some of these airbrush technologies in any case that there is a consumer responsibility to cover the eyes, to plug the nose, the mouth closed. You know what I mean because, if we knew that that those issues were being done during this

technology, then that goes to the use. It could be safely used. That's sometimes what we run into, that the potential does exist for these things to be safely used under the right conditions of use.

DR. BELSITO: Paul, we had the same issue. Paul, I don't know if you remember the Panel then with the acrylate use for nails.

DR. SNYDER: Yes. Yes, correct. Yes.

DR. BELSITO: Yes, you were because that was 9/11, and you were there. Okay. We like the document, and we're going to look at crafting a boilerplate that will go someplace in use and discussions section about airbrush technology. Is that where we're at?

DR. HELDRETH: Yes.

DR. BELSITO: Okay. Then, if I can just, one final comment on the document, Jinqiu. On page 86 of the PDF, that last sentence right at the bottom of the page talking about airbrush technology and you state, "Similar precautions and protection measures are thus advised to refrain from aerosol inhalation during applying spray-on liquid powders through low-pressure airbrush technology." Then it says, "Accordingly, additional studies are necessary to evaluate the safety of consumer products delivered via airbrush technology."

I guess, to me, that sentence almost didn't follow because you're talking about, okay, these particles are going to -- it sounds like you're saying the particle are going to be or the ingredients could be respirable, and that we're going to address that by using mitigation strategies to refrain from aerosol inhalation. I just wonder if other people had that question because we're not really talking about doing additional studies in that paragraph. That's just me thinking.

DR. SNYDER: Yeah, I had some issue on that. On page 89, Don, I also had -- some of the language that was incorporated -- I don't want to be -- I think we need to be careful in some of this language that we use, like on page 89, that second paragraph, "the purview of the Panel is exclusive to assessing the safety of ingredients." It's restricted by the charge of the Panel to only deal with cosmetics and not consider drug usage and things like that.

DR. BELSITO: Yeah. I flagged the same thing, Paul.

DR. SNYDER: Yeah. Like I said, I couldn't edit this. Every time I clicked on it, I got this thing, and a line moved across, and I couldn't stop it. I've taken notes on some of this. I would like to, I think -- while this is very, very good, I do think it needs some wordsmithing. We need to be careful about some of these statements in here, as you pointed out, too, Don.

DR. BELSITO: Sure. If you couldn't put that into your report, Paul, just send it off to Jinqiu Zhu.

DR. SNYDER: Yeah.

DR. BELSITO: Great.

DR. ZHU: Thank you.

DR. BELSITO: Are we done with inhalation? Can we move to another beast, silicates?

DR. HELDRETH: Yes.

### **Cohen Team Meeting - December 6, 2021**

DR. COHEN: The inhalation has been the topic of the quarter or the year that I've been here, and looking at all the memos, it seems like it's a bit of a hot potato because it doesn't seem like any specific agency has regulatory oversight over different parts of this. At the September meeting, we discussed particle size from a variety of aerosol sprays, with specific focus on this propellant driven sprays and airbrushes, and there's more nano enabled cosmetics out there. So the concept of reviewing this informative piece on inhalation came up.

We also got a number of materials in Wave II from the Women's Voices for the Earth discussing manual trigger sprays that actually had small particle sizes. There was an interesting citation from Swedish study in 2019 Journal of Occupational and Environmental Hygiene. I think it related to cleansing agents. Another issue that came up was the assumptions about the lengths of time customers would be exposed to aerosols and the volume being used, and I spent some time watching Tori Lenell's video on the use of dry shampoo application. So I learned a lot there.

So, before we go onto the boilerplate, I'm going to open it up for discussion and comment. Tom, did you want to start us off?

DR. SLAGA: Yeah. I felt that, overall, we covered all the issues that we talked about, and other than some minor little changes, I think it's becoming a very nice document.

DR. SHANK: I agree with that.

DR. PETERSON: I found it very helpful to read because now I felt better about the boilerplate that was being put in the document. I really think that the piece that gets put in the document needs to not only talk about where deposits and what its likelihood in this getting in but also deal with the issue of time of exposure and that -- because I think sometimes the boilerplate in the documents for the different ingredients refers mostly to the particle size. And I think that's an okay argument.

But the other, to me, more important piece of it is often the exposures are short. They're not very long, so the likelihood of -- it's that whole argument -- and I'm having trouble finding it now -- that talks about the duration of exposure is an important piece to add to the little blurbs that we put into the reports because, to me, that's the important piece. It's okay. You can argue that we don't think it's going to get in but if it does get in, the exposure's short. And for the only compounds we have to worry about that with, the short exposure -- one molecule getting in are for the things that cause harm, like the silicates -- these compounds that have the potential to cause mesothelioma, like asbestos or something like in the mined silicates.

You know that you don't know that there's a safe limit so one exposure could be a problem, and for those compounds we have to be very careful. But for the average compound that could potentially be inhaled that might have some toxicity, the reality is that the -- we have to consider, okay, particle size. But that's, to me, always going to be a little bit of hand-waving and setting yourself up for arguments, but if you add in the length of exposure, the duration of exposure, how much each exposure's going to be -- and there's a nice blurb here somewhere that talks about that -- that, to me, those two pieces together then really is nice.

So I actually thought that the whole piece was very thoughtful, considered all of the issues, and I am much more comfortable with a boilerplate at this point than I was before. So, thank you for the nice writing.

DR. COHEN: Yeah, I suppose -- oh, go ahead.

DR. SHANK: I have a question about these airbrush things. Several places we've heard that people spray their faces with these brushes for 20 to 30 minutes. Is that really true? Or do you say hold your breath for 30 minutes while you're --

DR. COHEN: Ron, they can go on a long time, and when you look at these -- the videos that were coming in through the correspondence, they can go on for a while. They are not a matter of a second or a minute.

DR. SHANK: So, do they cover their nose and mouth? Does the person who's using this airbrush -- are they breathing during all of this exposure time? They have to be.

DR. COHEN: Yeah, it's hard to hold your breath that long.

DR. SHANK: So, that would make a -- that would say that there certainly is going to be considerable exposure. In most uses of cosmetics that can be inspired, Dr. Peterson's absolutely right. It's very short. But this airbrush business with 20-to-30-minute exposure is an entirely different problem.

DR. PETERSON: Absolutely. Absolutely.

DR. BERGFELD: I'd like to make a comment. I think that somewhere there needs to be a summary statement that talks about particle size, the duration, and the volume or density that's dispersed.

DR. PETERSON: Yeah, I agree with that.

DR. BERGFELD: I mean, a very clear statement.

DR. SHANK: The report covers this, but everybody always talks about particle size. And yes, that's very important, but the chemical properties, the solubility, the reactivity of these particles is also important. So, I think we shouldn't constantly refer to only particle size. Particle size is very important, but it's not the only thing. And that is covered in this document.

DR. PETERSON: A short summary statement doesn't always include that both -- all of those pieces.

DR. SHANK: That's right.

DR. PETERSON: And I think if we start adding so that it includes all of those pieces, then I think it covers us. I think that it's a better statement of reality and less objective to concern.

DR. SHANK: Okay. I agree.

DR. BERGFELD: So, the question I have is would you include particle size in chemistry, duration of exposure, and volume or density? I mean, I would think that that -- and I'm not sure that's a correct term to use volume against (audio skip 01:38:35).

DR. PETERSON: Yeah, something like that. I think our boilerplate needs to address all of that.

DR. SHANK: How will it do that?

DR. PETERSON: (Audio skip) statements.

DR. COHEN: Right. Well, somewhere along there, there was a comment that the Panel does consider the data to be insufficient to assess the safety of airbrush delivered cosmetics. I mean, that could just be part of the boilerplate on this, right?

DR. BERGFELD: Yeah.

DR. SHANK: Yes.

DR. COHEN: Because, Ron, to your point, I have seen it applied on my own kids, and it takes a long time to airbrush the face.

DR. PETERSON: What do they do to protect the kids from breathing it in?

DR. SHANK: Yeah, good question.

DR. COHEN: Not much. You know, you can't hold your breath the whole time, but you take breaths between the activation of the trigger. It's on and off. So, we're not going to be able to come to a conclusion on every chemical that comes through that may be put into an airbrush. We're just not going to be able to do that.

DR. ANSELL: Yeah, and we agree that airbrush should be considered a separate exposure route different from the aerosol and other routes. And so, talking about a specific airbrush statement is, we think, the right way to go, too.

DR. BERGFELD: But there are other propellants, I mean, that may be equal to the airbrush or near equal to it that are being devised. And as David said, FDA is not taking ownership in any of its various sections, the device people, the cosmetic people, nobody. And the letter has to go back to them and say they have to highly suggest it for public safety.

DR. COHEN: So, Wilma, tomorrow after Don presents it and I'm presenting the conclusion, are you suggesting that we actually make the comment that FDA needs to reconsider regulating this?

DR. BERGFELD: I'm not sure of the terms we would use, but we want FDA to take a hard look at it and assign somebody to this effort. I don't know where it would be. I would think it would have to be a combo of chemistry and device, but I've served on both the device and the FDA committees. And they certainly can combine them because we have done that -- combine the faculty or the experts to give comment.

DR. COHEN: Yeah, the airbrush is the caricature of the problem. But some of the data we've seen suggests that newer pump -- non-propellant pump sprays are getting really good at creating small particles.

DR. ANSELL: I think in terms of the sprays and the aerosols, the data in terms of assessing dose as opposed to any particular element are well developed. The part that we agreed that the data on airbrushing -- that the data isn't there. And so, we think that it could be taken out as a general statement when considering incidental inhalation exposure of cosmetics. I don't think -- I think as the resource document points out the data on actual exposure to these materials is there and shows when considering all of the parameters that the exposure is really very, very small.

DR. SHANK: I wouldn't call airbrush use incidental exposure.

DR. ANSELL: No, I think airbrush should be taken out.

DR. SHANK: It's totally different.

DR. ANSELL: Yes.

DR. SHANK: Before we leave this, I'd like to go to page 89 -- PDF page 89 and let's see. There's a paragraph that begins on the other hand. The one just before that, that last sentence says that "The Panel generally agreed that inhalation exposure to ingredients in aerosolized cosmetic products is unlikely to be significant compared to the

dermal or other exposure.” That’s really not true. It may be quantitatively less significant, but toxicologically it could be more significant. So I would just delete that last sentence of the paragraph that begins with “The Panel will continue to review” and that last sentence I would just take out because that’s not true.

DR. COHEN: Okay. PDF page 89.

DR. SHANK: The other comments I had are basically editorial.

DR. COHEN: Just an administrative question. I think in the past we’ve come to split conclusions as our final decision where we say that we have insufficient data if it’s going to be used in an airbrush. It was part of our conclusion. If we’re making this as part of a boilerplate that the data’s insufficient to us as airbrush delivered cosmetics, we’re going to change the way we conclude on products if we’re going to put this in a respiratory boilerplate? Or am I making it too complicated?

DR. SLAGA: I’m not sure what you’re asking.

DR. COHEN: So, in our conclusion we’re safe as used -- split conclusion. Safe as used in present practices and concentrations but insufficient data on its use in airbrushes. That’s presuming we know that it’s in an airbrush, right?

DR. SHANK: Okay.

DR. COHEN: So, if we add it to the inhalation boilerplate, we’re saying we’re not doing an assessment on airbrushes at all, and it would change our final conclusion because it would be safe as used. Without the split -- I’m getting at it’s a split conclusion only when we know that you can put a few of these drops in an airbrush, but if we don’t know that, we’ll just come out safe as used and may never mention the airbrush issue.

DR. BERGFELD: We had agreed to take case-by-case in the previous discussions.

DR. SLAGA: Right. I think we have to do that.

DR. COHEN: Okay.

MS. FIUME: And David, also the safe as used, the part that’s missing, is as stated in this report. So, if airbrush isn’t specifically called out, that’s not part of the as used according to the report.

DR. SLAGA: Right.

DR. COHEN: Yeah, and I get that and from a technical perspective I think that’s completely correct. The question is how often will people dive into the report and search the term airbrush and not assume that a chemical is just safe?

MS. FIUME: I’m hoping they at least -- we put out our compendium as the abstract discussions and conclusions, and the discussion typically -- and if not -- an effort could be made by the Panel to point out the type of exposures or uses that they’ve looked at when they were discussing the document. I mean, it doesn’t have to be specific but just in general. You know, that’s always a comment is do they look at it, but unfortunately, it’s all the Panel really has to go on is what is presented to them. And that’s the only thing that can really put out to the public is, here’s what’s in our report; you need to do your due diligence as well and actually look at what we discussed and what we’re looking at.

DR. COHEN: Okay. Yeah, no. I understand. Any other comments on the inhalation document?

DR. BERGFELD: I think this document is going on, and we’re going to be adding and rediscussing it almost at every meeting.

DR. COHEN: I think you’re right, Wilma, and it’s going to come up in the next chemical we’re discussing. So, can we move on to methicones?

DR. SHANK: Okay.

MS. FIUME: So actually, I do have a question first because I know one of the questions Wilma had asked early on is what actual language gets put into the reports. Does that need to be discussed with this inhalation document? Will it be a case-by-case basis as you proceed through the reports as to what goes in it and what specific language? Will those changes be expected coming out of this meeting?

I know a lot of that can depend on the final discussion tomorrow but just as guidance for the writers because the statements are being made that this needs to change in the report. But if we could have guidance on what you want it changed to, that would be helpful for us as we go forward.

DR. COHEN: Yeah, you mean one of these changes going into effect, and is it at this meeting? And which chemicals are we putting it in?

MS. FIUME: Yes. Thank you.

DR. BERGFELD: Well, I think we're going to modify it according to what our risk assessment is via the documents that we reviewed. So, we have a basic document and then which will be modified.

MS. FIUME: So then will the guidance be given to the writers per each report on what modifications you would like to see in the use and/or discussion sections?

DR. BERGFELD: I think so.

MS. FIUME: Okay. Thank you.

DR. COHEN: Okay.

### Full Panel – December 7, 2021

DR. BELSITO: Yes. This is something that we last finalized in 2019. We began looking at in in 2020. In response to that we got a letter from the Women's Voices for the Earth on September 9, 2021. We note that perhaps the particle sizes we were quoting in sprays was not quite correct. We went back, and we did literature searches and reviewed the particles that were brought forward by Women's Voice of the Earth. And that was under Scranton. And at the September 2021 meeting we further discussed particle size distribution of various aerosol sprays, focusing on the propellant driven particularly for deodorants and the airbrush devices.

We also were looking more at nano-enabled cosmetics being formulated into aerosolized products. And we felt that the current draft really pretty adequately assesses where we are right now, and the only issue in the current draft was that we were sort of looking to the FDA for clarification on regulation and received a response back that that would not be their purview to regulate a cosmetic device and we would need to go to another federal agency whose name is escaping me right now. And Bart had agreed to consult with them regarding this issue. So we thought the document -- we made a few minor wordsmithing changes -- but pretty adequately reflected where we are right now.

DR. SNYDER: That agency was the Consumer Product Safety Commission, Don.

DR. BELSITO: Yes. Thank you, Paul.

DR. BERGFELD: Well, my impression for all that was no one was taking any responsibility for it yet, so I think we need to keep probing as to who is responsible for overseeing the safety of such a product.

DR. BELSITO: Well, we were told who would oversee it. We just haven't addressed the question to them, and Bart will be doing that -- the Consumer Product Safety group.

DR. HELDRETH: Yes, I actually sent them an initial message yesterday morning.

DR. BERGFELD: Okay. Well, we know that this is a living document, so it's open to change when we have our consultants advise us.

DR. BELSITO: Correct. And I'm hoping that Thomas for the Consumer Federation of America will also birdog the responsible federal agencies to look at this airbrush technology.

DR. GREMILLION: Yeah. We have Rachel Weintraub who some of you will remember works a lot with the CPSC, so that's on our to do list.

DR. BERGFELD: Okay. Is there any need to discuss anything else. Dr. Cohen, do you want to add to this discussion?

DR. COHEN: I thought Don's explanation was right on, and we were pleased with the new iteration. I think apropos to Don's comments about the in vitro test, the technology to deliver these cosmetic ingredients continues to evolve, and it impacts how people are interacting with these ingredients. We've mentioned this hot potato issue of no agency sort of taking this on right now, and hopefully that'll change.

Just one comment for the team on PDF 89 I'm just going to comment that the Panel agreed that general inhalation exposures to ingredients in aerosol cosmetic products is unlikely to be significant compared to the dermal or other exposure routes associated with the use of cosmetic products. And we thought that comment should be removed having reviewed some of those videos with the length of time and the particle sizes of some of these airbrush

products. So that would be our addition to the conversation.

DR. BERGFELD: Bart, you want to comment?

DR. HELDRETH: My main question is once the comments have been incorporated that Jinqiu received from Panel members is the Panel consensus that this document should go ahead and replace the 2019 version that's on the website?

DR. SLAGA: Yes.

DR. SHANK: Yes.

DR. COHEN: Yes.

DR. BERGFELD: Yes. Why don't we vote on it so it's official? All those agreeable that it should go up on the website as the official document as of 2021 just say yes.

GROUP: Yes.

DR. BERGFELD: Anyone opposing? No? So officially yes.

DR. BELSITO: David, could you just give me that page where you want to strike something again? I didn't follow that completely.

DR. COHEN: It's PDF page 89, Don. And it starts "The Panel agreed that generally" --

DR. SNYDER: The sentence at the end of the paragraph right above where "On the other hand," Don. "The Panel agreed that generally inhalation exposure" --

DR. BERGFELD: Jinqiu, do you need to comment? Would you like to comment?

DR. BELSITO: I agree that that sentence should be struck because it's just general inhalation exposure, and we're now obviously very concerned about airbrush and pressure spray deo. So yeah, that's fine.

DR. SNYDER: Yeah. I agree to strike that.

DR. BERGFELD: Jinqiu, you want to say something?

DR. ZHU: Yeah. I will delete that sentence.

DR. BERGFELD: Okay. You will delete it. Thank you for being on for us. All right. I think that we have dealt with the inhalation and we have agreed that it is the newest iteration that will go up. Yes, Jinqiu?

DR. ZHU: Dr. Belsito yesterday requested to delete one sentence on PDF page 86, the last paragraph, last sentence.

DR. COHEN: "However, the Panel noted" --

DR. BELSITO: The last sentence, David, in that paragraph -- the last paragraph on PDF page 86. It says "Accordingly, additional studies are necessary to evaluate the safety of consumer products delivered via airbrush devices." We've already sort of said that, but this entire area is dealing with just that. And it's not -- it's really more -- I just didn't think that sentence followed what we were talking about. We said that it's used in tanning salons and that in those cases they hold their breath -- they plug their noses, et cetera, et cetera.

And so it's "additional studies are necessary to evaluate the safety of consumer products delivered via airbrush devices." You know, what we're saying is, yeah, if you don't inhale them, they're going to be safe. And that's what's used in the tanning industry. We want to understand what is in the -- you know, what the size of the particles are, et cetera. I just didn't think that sentence followed.

DR. COHEN: You know, for airbrushing, it's not going to be an option to necessarily hold your breath for that long -- maybe while it's activated.

DR. BELSITO: I don't have any strong feelings. I just didn't feel that it sort of -- yeah, we're talking about all of the safety and precautions for tanning that we then say, well, we need to look at safety precautions or additional studies to evaluate safety. It seems like the tanning industry has done that, and then, you know, we could comment that we need to further understand how airbrush technology is used by consumers for applications of makeups and what the diameter sprays are. You know, we need to further understand the consumer use of these products for application in cosmetics. I just thought it didn't follow from what we were saying.

DR. LIEBLER: Just the term (audio skip) is inappropriate anyway.

DR. BERGFELD: I'm sorry, Dan, we didn't hear you.

DR. LIEBLER: Just the term "consumer products" in that sentence is not a good fit for our panel anyhow.

DR. BERGFELD: Okay. How about you, David? What did you want to say?

DR. COHEN: We could just move the sentence from there and put it towards the end, and we had discussed a summary at the end of this just outlining not only the importance of particle size but chemical properties, reactivity, duration, volume and dose of exposure all playing a part in the risk assessment for inhalation. And you can add that sentence in there as well and change "consumer products" to cosmetics.

DR. BELSITO: That's fine.

DR. BERGFELD: okay.

DR. SNYDER: So I know we're running short on time, but I would like to ask Carol page 82 on the inhalation exposure assessment -- I couldn't edit this document. Every time I tried to edit, I'd get a -- it does weird things and whatnot. But I would like to see this inhalation exposure assessment regarding the particle size follow the same sort of format that it does for the data that she asked for. In other words, I'd like to see it talk about sprays -- talk about propellant sprays, what the particle size distributions are, where they're utilized, aerosolized sprays, pump sprays -- follow that same sequence because that's what I always look at when I look at the frequency of use data is a I say okay, are there inhalation exposures and which types are they?

And I'm even going to do it more now going forward with this document as we do these ingredient class grouping specific templates. And so then you've got to have the airbrush in there because now we understand there's airbrush nanoparticle and non-nanoparticle. And so I would like to see this document kind of follow that same sequence so it would be easy to utilize it -- to go to this section and say okay, how are we going to wordsmith this because we know the particle size distribution for propellants are in this range based on the no tox data, based on the low concentration of use, max concentration of use?

There's no concern. So right now it's kind of all mixed up with pump sprays and propellant sprays. And, again, I think this also leads to we need to have a discussion down the road as to what kind of data do we want Carol to get for us. So can we get better details on those uses that are sprays?

DR. BERGFELD: Well, essentially, Paul, you're asking for reorganization of the document according to what you've stated following the directions of the Women's Voices of the Earth's response to us?

DR. SNYDER: Well, just this one section here in particular because to me this is the most critical section right here.

DR. BERGFELD: Again, what --

DR. SNYDER: I thought the document was excellent. It just needs to be in a fashion that's easy to get the data from it.

DR. BERGFELD: And that was on the PDF 81 that you started?

DR. SNYDER: Page 82.

DR. BERGFELD: 82. Okay. Well, I think Jinqiu can do that. Can you not? That seems to be a reasonable approach.

DR. ZHU: Will do.

DR. BERGFELD: Okay. Any other comments about the document? If that's so, then perhaps it should go up after the next meeting rather than go up immediately. Is that correct, Bart?

DR. HELDRETH: It's up to the Panel. To me, it sounds like the content isn't changing. We're just doing some minor editing to rearrange it and put it in an order that's consistent with the rest of the review process.

DR. SNYDER: I agree with that, and I'll send those comments to him so he understands what I'm talking about.

DR. BERGFELD: Okay. So unless anyone else has a comment, it sounds that that's a reasonable approach to treat as an edit and allow it to go up this year before 2022. Okay. Jinqiu?

DR. ZHU: Yeah. One more point. (Audio skip) suggest incorporating (audio skip) information, at least, from the memo dated October 2018 to the document. Does the panel agree with that?

DR. BERGFELD: Bart, can you clarify that for us?

DR. HELDRETH: What page are we talking about, Jinqiu?

DR. ZHU: No, I mean the CRSSC sent to incorporate more information. They're sample calculations in the document.

DR. LIEBLER: I also brought this up yesterday endorsing the council's recommendation. This is PDF 88. Jinqiu, when you were talking, you were breaking up and freezing. That's why nobody understood you.

DR. ZHU: Oh, okay.

DR. LIEBLER: But the request was for the sample calculations to be added from the 2018 council memo to flesh out the descriptions of the bulleted tier 1 and tier 2 examples, and I thought that was a good idea.

DR. BERGFELD: Okay. Will that take more time to do than just an editorial?

DR. BELSITO: No, it's already there.

DR. BERGFELD: Okay. Any other comments? Well, thank you very much, Jinqiu. Wonderful job and obviously a moving document to be looked at probably at least annually if not more as the issues come up. So we'll move on to the second to the last item, methacrylate ester monomers. Dr. Cohen.

## **DECEMBER 4-5, 2023 EXPERT PANEL MEETING**

### **Cohen Team Meeting - December 4, 2023**

DR. COHEN: Now, the next is the inhalation document and I thought it was actually very good. We can just open with any comments.

DR. BERGFELD: Well, I've got a comment that these are all living documents and so they're up to change at any time there's a need to do that.

DR. SLAGA: Yeah. It's very good right now so. But may change in the future.

DR. COHEN: Well, any other comments about it? I'm getting the impression that as the technologies for these sprays improve, the volume or the percentage of the respirable particles keeps increasing.

DR. BERGFELD: Absolutely.

DR. COHEN: And our boilerplate is used almost as a shield for us not to have to worry about it, but it looks like it's getting to a point where we got to worry about it more.

DR. BERGFELD: I think the FDA has to help us.

DR. ROSS: I agree.

DR. COHEN: In what way, Wilma?

DR. BERGFELD: Well, they have to inquire about these, and the nanometer particles are the smallest particles that are being dispersed. I mean, we cannot do all that ourselves, there has to be some guidance out of the FDA or what is safe.

DR. COHEN: Do we issue guidance or a comment to FDA?

DR. BERGFELD: We can ask a question. You know, we can ask them to do something. We can tell them we're having difficulty with this kind of delivery system and our impression is that the particles are getting smaller and more respirable. Could they give us guidance how they're handling it?

DR. COHEN: But, Wilma, are they handling it?

DR. BERGFELD: No. But I think they could be spurred to handle it. I'm trying to figure out ways to get a response from them. It'll be nice to have a response.

DR. ROSS: That's fair.

DR. TILTON: Generally, we have a boilerplate because a lot of times we don't know detailed information about

what the ingredients are delivered. So, we don't -- we can't estimate particle size.

DR. COHEN: But, Susan, we use the boilerplate that says it kind of reads we're comfortable with this because we don't expect most of these particles to be respirable. Like we use the boilerplate as a comfort tool for moving onto safe as used.

DR. BERGFELD: No, I thought we were inferring that this was insufficient, and we were uncomfortable with these aerosol products.

DR. COHEN: Well, we made a stand with the airbrush, right? We made a stand with the airbrush and the question is, is it starting to get gray with some of these other aerosol products? That's what I'm getting at here is it looks like a large fraction can be less than ten microns, right?

DR. BERGFELD: Yeah. Very scary. Very scary. Can go right through the skin. Everywhere. Even mucus membranes, obviously.

DR. COHEN: On page two it says, "However, a study published in 2023 reveal that among 15 propellant-based hair sprays currently available on the market an average of 15.25 percent of particles measured at an aerodynamic diameter less than ten microns --"

DR. BERGFELD: Right.

DR. COHEN: "-- with a range of 0.15 to 32 percent." So, our boilerplate may not have the same value it used to. Right?

DR. TILTON: It is making assumptions that the delivery is based on sort of traditional aerosol delivery. As opposed to any of these newer technologies or formulations, as in dry shampoos.

DR. BERGFELD: Well, more than that. The chemist and, I guess, the scientist are learning how to make these particles smaller and smaller and smaller and in dermatology for the cutaneous application this is advantageous because it gets into the skin that does something biologically active and the other thing leaves no residue on the surface. So, we've been aware of this.

It's been a really awful situation including with the sunscreens with the zinc and titanium. There was an FDA, I guess, large meeting a number of years ago -- maybe 20 at least -- where they showed the toxicology of the titanium particles and zinc particles getting into the blood system from the skin application because the particles were so small and being toxic to organs.

And it took them, what, 30/40 years to okay the sunscreens? That was partly because of the particle size.

DR. COHEN: Yeah. I mean, what I'm getting at is should our boilerplate be more robust in saying our assumptions are based on a certain -- I don't know what the fraction is. Like, what fraction makes us more comfortable. But I'm pretty sure 15 to 30 percent respirable is not comfortable, right?

DR. BERGFELD: No.

DR. COHEN: So, when I reread this, I got less comfort, not more comfort.

DR. BERGFELD: Maybe that can be an action internally to take a look at the boilerplate and then let us comment as a panel.

DR. COHEN: Susan, what are you thinking about the boilerplate, right, because we're using our boilerplate as a comment for us to move on to clear. It's not like we're not looking at this like we do with the airbrushes.

DR. BERGFELD: I think we're using it to be like non-sensitizing/non-irritating in the conclusion. So, it should not have respirable particles.

DR. COHEN: No, but we say because there aren't respirable particles we're moving on.

DR. BERGFELD: Well, maybe we should make it the negative a part of it. Reverse that a little bit. They should not have just like it should not be irritating should not be sensitizing in the final formulation.

DR. COHEN: We need to reevaluate our boilerplate, right?

DR. BERGFELD: Right.

DR. TILTON: Yeah, because typically we don't have that information.

DR. BERGFELD: Right.

DR. COHEN: No, we don't. We don't. But we make assumptions that if all coming in under this general term, like this old definition of pump sprays.

DR. BERGFELD: Right.

DR. COHEN: You know, like big droplets coming out.

DR. ROSS: Yeah.

DR. BERGFELD: Not so.

DR. COHEN: It's not. It's not that. One other thing, on page four the end of the first of the big, big paragraph, it says, "notably the nanomaterials did not display potential to translocate beyond the lung into the blood compartments." It says, "besides one, lungs, very small particle amounts were detected only in lung associated lymphoid nodes. The authors concluded that evidence was lacking to suggest that nanomaterials could move beyond the pulmonary region following a simulated occupational exposures."

I think if you're winding up in pulmonary lymphoid tissue, you've already demonstrated the capacity to move. They're coming out of lung parenchyma; you're coming out of the alveolus and going into a lymph node. To me that is movement, that is carry away. I know the author said that, but I don't know if I agree with that. Susan, what do you think?

DR. TILTON: I mean, it's making reference to an agglomeration, and I made a note here, actually, with regard to this paragraph that I mean, we should note that agglomeration is dependent on the formulation so it's possible that some of these products are formulated to minimize agglomeration of particles. And I think specifically here talking about getting into the blood system, but I don't know if you can assume across all formulations that agglomeration is going to prevent absorption.

DR. BERGFELD: I think we redo the boilerplate to make it more insufficient or so to the concept but more insufficient.

DR. COHEN: Okay.

DR. ROSS: Yeah. I mean, David is right in the sense that we do use this boilerplate as a platform to --

DR. BERGFELD: Move on.

DR. ROSS: -- yeah. Yeah, I'm just looking at the conclusion of the octoxynols, actually, and that's what we did there. We brought on the iteration from the previous panel, looked at that there. You know, looking at the old aerodynamic diameters and saying this is not relevant based on the sprays but as David pointed out in the intro it's now relevant.

DR. COHEN: Yeah. It's not an accurate boilerplate anymore and what we have to do is we have to transfer some of the responsibility to minimize the respirable fractions back to the manufacturers of the product and the dispensing manufact- -- the mechanical sprayers. They're probably two different people. You got your group making the material and they're trying to decide whether they want things to agglomerate or not and then you got your device maker who's also part of this. Right? That may make these ultrafine sprays.

DR. ROSS: Are the devices CPSC? Are they Consumer Product Safety Commission or are they FDA?

DR. BERGFELD: No, I think they're device.

DR. ROSS: Device?

DR. BERGFELD: Well, it's a part of the FDA but the device section.

DR. ROSS: Okay.

DR. COHEN: It's a delivery system.

DR. BERGFELD: Yeah, but under device, I think.

DR. COHEN: Yeah. Yeah. I know, it's a delivery system so I really think -- okay. We're all in agreement. It's just that this comes down to the boilerplate and I wonder if we could in that fourth page just dig a little deeper into this issue about the author's conclusion. I just don't know if I buy it. Okay. Everyone's hanging in.

### **Belsito Team Meeting - December 4, 2023**

DR. BELSITO: Okay. So, then we're moving on to the inhalation doc?

DR. HELDRETH: Yes.

DR. BELSITO: Admin Inhalation. I had no substantive comments, but I thought it could be tightened up a bit. That there was redundancy throughout the report.

DR. SNYDER: And I think that's a consequence of it being a living document, so I think that it's the time for it to have some consolidation, maybe, and elimination of some of those repetitive sections.

DR. BELSITO: I don't know how many times we have to say data from the Netherlands National Institute for Public Health and Environment. But I didn't wordsmith it. Curt and Allan, comments?

DR. RETTIE: On PDF 91 I was just struck by the statement in the nano material section. It says, "Notably the nano materials did not display potential to translocate beyond the lung and the blood compartment and the evidence was lacking to suggest that nano materials could move beyond the pulmonary regions following simulated occupational exposure." I don't know this area very well. That just seemed very positive to me. Is that really a fair reflection of the safety aspect? It may well be, I simply don't know. Paul?

DR. SNYDER: I would assume so. It's referenced. I didn't pull the reference -- the original reference -- but he's referencing that so I would assume that's correct.

DR. RETTIE: Which reference are you looking at? I didn't see a reference there. It's reference 41?

DR. ZHU: Yes. I think so.

DR. RETTIE: Yeah. Yeah. I'll just go and take a closer look at that. I just felt it was very positive and didn't know if that was fair to be that positive. Easy to check.

DR. BELSITO: Curt?

DR. KLAASSEN: Yeah. I definitely think that this reads like it's been written by the committee and it's kind of been written by sections and it needs to be smoothed out or it'd be nice if it was smoothed out. It's difficult to read as it is now. I thought in the background, the second paragraph, the first sentence bothered me right at the beginning. It says that, "The deposition and absorption of gasses and vapors in the respiratory tract depend mainly on water solubility and reactivity with the fluids or other components of the surfaces of the airways."

I mean, just thinking about that we usually think about lipid soluble compounds going across membranes much more than water soluble and so things like chloroform, ether, et cetera, which have been used as anesthetics, are definitely very lipid soluble. So, I kind of wondered about that sentence and maybe if it -- well, there are a couple of references which I haven't gone to look at. I wonder if that might be maybe talking about (inaudible) gasses or something rather than in general.

For example, absorption of water in soluble, non-reactive gas is negligible. I mean, this is the way we absorb solvents in the factory -- people that are working the factory -- these chlorinated solvents, they sure aren't water soluble. I don't know, that really bothered me. But I didn't go any further. So, I guess if we do rewrite this or look at that, I would suggest make sure that some of these statements that we make aren't due to the specific group of chemicals and if it is due to a special group of chemicals, then that should be noted.

DR. BELSITO: Okay. Any other comments?

DR. SNYDER: None for me.

DR. BELSITO: Okay, so if not, we'll move to the final.

### **Full Panel – December 5, 2023**

DR. BELSITO: This has been a living document, and I think it's time that it be cleaned up. It was extremely redundant and really needs to be completely rewritten.

DR. BERGFELD: Edited.

DR. BELSITO: Edited, right, and looked at again. So it needs to be --

DR. BERGFELD: And who are you recommending do that? Can that be done in house, Bart?

DR. HELDRETH: It's up to the Panel. You know, the more input we get from the Panel, for verbiage they'd like to see in there, the easier it'll be our job to write the Panel's thoughts and wishes in there.

DR. BERGFELD: Susan, any comment?

DR. SNYDER: I'd be happy to give it a thorough editorial review if you could send me a word document. I still can't edit these PDF's, so if you would send me a word document I'd be happy to give it a go.

DR. HELDRETH: We can certainly do that.

DR. BERGFELD: I thank you for your volunteering. I would suggest that we not have so many -- well, I want to say a sea of words, so we can somehow get rid of that thought when you start to read this, just a sea of words.

DR. BELSITO: Yeah.

DR. BERGFELD: And, then looking back at the next resource document that we're going to be looking at --

DR. BELSITO: Well, just one more comment here that --

DR. BERGFELD: No, I don't want to go on. I just want to finish this thought, Don. The Nitrosation one, Ron Shank went through this. He categorized it, easy to read, and I would like to use that as the model for the Inhalation, if we could. I'm sorry, Don, go ahead.

DR. SLAGA: Can we also get Ron to look at it, from an outsider?

DR. BERGFELD: Bart, is that possible?

DR. HELDRETH: Yes.

DR. BERGFELD: Thank you. Don?

DR. BELSITO: I mean, if we're having two people edit it, unless you --

DR. BERGFELD: I think Paul should do it first and then maybe Ron.

DR. SLAGA: Yeah.

DR. BELSITO: Okay. Or, otherwise you'd have to put it on a OneDrive so they can do it simultaneously.

DR. ROSS: The key thing is getting the headings in the right place so that people who are using it as a resource don't have to read the whole document, they could just stroll to the left.

DR. BERGFELD: Right, exactly.

DR. BELSITO: Right. And, the only other thing, when you're editing it, Paul, on PDF Page 90, where it says the fraction of respirable particles that would be admitted by applying cosmetics with airbrush devices remains ambiguous. I would not use the word ambiguous, I would say remains unknown.

DR. COHEN: Okay. Don, I agree with your comments. As I was reading this, though, I started to get a little more concerned about our respiratory boilerplate, which you described us using in the Yeast circumstances -- you know, there was new verbiage on Page 2 of the report that really struck me. It says, however a study published in 2023 revealed that among 15 propellant-based hairsprays currently available on the market, an average of 15.25 percent of particles measured at an a --

DR. BELSITO: What PDF page are you on?

DR. COHEN: I'm not on the PDF. It's under Inhalation Exposure Assessment.

DR. ZHU: It's 89.

DR. COHEN: Yeah, 89. I just printed the report out to read it. It's the second paragraph. The paragraph starts, both pump strays.

DR. BELSITO: Yeah.

DR. COHEN: Right, go down to the middle where you see a however. It's highlighted.

DR. BELSITO: Right.

DR. COHEN: So, aerodynamic diameters of less than ten microns with a range of up to 32.27 percent. So, I think we use the inhalation boilerplate as a method for us to move on to approve these products. But as the technology on these sprays is efficiently getting large fractions of respiratory particles, I'm not sure the boilerplate is covering -- I think the boilerplate was accurate for older pump technologies, but some of these new devices are creating respirable fractions more and more. And I don't think our boilerplate covers it the same way anymore. Is it really a very inconsequential amount is going to be respirable when we're looking at a third can be less than ten microns?

DR. BERGFELD: Curt, Tom, Susan, Allan, someone respond.

DR. SNYDER: Well, it's certainly is pertinent to exposure, you know, and if there's known toxicities. So, I agree we probably need to think about that and discuss that more thoroughly.

DR. KLAASSEN: I think in most circumstances the dose is still going to be very low, because you're only inhaling it for less than a minute. Rather like in these studies have we see they are inhaling it, the animals, for three hours and what have you. So, I think the amount we probably need to pay more attention to, if we can get some numbers for that.

DR. ROSS: That's certainly true to that, but, I mean, these things are going down. As David pointed out, you know, this technology is improving all the time. I think we're going to have to do something to address this with respect whether it's now or whether it's near future. We're going to have to address it at some point.

DR. KLAASSEN: I agree.

DR. BELSITO: Well, particularly when we have absolutely no inhalation toxicity on a material that is used in a spray. And we've been using this to clear that material.

DR. ROSS: Yeah.

DR. COHEN: Yeah, and I think to Curt's point, it probably is an affect from the low exposure, but that's not what the boilerplate says. The boilerplate discusses the size, the distribution of the particles.

DR. BERGFELD: Particle size.

DR. KLAASSEN: And what I'm saying is that we maybe need to move more to the amount rather than the sizes. But, yes, definitely we need to spend some more time on this. But I think the saving point will be the amount.

DR. SLAGA: Yeah, the amount is very important but we still need to know the size.

DR. KLAASSEN: Of course, but, if there's only 50 picograms that gets to your lung, then who cares?

DR. ROSS: Yeah, I think you're both correct. Susan, you've got any words of wisdom on this? We talked about this in our meeting yesterday.

DR. TILTON: Yeah, we did talk a lot about trying to understand the new technologies and new formulations. I think focusing on it now and recognizing that the boilerplate is about exposure, we may need to just evaluate certain instances where we will need toxicity data. But we should also recognize, I mean, these are averages across different types of technologies. And, there may be a point at which some of these we should pull out separately like dry shampoos, these aerosol powders, and consider them separately because they seem in the studies to consistently be in that higher group. And, just think about when we're evaluating ingredients in some of those products. But I don't know how much information we're going to have. We don't typically get a lot of information, when we review, about how it's delivered for certain ingredients.

DR. ROSS: Yeah, that was Don's point. We don't get much in these dossiers at all with respect to inhalation.

DR. BERGFELD: Well, it seems to me that this is a rather big job. We can take the job and move -- see what we can find out about other techniques and things that we can do about amount plus size. And maybe we can put this on the agenda for next meeting or the following meeting to see if we can modify some of our boilerplates. Maybe we need more than one title?

DR. COHEN: That's a good idea, Wilma; maybe one size doesn't fit all.

DR. BERGFELD: Right. That would be helpful. Anyone else wants to talk about the Inhalation Resource Document. We're going to have it re-reviewed by Paul, and a second review by Ron. We're going to look at the boilerplates. Jinqiu is going to head that up for us a little bit and then we can re-discuss it.

DR. HELDRETH: Yeah, I also propose that once Paul and Ron have gone through and cleaned it up to their satisfaction that we put it out for a formal 60-day comment period. So folks like at FDA or in industry that has

inside laboratory knowledge may have a chance to really provide input as well.

DR. BERGFELD: I think the Panel needs to see it before it goes out.

DR. HELDRETH: Okay.

DR. BERGFELD: After those reviews.

DR. HELDRETH: We can get it done.

DR. BERGFELD: Yeah.

DR. BELSITO: Would it be of interest to have someone who is knowledgeable about the various spray techniques that are used in cosmetics discuss with us what the -- I mean, there must be like criteria, why do you create propellants spray for one thing versus another. You know, why is the aerodynamic size of dry shampoos smaller than others? How does that work? What is the, sort of lack of a better word, framework for deciding what kind of propellant device you use for a particular cosmetic?

DR. COHEN: That's a great -- you mean like a talk on it, Don, right?

DR. BELSITO: Yeah, like in, you know, what size range do you want for a dry shampoo? What size range do you want for an underarm deodorant? Why would you choose one delivery system over another?

DR. BERGFELD: The FDA also has a device unit. Could we hear from the FDA about the review of devices for cosmetics? Anybody here?

DR. HELDRETH: Janet Zang.

MS. ZANG: Wilma, devices are devices; they're in a different Center. Cosmetics, we're basically focusing on the ingredients. So if you want to --

DR. BERGFELD: You don't share information?

MS. ZANG: If we need information we can reach out to them and sometimes they -- we do crosstalk. But it would be more helpful if you can send us what exactly the question you want to ask and we can definitely approach them.

DR. BERGFELD: I'm understanding then we would confer with you and you would confer with the device people? Or would we also talk to the device people?

MS. ZANG: Have you -- I'm not sure.

DR. BERGFELD: We have not talked to them.

MS. ZANG: Have you ever reached out to the device people before?

DR. BERGFELD: No. But we keep talking about devices so I suspect we need them in the circle. Well, let us pose some questions to you, and see if you can ask the device individuals over there. I did serve on the device committee at one time, so I am familiar with it.

MS. ZANG: Sure.

DR. BERGFELD: So, we can develop some questions. We have our two leaders from the teams to help us develop those with their teammates. And we'll field and see what we can get for the next meeting, okay?

MS. ZANG: Yes.

DR. KLAASSEN: I have a suggestion. It turns out that inhalation toxicology is a field that's become smaller and smaller, because the equipment that you need and the people that you need to do inhalation studies is very expensive. And large number of people, you need physicists, etcetera. And there is one place in the United States that specializes in this, and that's down in New Mexico.

And one of the people down there is Matt Campen. He works at the University as well as the Inhalation Institute. And, I think he might be a good person to contact that if he can come and give us a lecture. Or maybe he knows people down there that are even better than he is, could give us a lecture of what is the state of the art of inhalation. And, one can tell him our specific problems when we're talking about inhalation from hairspray, underarm deodorants, and even powders put on the face. And see if they can help us. At least that's where I would go to get information.

DR. BERGFELD: Can you send the address over to Bart.

DR. KLAASSEN: Sure.

DR. BERGFELD: He's at the University of what?

DR. ROSS: University of New Mexico.

DR. BERGFELD: New Mexico.

DR. ROSS: The University of New Mexico in Albuquerque. He was up giving a talk for us a couple of months ago. He's very good.

DR. SNYDER: It's the Loveless Biomedical Institute. It used to be called the Loveless Inhalation, now its name is now Loveless Biomedical.

DR. ROSS: Yeah. And, I'm not sure he's going to get at the cosmetic issues, but you could always split the presentation and have Matt and then someone else talk about cosmetics.

DR. COHEN: Yeah, I agree, I think Don's point to why you pick a certain size, or why you pick a delivery system would be helpful. And then, this person from New Mexico can help us interpret the toxicology.

DR. BERGFELD: Very good. I think we have a plan than for the next meetings. I'm not sure it'll be the next meeting. Bart, I think that developing some questions for FDA would be something we should do. And if you will contact individually the team leaders and their team members, see what questions they might ask. We can put them together in a summary.

DR. HELDRETH: Okay.

DR. BERGFELD: Okay, let's move on then to our Nitrosation Resource Document. I want to call out Dr. Ron Shank again for his help. And we do miss him. Dr. Cohen?

## **SEPTEMBER 30 - OCTOBER 1, 2024 EXPERT PANEL MEETING**

### **Cohen Team Meeting - September 30, 2024**

DR. COHEN: So, why don't we go to inhalation, and I have to thank you personally for an amazing document you put together on this and it is obviously a living document; it's really well done, and I have some comments and questions, but I think this is just for general comments at this meeting, right? We're just commenting on it. I can make a few starting comments.

We do use occupational exposure limits in here as sort of an anchor, right? We use the data from these occupational exposure limits, and these are OSHA PELs you're using sometimes, right? So, OSHA PELs are based on an eight hour day, five days a week for an adult worker who's going to work 30 years. I think that's the baseline.

The question is, I think it's a good number to start with, but I think people using personal hygiene products and cosmetics will be using them very early in their life, being used on a regular basis or level, although probably not eight hours a day, five days a week and will be using it for their lifetime. So, I think we need to use caution just using an OSHA PEL.

These are healthy adults working in industry, accepting a certain risk with their job and also, when appropriate, heavy personal protective equipment when needed and having a workplace that is hopefully appropriate for the kinds of exposures that they may have. And I think that is not the case when you're in a small windowless bathroom somewhere.

We have a discussion about dry shampoo having a very large percentage of droplet sizes, rather respirable, and do we look at, what, five minutes of the PEL would look like for OSHA to compare it to what five minutes of exposure

would be like? I'm not sure. It's just for contemplation. On PDF 7, there's a comment, "However, the Panel noted that the majority of droplet particles would not be respirable to any appreciable amount."

But I think it's clear in here that certain aerosol products have 25 to 30 percent respirable fractions like dry shampoo and underarm deodorants, and I think when we use the term majority, we're hiding behind the semantics of that. Twenty-five to 30 percent is a minority, but it's a lot, right? So, I think we need to think about that.

DR. TILTON: That's from the current boilerplate where you're referencing?

DR. COHEN: This was PDF 7 of the -- I think of the report.

DR. ZHU: Yes, that's the current boilerplate.

DR. COHEN: Current boilerplate.

DR. TILTON: Okay.

DR. COHEN: Yeah.

DR. TILTON: So, that's what's up for discussion for editing. Yeah. Yes.

DR. COHEN: And also, we have a comment, "Furthermore, droplet particles depositing in the nasal pharynx, or tracheobronchial region of the respiratory tract present no toxicologic concerns based on the chemical and biological properties of these ingredients." So, I think we have that comment for deep pulmonary toxicity and systemic absorption.

The question to the group, and to you, is, do we have enough confidence that the current respiratory tox that we have protects against chronic upper respiratory exposure, right? I think there are many chemicals that we adjudicate that are skin irritants, they'll likely mucosal irritants, and the term no toxicologic concern infers that repetitive mucosal exposure will have no long-term impact on structure, function, fibrosis, et cetera.

I think we need to modulate the tone of these, because it just seems like, well, if it just gets into your nose and throat, we've got nothing to really worry about unless we do, right? Might we look at ACGIH short term exposure limits when we have that capacity? TLVs tend to be more conservative. I think we need to rewrite the boilerplate that's not so resolutely assuaging concerns. We don't always have the answers regarding that, and we do have modern delivery systems that deliver a high fraction of respiratory particles, and that's the size of concern. So, what do you got, David? And then, Susan, you're going to take it.

DR. ROSS: I would agree with those comments. I mean, I think clearly dry shampoos and other products there are a much higher percentage of respirable particles than we were thinking of previously. So, I think, yeah, I thought your summary was good, David, because I do think we have to change the tone of that a little bit. And I've got a whole bunch of minor editorial stuff in here. But I think the major point -- David summarized that nicely.

I think the other point for me is that we're beginning to see some NOAECs, so no observed adverse effect concentrations, in the respiratory data. And again, it's rare, but when we see it, I would encourage us to use some form of quantitative risk assessment to actually come up with some degree of relative risk there that you could put a number on. And so, as those come through, I encourage us to do that. But, also, I do think we have to change the tone of that document.

DR. TILTON: I agree with both of your comments. I think the document that was put together was extremely helpful in reading through with information about specific product formulation and uses and recognizing that the boilerplate does not currently come to conclusions that support a lot of the information that's in this document.

So, one question I have, though, actually before kind of talking about the document in more detail. So we're talking about the boilerplate today. The information that is in this particular document isn't in the inhalation reference documents.

DR. ZHU: It's there. The particle size data is there but the calculation is not there.

DR. TILTON: Okay. Is the idea that some of this information will eventually go into the inhalation reference document?

DR. ZHU: Of course. Of course.

DR. TILTON: Okay. Because I mean, we can't summarize all of this in a boilerplate and that's what I've been really thinking about, kind of struggling with, is how do we create a boilerplate that is generic enough? Or maybe it's just flexible enough that we can include information on specific uses or formulations.

Sometimes the conclusion is either because we have no inhalation toxicity data, but we're basing it on our knowledge of the lack of systemic toxicity that would mean that there wouldn't be very much concerned if it were inhaled and absorbed. There's a lot of different scenarios that we're typically considering when we're reviewing a report and how does that get summarized into a boilerplate?

Or is the boilerplate primarily in the situation where we essentially have no data, and we are trying to have a reference paragraph that references the potential for exposure and other possible mitigating points. I mean, we want to make it as accurate as possible. And so, currently it's not very accurate when it broadly generalizes lack of exposure when we do have information on the potential for exposure even if a lot of these estimates are very conservative. Which I think is a great way to approach it is to have these conservative calculations.

But I'm just thinking about when boilerplates are typically developed and how they're applied by the CIR. How easy is it to come up with something that's flexible enough that we're not already going to be evaluating it on a case-by-case basis anyways.

DR. COHEN: I have two separate paragraphs that I tried with this. This one was one I mulled over a long time. One was the percentage of respiratory droplets in cosmetic sprays varies based on the products delivery mechanism and formulation. For most cosmetics sprays, the majority of droplets are non-respirable. Meaning they are typically deposited in the nasopharynx and tracheobronchial region and do not penetrate deep into the lungs. However, the long-term effect of chronic upper respiratory exposure to some chemicals in these sprays remains unclear.

Another paragraph, as some formulations and delivery systems have demonstrated, higher proportions of respiratory droplet sizes such as, but not limited to, dry shampoos and deodorants, where up to 30 percent of the particles, may be small enough to be inhaled into the lungs. Despite this, safety assessments suggest that short term intended use may pose no greater risk than other cosmetic aerosols. And then, however, the current data is insufficient to conclusively determine whether these products significantly increase the risk of lung exposure.

It's a start, but I saw through the original boilerplate language.

DR. TILTON: I mean, I would support moving in this type of direction. I'm assuming that we would reference the inhalation reference document as part of the boilerplate.

DR. BERGFELD: We don't usually reference boilerplates.

DR. TILTON: I mean, reference the --

DR. BERGFELD: Discussion.

DR. TILTON: -- the resource document. I'm using the wrong term.

DR. COHEN: So, this is just going to be a general discussion tomorrow, right? I mean, we're not voting on anything.

DR. BERGFELD: It's still in development, as far as I've seen, and I'm uncertain that when you see that the particle sizes, when they're large, it can go -- or the smaller ones go in further. That's what impression I have, and chronic use could put more in there. And you stated, or someone stated, that 25 percent are responsible or in some instances.

DR. COHEN: In certain delivery systems and certain product formulations.

DR. BERGFELD: And there's no way to tier that as to what would be acceptable five percent/ten percent, 25 -- I would think 25 is significant. No, I can't do it. It's not my area of expertise.

DR. COHEN: No.

DR. TILTON: Well, and it depends on the ingredient.

DR. BERGFELD: The active ingredient and the size.

DR. COHEN: But this boilerplate that we have we're putting all the time as sort of a shield, right? After we had some of those lectures two years ago or something, we're seeing very creative devices make mists that are very small particles. I just think that that boilerplate just doesn't hold up anymore because the term majority, yes, so what if 49 percent respirable; the majority are non-restorable? Any thoughts from you guys on this?

DR. EISENMANN: I was a little concerned, are you using spray to support loose power products?

DR. ZHU: So, I think in one literature the dry shampoo is classified as one type of loose power.

DR. EISENMANN: I don't know, I think it's a spray.

DR. ZHU: And this is in an important review paper.

DR. EISENMANN: They make the call, but I think it's a sp- --

DR. ZHU: The review paper -- let me check.

DR. COHEN: So, you're saying that the dry shampoo is a spray?

DR. EISENMANN: Correct.

MS. KOWCZ: It should not be classified as a loose powder.

DR. EISENMANN: And I know using it to say with sprays, but when I think of a loose powder I don't think of a dry shampoo, I think about --

DR. COHEN: Press powder.

DR. EISENMANN: -- press powder.

MS. KOWCZ: Foundation powder.

DR. EISENMANN: Right.

DR. COHEN: Or a loose powder that's applied with a brush.

MS. KOWCZ: Like a blush, yeah.

DR. EISENMANN: Right. So, I'm just a little concerned about using dry shampoo for those product categories.

DR. ZHU: But in that published study, the dry shampoo stays in the powder form, so how to classify --

DR. EISENMANN: But you're still spraying it.

DR. ZHU: Yeah, but I also mentioned in the review paper type of principles for safety evaluation of cosmetic powders. In that review paper it clearly states loose powders, including finishing powders, foundations, perfume, the body powders, cheek powders, eyeshadows, dry shampoos, or others. So, dry shampoos is there.

MS. KOWCZ: But we don't have to agree that that's correct, though, because the dry shampoo that you're formulating with, you're formulating the powder -- but the spray is what delivers it. It's not like you're -- it can't be compared to loose powder or loose blush or the powder type foundations that people use. It's not the same thing. So, I'm surprised that they would categorize it should dry shampoos as a powder because it's really not.

Dry shampoos are a delivery system for that.

DR. COHEN: Would you be able to find out if all of the dry shampoos that are marketed, that will respond to you, are they all sprays?

MS. KOWCZ: We can definitely find out.

DR. COHEN: I see the point, though, that you're making.

MS. KOWCZ: We can ask. I don't know if we'll get the answers to what we want, but we can definitely seek to get the information.

DR. COHEN: And I find a tricky thing with this whole thing is you have your formulations and your dry powders are in our purview, right? But taking a formulation that's in our purview and driving it through a device that's not in our purview gets tricky, right?

DR. EISENMANN: I wouldn't say it's not in your purview, just a spray product versus a dr- -- right now, I mean, I liked your suggestion, additional language maybe don't need to divide spray and powder and dry, but just the way it's divided currently.

DR. COHEN: Yeah, I get you.

DR. EISENMANN: You're talking about spray products and you're talking about loose powder products. So, I wouldn't call that to be a loose powder products.

DR. TILTON: I mean, there's also a distinction between pump sprays and propellant sprays, and the particle size that it was delivered out of those products are very different.

DR. EISENMANN: Especially, I think the paper -- if I recall correctly, in the paper the dry shampoos were spray products as far as I can recall.

DR. ZHU: Yeah, they call it propellant-based spray. But they have those in powder form.

DR. EISENMANN: No, it's not the data that the particle size is based on was a spray dry shampoo product. So that would be, to me, that's what it represents, not a -- I don't think it's appropriate to extend it to a loose powder product.

DR. ZHU: That's true. Okay. But the inhalation boilerplate language is not just based on loose powder, it's based on every type of cosmetic sprays. In 2018, industry saw need to data on propellant of the --

DR. EISENMANN: We're not arguing that shouldn't be used to develop the language for sprays, it should be. We just don't think it's appropriate to develop it to use that data for a loose powder product.

DR. ZHU: We just need to order the definition in the literature, like literature in that review paper I mentioned before.

MS. KOWCZ: Jinqiu, I think we just want to define it appropriately and correctly, that's all. We just don't want to equate the dry shampoo propellant type with your loose cosmetic powder. That's all. I mean, if we could just modify the language, that would be very helpful.

DR. COHEN: Okay. It's a minor editorial thing, it's not going to the heart of the analysis to that. So tomorrow we're just going to have a discussion. Is that right, Bart?

DR. HELDRETH: But if there's going to be changes to the Panel's boilerplate or to the resource document, there does need to be a consensus of the Panel.

DR. COHEN: Oh, yeah. Well, that'll be easy. Any other comments? Any suggestions on how I present this?

DR. ROSS: I think it would be good to have a plan as to how we move forward. I think we're going to send comments; who's going to pull those together. When are we going to see it again and those sorts of details. I think right now it's a bit nebulous in terms of --

DR. BERGFELD: You're all seeing what Curt Klaassen said to us about the inhalation part.

DR. ROSS: Yeah, I see that.

DR. BERGFELD: Okay.

DR. ROSS: And that, I don't know. Should that go in?

DR. TILTON: I mean, I think we just need to emphasize that the ten-micron criteria that are included is very conservative in terms of defining a respirable particle and especially if you're starting to think about what gets down into lower into the lung. It could be more like an order of magnitude lower than that.

DR. COHEN: I think it's easy, also, to get caught up to -- again, conflate issues. One, small respirable particles contribute to systemic exposure, right? And small respirable particles can lead to pulmonary disease and they're two separate things. And frankly, I don't know how these exposure calculations -- what the goal of them is because some can cause pulmonary disease without having systemic exposure, right? Like silicates, right?

It's not like I worry about them winding up in my kidneys, I worry about them being in the lungs. Whereas other particles will dissolve quickly and go systemic.

DR. TILTON: Yeah, I think previously, the boilerplate was used to -- mitigating statement about the fact that most - - regarding systemic toxicity primarily.

DR. COHEN: Yeah. Right. But when we have airbrush cosmetics that may not worry as much about certain particles being systemically absorbed but being deposited there for long periods of time, that's a different issue for

us. Even though we step away from airbrushes, these new pump mechanisms, these spray mechanisms, they're getting pretty sophisticated and getting pretty small -- those particles.

DR. BERGFELD: Because they work better. Because they get in.

DR. COHEN: No, I think from a cosmetic standpoint, they deposit better. They are indeed cosmetically more elegant and workable, right? So, the industry is providing what we're asking them to do -- give us better cosmetic products. It's just that fine line you cross.

DR. BERGFELD: Well, what hazards does that bring?

DR. COHEN: Yeah. Okay.

DR. HELDRETH: Yeah, for this boilerplate, I want to reiterate. I wouldn't want the Panel to feel like they have to use it even once we've agreed upon the verbiage there. You know, if it was like we're talking about dermal absorption and we just don't have the toxicokinetics data, we don't just say, well, things don't get absorbed, we ask for the data. We always want the Panel to be invited. We don't have to necessarily use this boilerplate if we're feeling shaky about what the actual particle size is or the mean diameter, or other endpoints that relate to respiratory tox.

DR. COHEN: So, in that vein, should we change our procedure that when we're looking at the dossier very early on, you know, we have that table that shows what data we have. Should there be boxes that check respiratory boilerplate, heavy metal boilerplate? We should be more firm because it always drops in and the eyes can go past it, right?

So, should we be more firm and say we did put the respiratory boilerplate in here or this one we need to stop and think a little bit more about what the boilerplate's saying.

DR. HELDRETH: Yeah. I mean, we could certainly do that. We could receive and make our SOP non-applicable until the Panel says, hey, we're comfortable with the situation even though we don't have --

DR. COHEN: But we should be prompted. I don't want it to be passive. It should be active. Maybe the writer can say, all right, guys before we move on, what are we doing with the boilerplates?

DR. HELDRETH: We could do that.

DR. COHEN: Yeah. Do you agree with that or no?

DR. ROSS: Yeah. I mean, I think having a checklist of which boilerplates could go in would be very useful. And I don't want anyone to rely on us to do it, but we could be asked. And, yes, yes, yes, and we could respond.

DR. BERGFELD: Have you all seen the boilerplate list that we have? We could maybe include a modified form of that with it in the document.

DR. COHEN: They're around, I've seen them.

DR. BERGFELD: We had them before but years ago.

DR. COHEN: Are they available online? I don't know.

DR. TILTON: They're not with the resource documents because I don't think that they're public.

DR. COHEN: Any other comments? Do you guys have any? Nothing. Okay. This is not going to get solved in one meeting.

MR. BJERKE: I do have one comment. So, what you can do with the boilerplate is clearly articulate what your assumptions are for the particle size distribution, and if that encompasses most of what -- most or all of what industry is doing then they're okay, but it'll call out if you have a delivery device that is outside of this box, then the manufacturer has to ensure safety inhalation. You can't use this as the default.

DR. COHEN: So that's assuming we know, and will we get -- I mean I'm trying to --

MR. BJERKE: There's no data that's submitted, I guess, from 2018.

DR. ZHU: Yeah, 2018. 2018 for propellant in deodorant, do you mean that data?

MR. BJERKE: For whichever products you're assessing.

DR. ZHU: In most cases when boilerplate language is used -- is using -- so the particle size data should be missing. Do you need the version that the boilerplate is based on the mist of the particle size data?

MR. BJERKE: Yeah, so I guess, for example, if you're looking at an aerosol deodorant and you want to use the boilerplate, you have to go back to the data and say less than this percent of particle sizes as reported by industry in 2018 is this percentage. If you vary from that then the manufacturer has to be able to support that inhalation data on their own. But what you guys are focusing on is what's within what industry has reported.

DR. COHEN: So, the present practices and concentrations.

MR. BJERKE: Exactly yeah.

DR. COHEN: It still wouldn't matter which chemical we're looking at.

MR. BJERKE: Absolutely. Absolutely. And like Bart said, you can choose not to use this. You can choose to modify it or when appropriate, you can choose to use it. But it's case by case, absolutely.

DR. COHEN: All right, I think we're going to have to just reword the boilerplate and then play with that live action as we go into the reports.

DR. BERGFELD: Well, I think that you've come to a decision, though, very important. The size, got to know it.

DR. COHEN: Yes.

DR. BERGFELD: Very important the vehicle of delivery, got to know it.

DR. COHEN: What we won't know is usually the --

DR. BERGFELD: Frequency maybe.

DR. COHEN: We won't know the type of device that's being used.

DR. COHEN: The what?

DR. COHEN: We won't know the device type.

DR. BERGFELD: That's what I said. How it's delivered, yeah.

DR. COHEN: Yeah.

**Belsito Team Meeting - September 30, 2024**

DR. BELSITO: Okay, the next is inhalation. And at the 2020 meeting we revised and then subsequently revised in December of 2023 to incorporate new findings on particle size distribution, particularly in dry shampoos. And we decided we need to modify our inhalation boilerplate. And then Curt sent some additional comments on particle size suggesting that particle size was actually larger in terms of what was respirable. Is that correct, Curt?

DR. KLAASSEN: Smaller.

DR. BELSITO: Smaller, rather, giving a larger margin of safety. So, that'd be Inhalation document here.

DR. KLAASSEN: Okay, I just sent those as some references of kind of what's out there, not necessarily saying that we needed or had to change. But I thought we should at least discuss this, and maybe you want to respond. You were kind of suggesting ten and a number of references now. And traditionally, I would say it has been ten. For the last fifty years, people have been talking about ten. But now there are references out there that have gone down to four to five. And you maybe know the literature better than I do. What are your two cents worth?

DR. ZHU: Yeah. But the thing is, the sample calculations were based -- I mean the published studies were based on the ten, so not based on four. So, the industry submitted the data in 2018. The propellant deodorant --

DR. KLAASSEN: Right.

DR. ZHU: -- particle size distribution data is still based on 10, not on 4. So, for us, we don't have much data on four. So, like most (inaudible) they define respirable particles based on 10, so that's the start point. I mean, if we based on 4, we need to identify additional studies and data. Maybe the industry can submit data for us. If we considered the less than 4 micrometer be considered respirable, then we need that data to start.

DR. BELSITO: But if we use 10, it's more conservative, right?

DR. ZHU: Yeah, that's true.

DR. SNYDER: Ten or less.

DR. ZHU: Ten less.

DR. BELSITO: Yeah, 10 or less.

DR. KLAASSEN: It's more conservative.

DR. BELSITO: It's more conservative.

DR. SNYDER: And I would think that there was an interested party and there's data that it could be five or less able to provide us that.

DR. BELSITO: Right.

DR. SNYDER: I mean, this has been out there for quite a long time.

DR. BELSITO: And it seems it is sort of -- ten is what's standardly accepted.

DR. SNYDER: Yeah. I was fine with leaving it what it is.

DR. KLAASSEN: Yeah, I have no problem leaving it. I just wanted to bring this up, that we were at least aware of this. And if maybe it could be said in the -- you know, give these references or something and say some people use four to five microns rather than ten. But to be on the safety side, we will continue to use 10 for this time. I mean, I don't know.

DR. BELSITO: Do we even need to comment on it?

DR. KLAASSEN: Well, it kind of indicates that we know the dataset that's out there and what people are thinking.

DR. SNYDER: I mean, we could put a caveat saying the Panel considers ten the threshold unless additional -- data to support less than ten is provided.

DR. BELSITO: Or we can put something after to say that there are reports that the respirable fraction, in fact, may be less than ten has been reported at four microns --

DR. SNYDER: As low as four.

DR. BELSITO: As low as four.

DR. SNYDER: Yeah.

DR. BELSITO: And to act conservatively --

DR. SNYDER: Yeah.

DR. BELSITO: -- and in accordance with other published reports, we will use ten.

DR. SNYDER: Yeah.

DR. KLAASSEN: That's exactly what I'm thinking.

DR. SNYDER: Okay, perfect.

DR. RETTIE: Just right.

DR. SNYDER: Yeah.

DR. KLAASSEN: Yeah.

DR. BELSITO: Okay. Jinqiu, in PDF 4, at the top of the page where we're talking about margin of exposure and you say, "To ensure consumer safety, margin of exposure should be at least a hundred for systemic effect, that is, dermal and oral exposure, and 25 for local effects in the lung, which is based on a default factor of 2.5 for interspecies." I thought ten was standard for interspecies.

DR. SNYDER: Intraspecies. Inter is --

DR. ZHU: Inter.

DR. BELSITO: It says interspecies.

DR. SNYDER: Yeah.

DR. ZHU: That statement is from the published literature. That --

DR. BELSITO: Two point --

DR. ZHU: Two point five. That's --

DR. BELSITO: You sure it's not changed? Intra -- 2.5, intraspecies, that's within. I mean, because interspecies I thought was always a factor of ten. There was never any difference in that.

DR. ZHU: That's the local effects. I mean, that may be based on the toxicokinetics.

DR. BELSITO: Curt.

DR. KLAASSEN: Well, what the problem with all of this really is a long, long time ago people tried to figure out how we can protect people, and so they just said, okay, let's make it -- if animals can be exposed at this dose and it doesn't produce toxicity, if we give one one one-hundredth of that dose, humans should be protected. And that's the science behind this whole thing.

DR. BELSITO: Yeah, it was.

DR. KLAASSEN: Right. And so, now to kind of make it a little bit more scientific, what is that really due to? Well, it's due to interspecies and differences going from rats to humans and going from various human sensitivity. So, we say now, like it's science, ten times ten equals a hundred. There's no science to that. Absolutely zero. So, this is a problem that we've run into. If it was completely up to me, I would say that we use a hundred-fold margin of safety. And if it's greater than a hundred, great. We don't worry about it.

DR. RETTIE: But use it across the board.

DR. KLAASSEN: Yeah. And not try to say how much is due to interspecies and intraspecies. What do you think about that, Paul?

DR. SNYDER: I think that's standard. I think that's fine. Yeah.

DR. KLAASSEN: Yeah. I mean, just use the hundred. There are chemicals that humans are less sensitive than mice, and an example is TCDD.

DR. SNYDER: Yeah.

DR. KLAASSEN: Yeah. So, this ten times ten is pseudoscience. They keep saying this ten times ten or ten times 2.5 or whatever. Just say that we used a safety factor of a hundred. This business of local effects in the lung, I guess where did that come from? That came from Reference 8.

DR. ZHU: Yes. It's --

DR. KLAASSEN: What is Reference 8? That's probably European people, right?

DR. ZHU: Yes.

DR. RETTIE: Yes.

DR. KLAASSEN: So, mainland.

DR. ZHU: It's from ECHA.

DR. KLAASSEN: Yeah.

DR. ZHU: Primary reference.

DR. RETTIE: Is the different numbers there -- written here in this paragraph for lung effects -- is this trying to reference or trying to reflect the concentration of certain types of compounds in the lung? The lung concentrates certain types of compounds, right, versus basics. So, is that why that's in there? It seems very specific.

DR. KLAASSEN: This is the first time I have ever seen this number from one --

DR. RETTIE: Twenty-five?

DR. BELSITO: Yeah.

DR. KLAASSEN: You know, and --

DR. ZHU: Yeah, because --

DR. KLAASSEN: I mean, you can make up anything you want to. It's not science. That's why leave it at a hundred.

DR. BELSITO: I would.

DR. ZHU: Because this sentence from I believe -- I think the review paper titled, "Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment." This is kind of --

DR. KLAASSEN: Yeah, that's their view. And you can write one also that you think you should use a number of four.

DR. ZHU: Sure. That's --

DR. KLAASSEN: You know, there's no science. And probably how it came about is that they have -- hate to say this, but they probably had a compound that when they used 10 it really looked bad, so then they changed it 2.5. "That looks good."

DR. BELSITO: Yeah, well, why not do that for interspecies rather than intraspecies?

DR. KLAASSEN: Yeah, see, that's why I'm saying don't use the 10 on the 10, or don't use the two --

DR. BELSITO: I've never seen --

DR. KLAASSEN: Just use the hundred.

DR. BELSITO: I've never seen an interspecies that wasn't 10 is my point.

DR. KLAASSEN: I haven't either. Just keep it simple.

DR. ZHU: Just keep the 100?

DR. KLAASSEN: Yeah.

DR. BELSITO: Yes.

DR. ZHU: Okay.

DR. BELSITO: Delete that sentence.

DR. KLAASSEN: Because that's what we end up with. That's the only part that we use in the end because we don't know anything about the interspecies or the differences between humans.

DR. ZHU: Sure. Yeah, because this --

DR. KLAASSEN: Because those are theoretical. And there are very good theoretical reasons, but there's nothing quantitative about it.

DR. RETTIE: I like that (inaudible). It's slightly simpler for me now based on that.

DR. BELSITO: Yeah. So, I would get rid of that entire sentence. So, "to ensure cosmetic safety," I don't think we need that. I mean, typically, we've used a hundred. So, when we're margin of exposure, we're not defining. So, I would just delete that whole sentence.

DR. ZHU: Sure.

DR. BELSITO: Okay. So, basically, we need to revise this boilerplate. On PDF Page 7, the paragraph, discussion, standard inhalation boilerplate, modify as needed, right after the bolded statement about not respirable to any appreciable amount, it says, "Furthermore, droplet/particles deposited in the nasopharyngeal or tracheobronchial region of the respiratory tract present no toxicological concerns." Is that true? What about respiratory irritants? What about a material that -- I mean, I guess there could -- what about a material that could induce granuloma but's not respirable?

DR. SNYDER: I think what this is saying, that if there's no data to support toxicologic concern, then --

DR. BELSITO: No, it says droplets deposited there are present no toxicologic concern. So, we're saying, if it's greater than ten microns, we're not concerned about toxicology of the materials, right?

DR. SNYDER: Oh.

DR. BELSITO: What about if it's carcinogenic?

DR. KLAASSEN: Yeah. No, that's --

DR. BELSITO: I don't think that's a correct statement.

DR. KLAASSEN: What they want to say is that it's not likely to be absorbed through the lung. But you're exactly right. If it hits there, the bronchials -- bronchi, et cetera, it can hurt the host cells; as well as the mucociliary system moves it up. And then you swallow it, and you can have, well, any kind of toxicity, just like oral toxicity. So, it's not --

DR. SNYDER: But --

DR. KLAASSEN: The bottom part is important for absorption.

DR. BELSITO: Right.

DR. KLAASSEN: But you can have toxicity all the way.

DR. BELSITO: Right.

DR. SNYDER: I think this is a boiler statement that we would modify that, compound X -- particles deposited into regions of the respiratory tract present no (inaudible) based on the properties of these ingredients as reported in this. It's not a global statement for all times. I thought it was ingredient-specific.

DR. BELSITO: No, I think that what we want to say is droplet/particles deposited in the nasopharyngeal or tracheobronchial region in the respiratory tract are not likely to be absorbed. I mean, I don't know. But they don't, to me, present no toxicologic concern.

DR. KLAASSEN: Nothing produces no toxicological concern.

DR. BELSITO: Right. So, that --

DR. SNYDER: I mean, unless we put some caveat based on mucociliary apparatus in swallowing.

DR. BELSITO: Well, but you could have a product deposited there that damages those tissues, right, in some way. So, that is a toxic concern.

DR. KLAASSEN: Sure. What we're really talking about here is absorption --

DR. BELSITO: Right.

DR. KLAASSEN: -- not toxicity.

DR. BELSITO: Right. So, how do we want to -- come on, Paul, you're our wordsmith.

DR. SNYDER: I mean, I don't -- I'll have to think about that. I thought we'd discussed this before. We thought that the swallowing mechanism and the mucociliary apparatus presents very little exposure because it's going to be coughed up and swallowed.

DR. RETTIE: So, present few toxicological concerns due to limited absorption?

DR. SNYDER: No, it's like -- limited --

DR. BELSITO: Present local toxicologic but not systemic toxicologic concerns.

DR. SNYDER: Yeah. Present no systemic toxicological concerns. Just put systemic in there because then we're not talking about local. That's it. Just put systemic in.

DR. BELSITO: I like keeping local in there.

DR. RETTIE: I think it helps, yeah.

MS. FIUME: But as written, is that implying that they will always present systemic --

DR. BELSITO: May present.

MS. FIUME: Oh, may present, okay. Thank you. I missed that word.

DR. BELSITO: So, deposited in -- may present local but not systemic toxicological concerns. That was all I had.

DR. SNYDER: Good.

DR. BELSITO: But what is our timeline for updating this respiratory boilerplate? Because, you know, you go online, it's still our old respiratory boilerplate where we just blow off everything, and we don't talk about the different particle sizes. We don't really talk that much about nanoparticles, et cetera.

MS. FIUME: So, Jinqiu, are we getting close? I know there's been a lot of changes each time we bring it, so it's been hard to publish it without having the final Panel approval of what the document looks like.

DR. BELSITO: Right.

MS. FIUME: So, it could depend on tomorrow's conversation. If you're happy with this, we can start changing the boilerplate online and then back fill and eventually get the whole document up to date.

DR. BELSITO: I mean, I think this document that we're looking at -- I think the boilerplate needs to be updated. But when you go into the boilerplate, it's much lengthier. So, what I would like to see is the actual revision on the boilerplate that would occur online. I think that changes that we're seeing here are good with the comments we've made today. But I think the whole -- what's going to appear online is what I'd like to look at next, not just simply new data on particle cells.

MS. FIUME: Okay. I'll definitely work on bringing that back to you so you can see it again.

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

DR. SNYDER: Not from me.

DR. BELSITO: Okay.

### **Full Panel – October 1, 2024**

DR. COHEN: Yeah. So, look, we had a long conversation about this. I'm not sure I really have a motion here, and we'd like to thank Jinqiu for putting a very good report together. We had a very long conversation about it. I could just highlight some of the discussion points. Know that we are anchoring on some occupational exposure limits that are -- this is OSHA baselines.

The OSHA PELs are predicated on an adult worker going eight hours a day for five days a week with about a 30-year career. And we should expect that the population of users of the chemicals that we adjudicate can start at infancy and go for a lifetime, and it may not always be so perfect to use that connection. We're using a dry shampoo for five minutes. It's not gonna be easy to bring that in.

On PDF 7, the statement, however, the Panel noted that the majority of droplets slash particles would not be respirable to any appreciable amount. Well, we do know that certain aerosols have 25 to 30 percent respirable fractions, and we think use of the term majority is not a good semantic use. It's hyperbolic. It doesn't articulate the risk very well.

Additionally, the comment, furthermore, droplets slash particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicologic concerns based on the chemical and biological properties of these ingredients. We don't feel we have enough confidence in the current respiratory (inaudible) of some chemicals that chronic upper respiratory exposure has no toxicologic concerns.

Any of the chemicals we adjudicate are (inaudible) irritants. So no toxicologic concerns refers that repetitive mucosal exposure will have no long-term impact (inaudible) of the upper respiratory tract.

Another comment that came up is, when we redo the boilerplate, I think for most boilerplates, we should affirmatively be asked whether we want the boilerplate in the report and not just drop them in because sometimes they're just not appropriate or they need to be modified based on the chemicals that we're using.

We may want to, when they are available, use STEL, short term exposure limits, because those often more approximate the kind of exposures cosmetic uses have. And we have some verbiage for new boilerplates that you can go through or we could just submit for later for review. That's what I got.

DR. BERGFELD: Any additional comments, Dr. Belsito?

DR. BELSITO: Yeah. We had discussed Curt's point about four microns, but we felt that the typical conservative approach is ten microns is respirable.

DR. COHEN: Yeah.

DR. BELSITO: And that's what we would go with. We struck through the text on PDF Page 4 that said, for instance, to ensure consumer safety, the margin of exposure should be at least 100 for systemic effects and 25 for local effects in the lungs. We didn't think that that was necessarily appropriate here, that that may vary from substance to substance, depending upon what we found.

We questioned the 2.5 use for local effects in the lung and again thought that might be dependent upon the specific material we're looking at and should not be in the boilerplate. And, regarding the point you made, David, on PDF Page 7, that, furthermore, droplet particles deposited in nasopharyngeal or tracheobronchial region of the respiratory tract present no toxicologic concern, we changed that.

We deleted no toxicologic concern. We said deposited in respiratory tract have may present local but not systemic toxicological concerns.

DR. COHEN: Yeah. That's right on with what we were thinking. There was also a discussion about the (inaudible). It's an aerosol, it seems like, most of the time, not a powder, not just a simple powder formulation. So, we should be clear when we're having that (inaudible) in the resource document.

DR. BELSITO: Right. And then, the last thing is, the next time we see this, we'd like to see the full respiratory boilerplate as it would exist and not just the little parts that we're looking at tweaking.

DR. BERGFELD: Are you talking about the resource document that contains the actual boilerplate?

DR. BELSITO: Yeah. Looking at the entire resource document.

DR. BERGFELD: Uh-huh.

DR. ROSS: Yeah. I found that hard to piece together from the smaller parts.

DR. BELSITO: Yeah. I went through the resource document just wondering how this is all going to be integrated and how it will read. And, so, I would like to see the whole resource document with these included at the next iteration.

DR. ROSS: And I like your comment on the 2.5. We didn't discuss that yesterday, but it's in my returns exactly the same.

DR. BERGFELD: So, it seems to me -- any other comments because this is a work in progress.

DR. COHEN: I have some --

DR. BERGFELD: Okay. Go ahead.

DR. COHEN: -- possible boilerplate substitutions in my returns verbiage for them.

DR. BERGFELD: Okay. So you will see some in the reports that come back?

DR. ZHU: Yes, I will update them.

DR. BERGFELD: All right. And the thought that this would come back next time or how far from now, two times?

DR. HELDRETH: A future meeting.

DR. BERGFELD: A future meeting, not specific. Okay. All right. I think that's a good discussion then. Dr. Belsito, you have the last item today, and that's Priorities.



## Memorandum

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

**FROM:** Alexandra Kowcz, MS, MBA  
Industry Liaison to the CIR Expert Panel

**DATE:** November 30, 2023

**SUBJECT:** Resource Document: Respiratory Exposure to Cosmetic Ingredients (draft prepared for the December 2023 meeting)

The Personal Care Products Council respectfully submits the following comments on the resource document, Respiratory Exposure to Cosmetic Ingredients.

**Inhalation Exposure Assessment** – In the second paragraph, it is not clear what is meant by hair sprays (also stated as hairsprays). The following suggests that the term “hairsprays” is being used as a general term for spray products applied to the hair as well as for the traditional “hair spray” – which holds hair in place: “out of the thirteen propellant-based hairsprays examined, eleven – including three hairsprays and eight dry shampoos – emitted respirable droplets/particles...” The type of product studied should be clearer.

**Measurement of Particle Size Distribution** – Can ICP-MS/MS also be used to quantify the nanoparticles in powder products? What was the mass (or numbers) of particles that were smaller than 100 nm?

**Last paragraph** – The process of updating the FDA product categories is ongoing. It would be more accurate to state that FDA has proposed changes to the cosmetic product categories (rather than “has updated”). It is unrealistic to expect that the FDA product categories will clearly define all cosmetic products. It is expected that FDA will continue to have “other” categories to allow for innovative products that are not easily categorized.

<b>Expert Panel Resource Document: Respiratory Exposure to Cosmetic Ingredients</b> <b>March 28-29<sup>th</sup>, 2024 Panel Meeting – Jinqiu Zhu</b>	
<b>Comment Submitter: Personal Care Products Council</b> <b>Date of Submission: 11/30/2023</b>	
<b>Comment</b>	<b>Response/Action</b>
Inhalation Exposure Assessment – In the second paragraph, it is not clear what is meant by hair sprays (also stated as hairsprays). The following suggests that the term “hairsprays” is being used as a general term for spray products applied to the hair as well as for the traditional “hair spray” – which holds hair in place: “out of the thirteen propellant-based hairsprays examined, eleven – including three hairsprays and eight dry shampoos – emitted respirable droplets/particles...” The type of product studied should be clearer.	The study lacks a clear definition of the term “hairsprays”. According to Figure 1 in the study by Berrada-Gomez et al. (2023), the hairsprays analyzed include both propellant-based and pump sprays. However, the researchers do not categorize dry shampoo as a subtype of hairsprays; instead, they classify it as a type of propellant-based spray.
Measurement of Particle Size Distribution – Can ICP-MS/MS also be used to quantify the nanoparticles in powder products? What was the mass (or numbers) of particles that were smaller than 100 nm?	ICP-MS/MS can also be utilized to quantify the nanoparticles in cosmetic powders, e.g., respective particle densities and mass fractions of each nanoparticle type identified.  The number of particles can be determined by Masshunter Software; however, the total mass of particles that were smaller than 100 nm was not analyzed by the authors (in the current study, spICP-MS/MS was used as a screening method to detect nanoparticles in powder-based facial cosmetics)
Last paragraph – The process of updating the FDA product categories is ongoing. It would be more accurate to state that FDA has proposed changes to the cosmetic product categories (rather than “has updated”). It is unrealistic to expect that the FDA product categories will clearly define all cosmetic products. It is expected that FDA will continue to have “other” categories to allow for innovative products that are not easily categorized.	Addressed



## Memorandum

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

**FROM:** Alexandra Kowcz, MS, MBA  
Industry Liaison to the CIR Expert Panel

**DATE:** September 24, 2024

**SUBJECT:** Comments on Inhalation Boilerplate Language Revisions Considered During the September 30-October 1, 2024, CIR Meeting

The Personal Care Products Council respectfully submits the following comments on the Inhalation Boilerplate Language Revisions considered during the September-October 2024 CIR meeting.

The data on dry shampoos and propellant-based aerosols should not be used to support exposure to particles from loose powder cosmetic products, as these products are not loose powder products.

Particle size determinations are dependent on the method. When summarizing a study that measured particle size, some indication of the method used and the range of particle sizes that could be measured should be stated.

The values selected for product exposure should be more transparent. Rather than using a secondary source, e.g., SCCS notes of guidance, it would be helpful to use the primary source. What the value represents should also be stated. For example, the SCCS uses 90<sup>th</sup> percentile values. The exposure information for the dry shampoo was the mean value (Ficheux et al. 2016 also provide 50<sup>th</sup> and 95<sup>th</sup> percentile values).

<b>Expert Panel Resource Document: Respiratory Exposure to Cosmetic Ingredients December 2-3, 2024 Panel Meeting – Jinqiu Zhu</b>	
<b>Comment Submitter: Personal Care Products Council Comments on Inhalation Boilerplate Language Revisions Date of Submission: 9/24/2024</b>	
<b>Comment</b>	<b>Response/Action</b>
The data on dry shampoos and propellant-based aerosols should not be used to support exposure to particles from loose powder cosmetic products, as these products are not loose powder products	Addressed.  It should be noted in some literatures, dry shampoos may be classified as loose powder cosmetic products. For example, it is stated in Steiling et. al, 2018 review paper*: “ <b>Loose (flow) powders</b> include finishing powders, foundations, perfumed body powders, cheek powders, eye shadows, <b>dry shampoos</b> or others. As already mentioned, the composition of loose powders is generally standardized, e.g. a dry shampoo typically contains two or more powdered ingredients to absorb the scalp sebum (oil).”
Particle size determinations are dependent on the method. When summarizing a study that measured particle size, some indication of the method used and the range of particle sizes that could be measured should be stated.	Addressed.
The values selected for product exposure should be more transparent. Rather than using a secondary source, e.g., SCCS notes of guidance, it would be helpful to use the primary source. What the value represents should also be stated. For example, the SCCS uses 90th percentile values. The exposure information for the dry shampoo was the mean value (Ficheux et al. 2016 also provide 50th and 95th percentile values).	Addressed.

\* Steiling W, Almeida JF, Assaf VH, et al. Principles for the safety evaluation of cosmetic powders. *Toxicol Lett.* 2018; 297:8–18. doi: 10.1016/j.toxlet.2018.08.011.



## 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.<sup>1</sup>

A preferred approach for the evaluation of inhalation safety is described in the 2014 publication by Steiling et al.<sup>2</sup> 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 m<sup>3</sup> 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.

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<sup>1</sup> 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.

<sup>2</sup> 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 (95<sup>th</sup> percentile from Loretz et al., 2006<sup>3</sup>)

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/minute<sup>4</sup>
- 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., 2012<sup>5</sup>).

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<sup>3</sup> 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.

<sup>4</sup> 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 available<sup>6</sup>.

### 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).<sup>7</sup> 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/antiperspirant<sup>8</sup> particle size. While no pump hairspray data were received, the

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<sup>5</sup> Steiling W et al. (2012) Skin exposure to deodorants/antiperspirants in aerosol form. *Food Chem Tox* 50: 2206-2215.

<sup>6</sup> 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](http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_004.pdf)

<sup>7</sup> Schwarz K, et al. (2018) A methodology for the assessment of inhalation exposure to aluminum from antiperspirant sprays. *Archives of Toxicology* 92: 1383-1392.

<sup>8</sup> 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.<sup>9</sup> 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 Federation<sup>10</sup>. 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.<sup>11</sup>

## **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 below<sup>12</sup>. Also included in the table is the percentage of particles/droplets <10 µm.

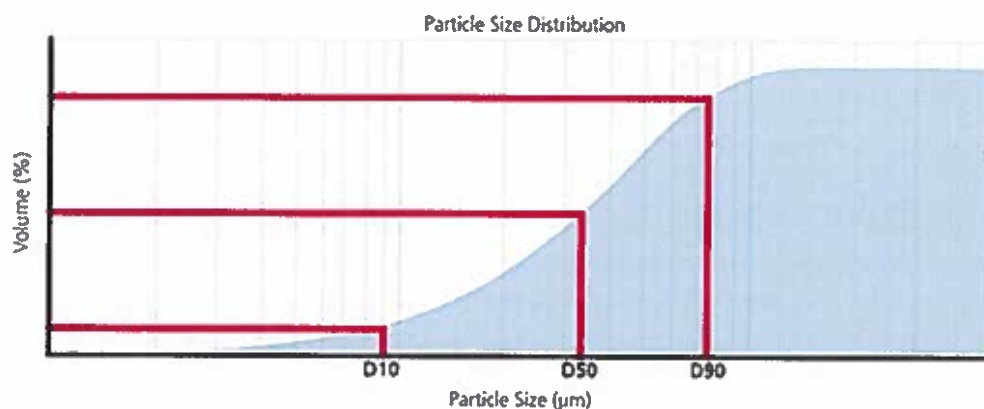
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<sup>9</sup> Rothe H et al. (2011) Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett.* 205:97-104.

<sup>10</sup> European Aerosol Federation. (2009) Guide on Particle Size Measurement from Aerosol Products.

<sup>11</sup> Steiling et al. (2014) op. cit.

<sup>12</sup> 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 µM
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;

% &lt; 10 µM: (n=53) 3.24 ± 4.48

Table 2 - Aerosol Deodorant/Antiperspirant Particle Size Data

Company	Product Type	Dv10	Dv50	Dv90	% < 10 $\mu$ 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  $\pm$  2.63Dv50: (n=26) 22.96  $\pm$  33.18Dv90: (n=21) 35.29  $\pm$  7.60%<10  $\mu$ M: (n= 26) 26.63  $\pm$  13.43