Supplement 2

Aerosols Precedents and Framework Document

Comments & Draft Responses

CIR EXPERT PANEL MEETING

APRIL 10 – 11, 2017

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Ivan J. Boyer, Senior Toxicologist
Date: April 4, 2017
Subject: Comments on from Women's Voice's for the Earth on the Aerosols Precedents and Framework Document

Enclosed is a letter received 3 April 2017 from Ms. Alexandra Scranton, Director of Science and Research, Women's Voices for the Earth, presenting 1 general comment and 8 specific comments on the Draft Revised Aerosols Precedents and Framework Document (Aerosols Document) to be reviewed by the CIR Expert Panel (Panel) at the 10-11 April 2017 Meeting.

The comments are summarized briefly, below, along with preliminary responses and other information that may be helpful for addressing the comments.

Summary of General Comment: **The Aerosols Document implies that respiratory harm from any cosmetic spray or powder is not likely because of the large sizes of the particles released to the air during the use of such products. However, epidemiological studies indicate that workplace exposures are associated with asthma and other respiratory diseases in hairdressers and beauticians.**

Draft Response to General Comment: As noted in the Aerosols Document, respirable particles typically constitute a small fraction (≤ 5%) of the overall particle-size distribution of airborne particles in the breathing zone during use of cosmetic spray products, as Dr. Rothe noted in her publication and presentation to the Panel in 2011 (both references are cited in the Aerosols Document – the transcript of the presentation is posted on the CIR Website: http://www.cir-safety.org/sites/default/files/092711-CIR%20PANEL.pdf). The Aerosol Document states:

Pg. 4, Par. 6

"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 Aerosol document explains why this parameter is important:

Pg. 1, Par. 1

"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."

Pg. 1, Par. 3

"The physical parameter most strongly associated with the deposition pattern of an aerosol in the respiratory tract is the aerodynamic equivalent diameter, d_{ae}."

As described on page 1, paragraph 5 of the Aerosols Document, the particles of an aerosol can be divided into three mass fractions: the inhalable fraction, the bronchial fraction, and the respirable fraction. Only the respirable fraction (median aerodynamic equivalent diameter [d_{ae}] = 4 µm) can enter the pulmonary region of the lungs to any significant amount. The alveoli of the pulmonary region do not have the protective mucociliary blanket of the nasopharyngeal and bronchial regions of the respiratory tract. Particles larger than about 5 µm are generally considered to have less potential to damage the lungs because the majority of them become trapped in the upper respiratory tract, including the nose and the windpipe. Nonetheless, the Panel is not concerned only with potential effects in the pulmonary region of the lungs:

Pg. 1, Par.

"However, the potential for toxic effects is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and bronchial regions of the respiratory tract may cause toxic effects in these regions depending on their chemical and physical properties."

In fact, the size distribution of the particles emitted from cosmetic sprays and loose powder products is only one of many factors that the Panel considers when evaluating the potential for the incidental inhalation of an ingredient to cause effects in the respiratory tract. For example:

Pg. 1, Par. 3

"The deposition, absorption, clearance and, ultimately, the effects of ingredients in aerosols (liquid droplets or solid particles) in the respiratory tract depend on the solubility, reactivity, and toxicity of the ingredients."

Pg. 3, Par. 5

"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"

Pg. 4, Par.6

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

Pg. 4, Par.7

"…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…"

Pg. 5, Par. 5

"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."

Generally, the Panel considers the weight of the evidence on a case-by-case basis to evaluate the potential for systemic or local effects from the incidental inhalation of an ingredient in spray and loose-powder cosmetic products.

As noted in the Comment, epidemiological studies indicate that beauticians, hair-dressers and other workers in beauty salons may be at increased risk of asthma and other respiratory illnesses. However, salon workers are typically exposed simultaneously to many different cosmetic compounds in the air of their workplaces for up to 8 hours per day, 5 days a week, or more, for years. Furthermore, some products used in salons may contain ingredients at concentrations substantially greater than those in products sold to the general public for home use. Agencies like the US Occupational Safety and Health Administration (OSHA) and its state counterparts are charged with regulating salons and beauty schools to protect the safety of employees and clients. In contrast, CIR is charged with evaluating the safety of cosmetic ingredients as used in products sold to the general public and intended for home use. Generally, the scope of CIR's purview does not extend to workplace safety and health.

Summary of Specific Comment #1: **Page 3, paragraph 2 of the Aerosols document states "*Usually, 1% to 2.5% but no more than 5% of the droplets/particles emitted from propellant hair sprays are within the respirable range,*" and page 4, paragraph**

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

These statements are not consistent with page 3, paragraph 3, which states *"In contrast, analogous estimates indicate that the tested deodorant-spray aerosols have a median d_{ae} of 10 µm with a coefficient of variation of 0.3, suggesting that half of these particles are within the range considered to be respirable"* The reports cited in the Aerosols Document clearly indicate that up to 50% of particles from deodorant sprays have d_{ae}s < 10 µm and would be respirable (e.g., see page 19 and 20 of the *rivm* report, available at http://www.rivm.nl/bibliotheek/rapporten/320104005.pdf).

Draft Response to Specific Comment #1: Based on the available evidence, the first two sentences quoted in the Summary of Specific Comment #1, above, apply to cosmetic spray products other than deodorant spays. The third statement quoted notes that deodorant sprays may be exceptions. However, the evidence is sparse.

Based on the data presented in Table 2 on page 20 of the *rivm* report referred to in the Comment, only 3 different deodorant spray products were tested, with 13%, 20%, and 33% of the respective particle-size distributions within the respirable range. These values are lower than the over-conservative, statistically-derived estimate of 50% mentioned in Bremmer, 2006 (cited in the Aerosols Document), but greater than 5%, which appears to be the upper limit of the respirable fraction released during use of hair sprays (e.g., 1% to 2% in Table 2 of the *rivm* report) and other types of cosmetic spray products. This is why the Framework of the Aerosols Document includes the following statement, as the Commenter notes, which is incorporated into the cosmetic Use section of CIR safety assessments whenever appropriate:

Pg. 7, Par. 1

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

It is not clear to what extent the 3 deodorant sprays tested are representative of deodorant sprays in general. As stated in the Aerosols Document:

Pg. 4, Par. 5

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

Note also the following statements in the Aerosols Document:

Pg. 3, Par. 4

The inhalation of respirable droplets/particles from cosmetic products, including pump and propellant hair sprays and deodorant sprays, is likely to be very small, even negligible, compared with dermal contact and other exposure routes associated with the use of these products. Further, products like underarm deodorant and 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."

Pg. 4, Par. 1

Industry can ensure that inhalation exposures to cosmetic sprays and powders are minimized. 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.

Thus, the Aerosols Document, including the Framework, accurately reflects the current state of the knowledge and uncertainties in this area. The Framework and the Background section constitute the two integral parts of the whole Aerosols Document, as indicated by the following statement, which is included in every CIR safety assessment report for which it is appropriate:

Pg. 9, Par. 6

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

Summary of Specific Comment #2: **The Aerosols Document, page 5, paragraph 1, presents a conservative estimate of inhalation exposure to an ingredient in a deodorant spray product based on the assumption that the respirable fraction was 5%.**

The Commenter observed that the assumption should have been 50% to be consistent with page 3, paragraph 3, which states *"In contrast, analogous estimates indicate that the tested deodorant-spray aerosols have a median d_{ae} of 10 µm with a coefficient of variation of 0.3, suggesting that half of these particles are within the range considered to be respirable*." The Commenter suggests that 5% may be a typo.

Draft Response to Specific Comment #2: This calculation was based on the assumption that 5% of particle distribution consisted of respirable particles. This is consistent with the sample calculation submitted to CIR in a memorandum from the Personal Care Council (PCPC) CIR Science and Support Committee (CIR SSC; memorandum attached, and available on the CIR Website: http://www.cir-safety.org/sites/default/files/admin_web_0.pdf).

The Draft Response to Specific Comment #1, above, applies to Specific Comment #2. Note that the uncertainty associated with the 50% figure, the likelihood that underarm deodorants would not be sprayed in the direction of the face, and the overly conservative nature of the other assumptions used in the calculation were all considerations supporting the use of the 5% assumption.

In any case, 33% was the greatest respirable fraction reported for the particle distributions measured for 3 deodorant spray products, as noted in the Draft Response to Specific #1, above. Repeating the calculation assuming 33% as the respirable fraction, rather than 5%, results in an inhalation exposure of no more than 20 µg/kg/day of an ingredient present at a concentration of 10% in a deodorant spray product. Assuming 50% as the respirable fraction yields an estimated exposure of no more than 30 µg/kg/day. In comparison, the estimated exposure to the ingredient in a hair spray, as noted in the Aerosols Document, is no more than 20 µg/kg/day. Thus, as stated in the Framework of the Aerosols Document:

Pg. 7, Par. 1

"… the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays."

Summary of Specific Comment #3: **The Commenter refers to two scientific articles that report the size distributions of airborne particulates released from consumer spray products, including nanotechnology-based and "regular" (i.e., not specified as nanotechnology-based) cosmetic products (Nazarenko et al., 2011 – https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4027967/; Nazarenko et al., 2014 – https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4027967/). These reports indicate that the fraction of respirable particles released from cosmetic sprays, including "regular" sprays, is much greater than specified in the Aerosols Document. The Commenter quotes from the Abstract of Nazarenko et al. (2014), which states:**

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

The Commenter notes that up to 10% of the aerosol dose from cosmetic sprays would be deposited in the pulmonary region, based on the results of these studies (Nazarenko et al., 2014). She also notes that Nazarenko et al. (2011, 2014) used more than one analytical technology to measure particle sizes.

The Commenter states that the Panel should evaluate the research presented in these papers, and revise the Aerosols Document accordingly.

Draft Response to Specific Comment #3: Nazarenko et al. (2011, 2014) studied the particle sizes of paired nanotechnology-based and "regular" consumer spray products, including pairs of personal care silver sprays, vitamin-containing facial mists, antioxidant-containing body mists, and hair care sprays. The nanotechnology-based products were identified as such by the manufacturers' reports of the presence of nanocomponents in them; Nazarenko et al. (2011) emphasized that "*there is no certainty that any given product in the inventory includes nanotechnological components*" (Pg. 4, Par. 2).

Nazarenko et al. (2011, 2014) used photon correlation spectroscopy to measure hydrodynamic particle sizes and transmission electron microscopy (TEM) to measure particle sizes and other parameters in the liquid formulations. The sizes of particulates in the liquid formulations may be related to the sizes of particulates released to the air during the use of the spray products containing these formulations. However, like the experiments involving the aerosolization of the formulations using a nebulizer in these studies, the results of these experiments are not directly relevant to the characterization of the airborne particle size distributions and inhalation exposures that can be expected from the intended use of cosmetic spray products.

As noted by the Commenter, both a Scanning Mobility Particle Sizer (SMPS) and an Aerodynamic Particle Sizer (APS) were used in these studies to measure the sizes of particles collected from the breathing zone (i.e., 10 cm away and to the right of the nose of a mannequin's head; the inlet to the collection tube was located in the nostrils of the mannequin, and the nostrils were in the path of the spray cone. The sprays were operated manually, approximately one spray per second for 3 minutes for each test run (3 minutes is the minimum time needed for the SMPS). The concentrations and size distributions of the aerosolized particles collected were measured continuously during each test run.

It is important to note that the measuring equipment used in these studies have an upper limit of 20 µm, ranging from about 0.014 to 0.7 µm for the SMPS and from approximately 0.6 to 20 µm for the APS (Nazarenko et al., 2011, 2014). Thus, the method used does not cover the full spectrum of particle sizes typically released from cosmetic sprays, which can peak at around 50 µm and range from up to 100 to 150 µm for hair sprays and peak at around 20 µm and range up to 100 µm for deodorant sprays, based on the data presented in Table 2 of the *rivm* report referred to in specific Comment #1, above.

Another important factor to consider is that nanoparticles, which consist of particles ranging in size from 0.001 to 0.1 µm by definition, usually remain suspended in the air in the respiratory tract. In general, particles less than about 0.5 µm in size will be expelled when exhaling. A small fraction of such particles entering the alveoli may stick to the alveolar surface, but the overall mass deposited in the alveoli in this way can be expected to be very small.

These observations are consistent with the exposure simulation/mathematical modeling experiments conducted by Nazarenko et al. (2014). The authors assumed an exposure duration of 1 minute, for the purpose of modeling exposure and deposition in the head airways, tracheobronchial region, and pulmonary (alveolar) region of the respiratory tract.

For 8 of the 10 products tested, 0.016 to 1.34 µg/kg/application would be deposited, in total, in the respiratory tract under the conditions assumed in the study. Of these amounts, ≥ 85% (0.013 to 1.17 µg/kg/application) would be deposited in the airways of the head and < 10% (~7% to 9.5%) would be deposited in the pulmonary region.

For the two silver spray products, the total amounts deposited in the respiratory tract would be ~0.0001 m and ~0.0003 µg/kg/application), or 2 to 4 orders of magnitude less than the amounts estimated for the other 8 products. About 52% to 64% (~0.00006 and ~0.00017 µg/kg/application) of the total amounts estimated for these 2 products would be deposited in the head airways and 30% to 40% would be deposited in the alveolar region.

The estimates of exposure and deposition of all particulates ≤ 20 µm in size (i.e., ≤ 1.34 µg/kg/application), as reported for cosmetic spray products by Nazarenko et al. (2014), is less than (often orders of magnitude less than) the overly conservative estimates of incidental inhalation exposures to respirable particles released from cosmetic spray products, as presented in the Aerosols Document (i.e., 7 to 20 µg/kg/day).

Summary of Specific Comment #4: **The Commenter notes that two papers were published by Nazarenko et al. in 2012 (**https://ehp.niehs.nih.gov/1104350/ **and** https://www.ncbi.nlm.nih.gov/pubmed/23175627**) using up-to-date analytical methods**

and showing that the vast majority of airborne particles in the air during the use of loose powder cosmetic products are within the respirable range. The Commenter noted that the results reported in Nazarenko et al. (2012) contradict the Aerosols Document, which should be revised to incorporate the up-to-date studies. The Commenter further notes that the Aerosols Document cites an unpublished memorandum from the Personal Care Products Council (PCPC), which does not appear to be publicly available.

Draft Response to Specific Comment #4: Nazarenko et al. (2012) use the same experimental apparatus and analytical equipment/methods described in Draft Response to Specific Comment #3, above, to analyze the particle sizes and estimate particle deposition in the respiratory tract during use of loose powder cosmetic products. Three of the products were described by the manufacturers as "nanoproducts" or nanopowders" and three were from manufacturers that did not claim to include nanomaterials. In this case, the researchers applied each powder to the face of the mannequin, simulating actual product usage, using brushes or pads included with the products.

Much of the Draft Response to Specific Comment #3 applies to Specific Comment #4 as well. Again, the measuring equipment used in these studies have an upper limit of 20 µm, ranging from about 0.014 to 0.7 µm for the SMPS and from approximately 0.6 to 20 µm for the APS. This does not cover the full spectrum of particle sizes that would be expected from the use of loose cosmetic powders.

Likewise, the estimated masses of particulates that would be deposited were small, based on the results of these studies. The results indicate the 0.037 to 32 µg/kg/application, total, would be deposited in the respiratory tract; deposition in the pulmonary region would range from 0.002 to 2 µg/kg/application.

These estimates are orders of magnitude less than, or comparable to the overly conservative estimates of incidental inhalation exposures to respirable particles released from lose powder cosmetic products, as presented in the Aerosols Document (i.e., 0.1 to 1.05 µg/kg/day).

The PCPC memorandum cited in the Aerosols Document is available to anyone upon request, and is attached.

Summary of Specific Comment #5: **The Commenter takes issue with the following:**

Pg. 4, Par. 3

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

This is because the methods used by Nazarenko et al. (2012), including the use of SMPS, APS, and TEM, represent up-to-date methods that have been applied to analyze the particle sizes and estimate particle deposition in the respiratory tract during use of loose powder cosmetic products, as described in Specific Comment #4. Thus, the conclusion that "*it is not clear whether these methods are amenable to characterizing the aerodynamic equivalent diameters of such particles*" appears to be incorrect.

Draft Response to Specific Comment #5: As noted in the Draft Response to Specific Comment #3 and Specific Comment # 4, the measuring equipment used in the Nazarenko et al. (2012) studies have an upper limit of 20 µm, ranging from about 0.014 to 0.7 µm for the SMPS and from approximately 0.6 to 20 µm for the APS. This does not cover the full spectrum of particle sizes that would be expected from the use of loose cosmetic powders.

Nazarenko et al. (2012) used TEM to assess the diameters, shape, and degree of agglomeration in a minute quantity of each cosmetic product "in their original state" placed on a TEM grid. They reported that "nanoparticles dominated in two of three nanopowders… and constituted a considerable fraction" of one of the "regular" powders. However, the extent to which these observations correlate with the size distributions of the particles released from loose powder products under use conditions has not been explored.

In any case, the results of the simulation experiments conducted by Nazarenko et al. (2012) using SMPS and APS equipment indicate that the estimated masses of particulates that would be deposited in the pulmonary region of the respiratory tract under

use conditions are orders of magnitude less than, or comparable to the overly conservative estimates of incidental inhalation exposures to respirable particles released from loose powder cosmetic products (as presented in the Aerosols Document and noted in Draft Response to Specific Comment #4).

The statement on page 4, paragraph 3 of the Aerosols Document that "*…these measurements do not correlate well with the size distributions of the* particles released from the product under use conditions" applies specifically to methods used to measure the particle sizes involving "*dispersing the powder in a solvent or applying a pressure differential to break up the agglomerated particles*." This is still true. Furthermore, based on the foregoing discussion, the methods used by Nazarenko et al. (2012 do not appear to be amenable to characterizing the complete distributions of aerodynamic equivalent diameters of particles released to the air during the use of loose powder cosmetic products.

Summary of Specific Comment # 6: **The Commenter notes the following statement in the Framework of the Aerosols Document:**

Pg. 7, Par. 1

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

The Commenter observes that the comparison of inhalation exposure estimates with guidance limits for airborne respirable particles is from the PCPC CIR Science and Support Committee (CIR SSC) memorandum cited in the Aerosols Document. The regulatory and guidance limits referred to in this passage are not specified in the Aerosols Document. The Commenter also notes the controversy about whether workplace regulatory limits are protective.

Draft Response to Specific Comment #6: The calculations were modeled after the calculation of exposure factors in Russell et al. (1979), which is cited in the CIR SSC memorandum (attached and available on the CIR Website http://www.cir-safety.org/sites/default/files/admin_web_0.pdf) and in the Framework of the Aerosols Document. In that paper, exposure factors were defined as the ratio of the American Conference of Governmental Industrial Hygienists (ACGIH) workplace Time-Weighted Average (TWA) Threshold Limit Value (TLV) for respirable particles (3 mg/m^3) and the corresponding TWA concentrations of respirable particles to which infants and adults are estimated to be exposed during the use of cosmetic powders. Russell et al (1979) assumed that adults powder once a day and infants are powdered 3 times a day, 7 days/week, to calculate exposure factors of 600 and 2,182 for adults and infants, respectively. Assuming more conservatively that that adults powder an average of 1.5 times a day and infants are powdered an average of 6 times a day, 7 days/week, yields exposure factors of 400 and 1,091 for adults and infants, respectively.

Workplace exposure limits, such as the ACGIH TWA-TLV, are likely to be protective for occupational exposures at the workplace. However, the use of such values as benchmarks against which to gauge exposures to the general public can be informative. In this case, the TWA concentrations derived from a workplace exposure limit (i.e., the ACGIH TWA-TLV for the respirable fraction of nuisance dusts) are 2 and 3 orders of magnitude greater than conservative estimates of TWAs for cosmetic powder use at home. This wide margin supports the statement from the Framework of the Aerosols Document, as quoted in Specific Comment #6.

Summary of Specific Comment #7: **The Aerosols Document does not address the potential hazards of incidental inhalation of nanoparticles, which are used increasingly in cosmetic products. Nazarenko et al (2011, 2012, and 2014) have shown that cosmetic spray and loose powder products, including nanotechnology-based and "regular" products release inhalable and respirable nano-size particles to the air, as noted in Specific Comments #3 and #4, above. The Aerosols document should mention the potential for incidental inhalation exposures to such particles, or at least include a statement acknowledging the attendant uncertainties.**

Draft Response to specific Comment #7: As the Commenter indicates, nanotechnology research continues evolve. The studies by Nazarenko and co-authors noted above clearly indicate that cosmetic sprays and loose powders can release nanoparticles to the air during the use of such products. The Panel should consider whether this issue warrants addressing in the Aerosols Document.

Specific Comment #8: **The Commenter recommends that the CIR Expert Panel discuss whether they still believe that the following statement is accurate and protective of the public health:**

Pg. 4, Par. 4; Pg. 7, Pars. 1 & 2; Pg. 8, Par. 8

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

Draft Response to Specific Comment #8: The Panel should consider whether this statement should be revised or replaced, and the Aerosols Document updated accordingly, based on the General and Specific Comments submitted by Women's Voices for the Earth.

WOMEN'S VOICES FOR THE EARTH

OUR HEALTH. OUR FUTURE. TOXIC FREE.

By email: cirinfo@cir-safety.org

April 3, 2017

To: Cosmetic Ingredient Review Expert Panel Members and Liaisons,

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

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

Comments:

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

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

Further on this page it states:

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

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

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

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

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

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

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

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

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

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

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

3) Furthermore, the Aerosols document states:

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

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

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

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

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

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

The paper concludes:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Sincerely,

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

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: December 12, 2011

SUBJECT: Sample Exposure Calculations

To illustrate the low level of exposure resulting from some cosmetic spray products, the CIR Science and Support Committee (CIR SSC) has completed some calculations of potential inhalation exposure from cosmetic spray products. As the sample calculations provided below illustrate, even with very conservative assumptions, (e.g., all of the product used is airborne when it has been suggested by the ConsExp model that 85% of the product lands on the target site; duration of exposure 20 minutes, when ConsExpo model suggests a 5 minute exposure), potential exposure via inhalation is small.

The sample calculations were completed based on information provided in the Rothe et al. (2011) paper, and assume that the deodorant and hair spray products contain 10% of the ingredient of concern. The calculations suggest that habits and practices information (amount of product used), ingredient concentration and particle size distribution are important factors determining potential inhalation exposure.

<u>Aerosol Hairspray</u>
Assumptions

Amount used per day: 9.89 g (95th percentile from Loretz et al., 2006)
100% available for inhalation
distributes in 1000 L in the first 2 minutes (Rothe et al. 2011)
distributes 10,000 L in the next 18 minutes (Rothe et al. 2011)
Breathing rate: 10 L/minute
5% of particles respirable (<10 μm)
Body weight: 60 kg

Estimates of exposure to an ingredient contained in the product at 10% (using equations described in Rothe et al. 2011)

9.89 g x 0.1 (ingredient) = 0.989 g (989 mg)

First 2 minutes: 989 mg/1000 L x 10 L/minute x 2 minutes = 19.8 mg
Next 18 minutes: 989 mg/10,000 L x 10 L/minute x 18 minutes = 17.8 mg

Total exposure 19.8 mg + 17.8 mg = 37.6 mg

25% exhaled (0.75 exchange factor)
37.6 x 0.75 = 28.2 mg

5% of inhaled material in particles <10 μm
28.2 mg x 0.05 = 1.41 mg

1.41 mg/60 kg = 0.02 mg/kg/day inhalation exposure

Pump Hair Spray
Assumptions

Amount used per day: 15.6 g (95th percentile from Loretz et al., 2006)
100% available for inhalation
1000 L in the first 2 minutes (Rothe et al. 2011)
10,000 L in the next 18 minutes (Rothe et al. 2011)
Breathing rate: 10 L/minute
1% of particles respirable (<10 μm)
Body weight: 60 kg

Estimates of exposure to an ingredient contained in the product at 10% (using equations described in Rothe et al. 2011)

15.6 g x 0.1 (ingredient) = 1.56 g (1560 mg)

First 2 minutes: 1560 mg/1000 L x 10 L/minute x 2 minutes = 31.2 mg
Next 18 minutes: 1560 mg/10,000 L x 10 L/minute x 18 minutes = 28.1 mg

Total exposure 31.2 mg + 28.1 mg = 59.3 mg

25% exhaled (0.75 exchange factor)
59.3 x 0.75 = 44.5 mg

1% of inhaled material in particles <10 μm
44.5 mg x 0.01 = 0.445 mg

0.445 mg/60 kg = 0.007 mg/kg/day inhalation exposure

Aerosol Deodorant
Assumptions

Amount used per day: 1.43 g (SCCS 2010 [as cited in Rothe et al., 2011])
100% available for inhalation
1000 L in the first 2 minutes (Rothe et al. 2011)
10,000 L in the next 18 minutes (Rothe et al. 2011)
Breathing rate: 10 L/minute
10% of particles respirable (<10 μm)
Body weight: 60 kg

Estimates of exposure to an ingredient contained in the product at 10% (using equations described in Rothe et al. 2011)

1.43 g x 0.1 = 0.143 g (143 mg)

First 2 minutes: 143 mg/1000 L x 10 L/minute x 2 minutes = 2.86 mg
Next 18 minutes: 143 mg/10,000 L x 10 L/minute x 18 minutes = 2.57 mg

Total exposure 2.86 mg + 2.57 mg = 5.43 mg

25% exhaled (0.75 exchange factor)
5.43 mg x 0.75 = 4.1 mg

5% of inhaled material in particles <10 μm
4.1 mg x 0.05 = 0.205 mg

0.205 mg/60 kg = 0.003 mg/kg/day inhalation exposure

References

Loretz L, Api AM, Barraj L, et al. 2006. Exposure data for personal care products: Hairspray, spray perfume, liquid foundation, shampoo, body wash and solid antiperspirant. Food and Chemical Toxicology 44: 2008-2018.

Rothe H, Fautz R, Gerber E, et al. 2011. Special aspects of cosmetic spray safety evaluations: Principals on inhalation risk assessment. Toxicol Lett. 205(2): 97-104.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: November 3, 2015

SUBJECT: Cosmetic Powder Exposure

At the September 2015 CIR Expert Panel meeting, the Panel requested information on the potential for inhalation exposure following the use of personal care products in powder form[1]. This memo provides an example of exposure estimation for powder products.

The CIR SSC based its exposure calculations on loose talc-based powder products, representing a worse case scenario for exposure to powder products.

Aylott et al. (1979)[2] measured respirable talc and reported a mean atmospheric concentration of 0.48 mg/m^3 during normal use of a loose face powder (average 17.5 seconds talcing time), and 1.13 mg/m^3 during use of adult dusting powder (average 39 seconds talcing time). In a second study by Russell et al. (1979)[3], average respirable talc air concentrations of 2.03 mg/m^3 were measured during routine application of talcum powder (average exposure 1.23 minutes).

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[1]This memo does not address the toxicology of inhaled particles. The toxicology of poorly soluble particles is well studied and additional information may be found in the report by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 122 Poorly soluble particles/Lung overload. Available from http://www.ecetoc.org/publications.

[2]Aylott RI, Byrne GA, Middleton JD et al. 1979. Normal use levels of respirable talc: preliminary study. *International Journal of Cosmetic Science* 1: 177-186.

[3]Russell RS, Merz RD, Sherman WT, et al. 1979. The determination of respirable particles in talcum powder. *Fd Cosmet Toxicol* 17: 117-122.

Using a breathing rate of 0.01 m^3/minute[4] the following exposures per application are calculated:

Loose face powder:	0.48 mg/m^3 x 0.01 m^3/min x 0.3 min = 0.00144 mg/application
Adult dusting powder:	1.13 mg/m^3 x 0.01 m^3/min x 0.65 min = 0.0074 mg/application
	2.03 mg/m^3 x 0.01 m^3/min x 1.23 min = 0.025 mg/application

For comparison, exposure to the 2 mg/m^3 ACGIH talc TLV[5] (ACGIH 2014) for one working day (female breathing rate light activity 9.12 m^3/day[6]) would result in an exposure of 18.2 mg. Powder products consisting of primarily inert particles may be compared to OSHA Permissible Exposure Limits (PEL) values for nuisance dust, which are 5 mg/m^3 for the respirable fraction and 15 mg/m^3 for total dust.

Based on the low exposure, the CIR SSC believes that inhalation is not a significant route of exposure for personal care products in powder forms.

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[4]Breathing rate used in the CIR Aerosol document found at http://www.cir-safety.org/sites/default/files/aeroso092012rep_0.pdf

[5]The concentration to which a worker can be exposed day after day for a working lifetime without adverse health effects.

[6]EPA Exposure Factors Handbook 2011, Table 6-26 http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252