EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

Resource Document

Respiratory Exposure to Cosmetic Ingredients

12/2021

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.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This resource document was prepared by Jinqiu Zhu, Ph.D, D.A.B.T., E.R.T, CIR Toxicologist.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢
cirinfo@cir-safety.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.[1]

The deposition and absorption of gases and vapors in the respiratory tract depend mainly on their water solubility and reactivity with the fluids or other components of the surfaces of the airways.[2-4] For example, absorption of a water insoluble, non-reactive gas is negligible. A moderately-soluble or reactive gas will be deposited throughout the respiratory tract. A highly-soluble or reactive gas will be rapidly deposited or absorbed almost entirely in the nose and upper airways. A highly-reactive gas will also be consumed by chemical reactions, such as hydrolysis.[1,3,5]

Aerosols are broadly defined as multiphase systems of particulate solids or liquids dispersed in air or other gases, including mists, fumes, and dusts. The deposition, absorption, clearance, and, ultimately, the effects of ingredients in aerosols (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,[6] although the mechanisms of overload-induced tumor formation are not completely understood.[6-9] 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^3 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).[1,10]

Droplet/particle size is variable across individual products. Industry can ensure that inhalation exposures to cosmetic sprays and powders are minimized.[10] For example, particle size distributions can be characterized and exposures estimated each time a significant change is made in the formulation or spray mechanisms of spray products to ensure that potential inhalation exposures are very low. Similarly, industry can minimize airborne particles from cosmetic powder products by controlling the milling of the ingredients and adding binding materials, such as oils, waxes or hygroscopic ingredients, to the formulations.[11] The binding materials foster the agglomeration of the ingredients and substantially increase their cohesivity. These measures increase the size of the particles in the product.

REGIONAL PARTICLE DEPOSITION

The physical parameter most strongly associated with the deposition pattern of an aerosol in the respiratory tract is the aerodynamic equivalent diameter (d_{ae}).[12,13] The d_{ae} of a droplet/particle is defined as the diameter of a hypothetical, smooth sphere of unit density (e.g., 1 g/cm^3) that has the same gravitational settling velocity as the droplet/particle in calm air, regardless of its actual geometric size, shape and density.[5,14]

The droplets/particles of an aerosol can be divided into three mass fractions, based on the depth to which they will penetrate the respiratory tract. These fractions include the inhalable fraction (median d_{ae} ~ 100 µm), which can enter the nasopharyngeal region through the nose or mouth, the bronchial fraction (median d_{ae} ~ 10 µm), which can pass through the larynx to enter the trachea, bronchi and bronchioles, and the respirable fraction (median d_{ae} ~ 4 µm), which can enter the alveolar region of the lungs.[1-3,15] In the nasopharyngeal and bronchial regions of the respiratory tract, mucus-secreting and ciliated cells form a protective mucociliary blanket that carries deposited droplets/particles to the throat. Thus,

droplets/particles deposited in these regions can be cleared via mucociliary action, sternutation, expectoration, or deglutition.[16] In the pulmonary region, the clearance of inert, poorly soluble particles is mediated primarily by alveolar macrophages, and is slow and limited by comparison. However, the potential for toxic effects is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and bronchial regions of the respiratory tract may cause toxic effects in these regions, 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 µm into the pulmonary region is essentially zero.[1,5,17-21] Thus, only droplets/particles with $d_{ae} \leq$ 10 µm are considered to be respirable. This is a conservative assumption because a d_{ae} of 5 µm or less is often reported in the scientific literature as the threshold below which droplets/particles can reach the alveoli.[1,22] In addition, there is consensus that droplets/particles with d_{ae} > 15 µm are deposited almost exclusively in the nasopharyngeal and bronchial regions of the respiratory tract, and that healthy people will clear particles with d_{ae} > 7 µm from these regions within 24 hours through mucociliary action.[1]

INHALATION EXPOSURE ASSESSMENT

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

Both pump sprays and propellant sprays (also called “aerosol sprays”) produce aerosols, but the aerosols from propellant sprays have larger fractions of respirable droplets/particles than aerosols from pump sprays. For example, the median d_{ae} of the airborne droplets/particles of pump hair sprays range from 60 µm to 80 µm.[1,10,23] Typically, < 1% of the airborne droplets/particles released from pump sprays are in the range considered to be respirable (i.e., d_{ae} < 10 µm). In comparison, the median d_{ae} of the airborne droplets/particles of propellant hair sprays range from 25 µm to 50 µm.[1,10,23] Usually, 1% to 2.5%, but no more than 5%, of the droplets/particles emitted from propellant hair sprays are within the respirable range,[10,27] while a larger fraction of respirable particles would release from propellant deodorant sprays, as reported by simulated test data, in silico model outputs, and industry survey.[23,28-31]

Furthermore, different types of propellant-spray products may yield substantially different particle size distributions. For example, conservative estimates indicate that propellant hair spray aerosols have a median d_{ae} of 35 µm with a coefficient of variation of 0.3.[17,23] Thus, the insoluble aerosol particles inhaled during hair spray use will be deposited primarily in the nasopharyngeal and bronchial regions, where they can be trapped and cleared from the respiratory tract through mucociliary action. In contrast, analogous estimates indicate that the tested deodorant spray aerosols have a median d_{ae} of 10 µm with a coefficient of variation of 0.3, suggesting that approximately half of these particles are within the range considered to be respirable.[17,23]

The available data, however, are insufficient to determine median particle sizes (and distributions) resulting from airbrush device use. Thus, the fraction of respirable particles that would be released by applying cosmetics with airbrush devices is not yet well-defined.

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. This

is because they suggest that the margin of safety may be lower for propellant sprays compared to pump sprays, and for propellant deodorant sprays compared to propellant hair sprays. The systemic exposure resulting from inhalation of respirable droplets/particles from cosmetic products, including pump and propellant hair sprays and deodorant sprays, is likely to be very small, even negligible, compared with dermal contact and other exposure routes associated with the use of these products. Further, products like foot sprays are not usually sprayed in the direction of the face, so less of these products will likely be sprayed directly into the users breathing zone compared with hair sprays, for example. However, the limited evidence currently available does not provide adequate support for these assumptions.

The droplets/particles released from a propellant hair spray are distributed within a 1 to 2 m^3 space in the breathing zone during the first 2 minutes after spraying, which expands to form a homogenous 10 m^3 cloud over the subsequent 18 minutes.[1,10] Simulation studies revealed that all of the droplets/particles released from both pump sprays and propellant sprays settle quickly after spraying, including the respirable and inhalable fractions, which substantially reduces the overall potential for inhalation exposure.[5,10,14,23,24] Specifically, about 35% of the airborne droplets/particles drop away from the breathing zone in the first minute, 60% in the second minute, 90% in six minutes, and 95% in eight minutes after spraying.[10] The droplets/particles are likely to be undetectable in the breathing zone within 10 minutes after spraying.

One industry survey provides volume weighted particle size distribution data, measured using laser diffraction, for propellant hair sprays and propellant deodorant/antiperspirant sprays.[31] 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, data are reported as volume diameter defined by 10%, 50% (volume median), and 90% of the cumulative volume undersize (Dv10, Dv50, and Dv90, respectively). The 90% particle sizes (Dv90) of droplets/particles released from propellant hair sprays are distributed within the size range of 23.5 – 409 µm, whereas the mean (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.

Due to the compressed format and low usage amounts, inhalation exposure to compact powders is not expected at use conditions.[32] 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. One study quantified one minute exposure to airborne particles ranging from 14 nm to 20 µm due to the use of three nanotechnology-based, and three regular, cosmetic powders functioning as moisturizer, blusher, blot powder, etc.[33,34] Results therein illustrated that the coarse aerosol fraction (2.5 – 10 µm) represented the highest inhaled particle mass, while the minimal inhaled, mass was made by particles < 100 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 ~ 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.[35] 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 µg for particles with $d_{ae} \leq 10$ µm and 200 µg for particles with $d_{ae} \leq 2.5$ µm. 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).[36,37] The electron microscopy and airborne particle measurements data suggested that airborne concentrations of particles between 100 nm and 20 μm 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 μm, while exposure to nanoparticles was mainly through agglomerates of 5 - 10 mm and larger,[37] and predominant deposition of nanomaterials occur in the tracheobronchial and head airways but not in the alveolar region.

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.[10,11,32] 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.[38,39] 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.[36,40] 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.[41]

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).[42] During the application of all investigated sprays, particles ranging from 13 nm to 20 μm 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.[43] 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.[44,45] 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.[35,36,44-46] 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.[44,45] Aerosols were monitored using both a scanning mobility particle sizer (SMPS) that measured particle size distributions between ~ 10 – 435 nm and an optical particle sizer (OPS) that measured size distributions between 0.3 – 10 μm. A spray duration/aerosol generation of 20 minutes represented a worst-case scenario of application with 8 –12 drops (~ 400 – 600 cm^3) of liquid powder cosmetics placed in the reservoir of the nebulizer as per airbrush manufacturer's instructions.[1,44,45] Results indicated peak emissions of particles were color shade dependent and varied between 12,000 – 22,000 particles/cm^3 with modal diameters ranging from 36 nm – 1.3 μm, and the majority of monitored mean particle diameters were ≤ 100 nm for all products. Peaks of larger particles with a mean diameter sized 0.3 – 2 μm were also observed, indicating agglomeration during consumer application. While these larger particles were fewer (≤ 5000 particles/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 (TiO_2) and iron oxide (Fe_2O_3), which are commonly found in powder-based makeup, functioning as pigmentation to produce various shades of cosmetics.[47-50] 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 multiple path particle dosimetry (MPPD) model.[45] For nano-sized particles, the entire exposure duration of 20 minutes could cause lung surface loading of 60 $\mu g/m^2$ based on the peak deposition mass flux of 3 $\mu g/min/m^2$, and for micro-sized particles, an inhaled dose within 20 minutes of exposure was estimated to be 1.1 mg/m^2, based on the peak deposition mass flux of 55 $\mu g/min/m^2$. 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 (TiO_2 and Fe_2O_3).[45] 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.[44]

The application of regular eyebrow powders may result in user exposure to respirable particles.[51] The concentration of TiO_2 in airborne particle fractions (particles with $d_{ae} \leq 10$ µm or ≤ 4 µm) was proportional to the presence of 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).[42,44,45,51]

Inhalation Exposure of ENPs from Aerosolized Consumer Products

Due to insoluble/poorly-soluble, biopersistent, and surface-reactive nature, the interaction of nanoparticles with biological entities may occur at the near-molecular level.[41,52,53] 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.[33,54-57] 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.[37,44,58] Studies demonstrated certain chemicals, such as organic solvents and volatile organic compounds within the complex mixture, may transform constituent nanoparticles by modifying particle surfaces.[59-62] Surface modification may further cause profound changes in a nanomaterial with regard to certain physicochemical properties and potentially the altered toxic effects.[53] 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.[44,63] For example, addition of surfactants can cause a more stable nanoparticle suspension as a whole by creating micelles.[58] 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.[44,58] 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.[36,45,64] 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 NEP 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.[44,45] 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 Expert Panel for Cosmetic Ingredient Safety (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 ≤ 100 nm, and the majority of the collected aerosols contained agglomerates sized < 2 μm), and all of the four investigated products may have similar size distributions.[44,45] 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.[65-69] 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.[70] 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),[71] 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),[72] 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 TiO_2 and Fe_2O_3, which poses public health risks.[35,44,45,48] For instance, TiO_2 is classified as a “Carcinogen Category 2 (inhalation)” by the European Commission,[73] and in the EU, several nanomaterials (e.g., nano form of TiO_2, 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.[38,74] 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.[75-77] In addition, the majority of seventeen surveyed tanning booth locations simply suggested the customers hold their breath through spray tanning.[78] 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.[11] Thus, these measurements may not correlate well with the size distributions of the particles released from the product under consumer use conditions. Some photographic methods are being developed to characterize the actual sizes and shapes of the particles released from powder products during use, such as 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 μm,[36,43] which does not cover the full spectrum of particle sizes typically released from cosmetic sprays (with the largest portion being in the 50 – 300 μm range). In 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.[32] Organic particles or a more complex mixture are hard to detect using electron microscopy.[34] It is not clear whether these methods are amenable to characterizing the aerodynamic equivalent diameters of the particles under real use conditions, because factors such as particle/droplet density and maturation are also important considerations.[34] 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.[34,79,80]

Data obtained from the Netherlands's National Institute for Public Health and the Environment (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 μm.[1,17,23,31] 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.[1,81,82] 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.[32,34,80,82] 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).[81] 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").[83] 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).[31,83] 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.[32]

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.[31] 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:[82]

- 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^3 for cosmetics sprayed towards the body). This simple, very conservative exposure assessment value is then compared to a systemic threshold and if the outcome is acceptable, no additional work is needed.
- Tier II 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.

Sample Exposure Calculations

Sample exposure calculations utilizing the approach described above are presented here for an aerosol hair spray product.[31]

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

  Aerosol hairspray assumptions:

  Amount used per day: 9.89 g (95^{th} percentile)[84]
  Ingredient makes up 2% of product
  Body weight: 60 kg

  Exposure estimate:

  9.89 g x 0.02 (ingredient) = 0.198 g (198 mg)

198 mg ÷ 60 kg = **3.3 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,[1] 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[85]
  - 25% exhaled

  Exposure estimate:

  First 2 minutes: 198 mg/1000 L x 10 L/minute x 2 minutes = 3.96 mg

  Next 18 minutes: 198 mg/10,000 L x 10 L/minute x 18 minutes = 3.56 mg

  Total exposure 3.96 mg + 3.56 mg = 7.52 mg

  25% exhaled (0.75 exchange factor)

  7.52 x 0.75 = 5.64 mg

  5.64 mg ÷ 60 kg = **0.094 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.[81]

  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 mg/kg/day x 0.05 = **0.0047 mg/kg/day**

  Calculations for deodorant would be conducted similarly. Spray deodorant habits and practices data are available.[53]

- Realistic Exposure Measurements under Simulated Use Conditions

  An example of exposure assessment for antiperspirant spray products, mimicking in-use conditions and incorporating particle/droplet size data, has been reported.[83] Exposure to aluminum from four antiperspirant sprays containing up to 1.5% aluminum is assessed using a simple two-box model, with calculation of the inhaled aluminum dose over 12 minutes. Within this approach, real-world consumer habits and practices data on frequency, duration, and amount per use for all cosmetic product categories (based on a database of more than 26,000 EU consumers) are considered. Systemic exposure of the upper respiratory tract and deep lung deposition were calculated using the MPPD Model. The total systemic exposure via inhalation was found to be **less than 0.5 μg per application** (i.e., less than **0.0084 μg/kg/application** for a 60 kg person). In this study, inhalation exposure estimates when the product was sprayed against a skin surrogate were further compared to spraying in the air ("free spraying"). Free spraying overestimated uptake by more than a factor of two. The results suggest that exposure estimates incorporating spray product use levels and ingredient concentrations and adjusted for distribution in two-box model result in highly conservative estimates of lung exposure.

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.[86]

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 access 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).[87] 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_2 and Fe_2O_3, 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. Therefore, a question currently remains unanswered: "**Is the delivery of certain consumer products via airbrush delivery systems considered to be a cosmetic use within the US regulatory structure?"** 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]).

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

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

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_{ae} ranging from 1 to 4 μm, which is well within the range considered to be respirable. However, this ingredient, as supplied to formulators, has an average d_{ae} of about 20 μm, and the ingredient aggregates and agglomerates to form clusters and chains with d_{ae} > 125 μm, and none < 90 μm. Thus, the formation of granulomas in the animals was not considered to be relevant for evaluating the inhalation safety of this ingredient as used in cosmetic products.

The Panel also noted data are currently insufficient to assess the inhalation exposure 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.

References

1. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett.* 2011;205(2):97-104.
2. Bailey MR, Ansoborlo E, Etherington G, et al. Proposed updating of the ICRP human respiratory tract model. 12th International Congress of the International Radiation Protection Association. Buenos Aires, Argentina. 2008.
3. Bakand S, Winder C, Khalil C, Hayes A. Toxicity assessment of industrial chemicals and airborne contaminants: transition from in vivo to in vitro test methods: a review. *Inhal Toxicol.* 2005;17(13):775-787.
4. Roy M. IRPA International Conference: Dosimetry of the respiratory tract. Vienna, Austria. Vol. 1, No. 4. Fontenay-aux Roses, France: International Radiation Protection Association (IRPA). 1996;1:153-159.
5. World Health Organization (WHO). *Hazard Prevention and Control in the Work Environment: Airborne Dust.* Geneva, Switzerland.1999. WHO/SDE/OEH/99.14.
6. Morrow PE. Mechanisms and significance of "particle overload". In: Mohr U DD, Mauderly JL, Oberdörster G, ed. *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract.* Washington, DC: International Life Sciences Institute (ILSI) Press; 1994:17-26.
7. Mossman BT. Mechanisms of action of poorly soluble particulates in overload-related lung pathology. *Inhal Toxicol.* 2000;12(1-2):141-148.
8. Nikula KJ. Rat lung tumors induced by exposure to selected poorly soluble nonfibrous particles. *Inhal Toxicol.* 2000;12(1-2):97-119.
9. Oberdorster G. Lung particle overload: implications for occupational exposures to particles. *Regul Toxicol Pharmacol.* 1995;21(1):123-135.

10. Rothe H. Special aspects of cosmetic spray safety evaluation. Unpublished information presented at the 26 September 2011 CIR Expert Panel Meeting. Washington, DC. 2011.
11. Rothe H. Special aspects of powders in decorative cosmetics. Unpublished information presented at the 26 September 2011 CIR Expert Panel Meeting. Washington, DC.; 2011.
12. de Winter-Sorkina R, Cassee FR. *From concentration to dose Factors influencing airborne particulate matter deposition in humans and rats.* 2002. RIVM 650010031/2002.
13. Phalen RF, Mendez LB, Oldham MJ. New developments in aerosol dosimetry. *Inhal Toxicol.* 2010;22 Suppl 2:6-14.
14. Phalen RF, Oldham MJ. Aerosol dosimetry considerations. *Clin Occup Environ Med.* 2006;5(4):773-784.
15. European Commission Joint Research Center. *Guidance Document on the Determination of Particle Size Distribution, Fibre Length and Diameter Distribution of Chemical Substances.* Luxembourg 2002. EUR 20268 EN.
16. Witschi HP, Last JA. Toxic Responses of the Respiratory System. In: CD K, ed. *Casarett & Doull's Toxicology: The Basic Science of Poisons.* 6 ed. New York: McGraw-Hill; 2001:515-534.
17. Bremmer HJ, Lodder LCHPhd, Engelen JGMv. *General Fact Sheet: Limiting conditions and reliability, ventilation, room size, body surface area; Updated version for ConsExpo 4.* Bilthoven, Netherlands 2006. RIVM 320104002/2006.
18. Heyder J, Gebhart J, Rudolf G, Schiller CF, Stahlhofen W. Deposition of particles in the human respiratory tract in the size range 0.005-15 µm. *J Aerosol Sci.* 1986;17(5):811-825.
19. Hatch TF. Distribution and deposition of inhaled particles in respiratory tract. *Bacteriol Rev.* 1961;25:237-240.
20. International Commission on Radiological Protection (ICRP). *Human Respiratory Tract Model for Radiological Protection.* Didcot, Oxfordshire, England.1994. ICRP Publication 66. Ann. ICRP 24 (1-3).
21. Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect.* 2005;113(7):823-839.
22. Brown JS, Gordon T, Price O, Asgharian B. Thoracic and respirable particle definitions for human health risk assessment. *Part Fibre Toxicol.* 2013;10:12.
23. Delmaar JE, Bremmer HJ. *The ConsExpo Spray Model.* 2009. RIVM 320104005/2009.
24. Eickmann U, Eickmann J, Tischer M. Exposure to Sprays: Comparison of the available exposure models. *Gefahrstoffe - Reinhaulting der Luft.* 2007;67(7/8):305-318.
25. Greim H, Borm P, Schins R, et al. Toxicity of fibers and particles. Report of the workshop held in Munich, Germany, 26-27 October 2000. *Inhal Toxicol.* 2001;13(9):737-754.
26. Muhle H, Mangelsdorf I. Inhalation toxicity of mineral particles: critical appraisal of endpoints and study design. *Toxicol Lett.* 2003;140-141:223-228.
27. European Aerosol Federation (FEA). *Guide on Particle Size Measurements from Aerosol Products.* Belgium. 2009.
28. Bremmer HJ, Lodder LCHPhd, Engelen JGMv. *Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4.* 2006. RIVM 320104001/2006.
29. Tuinman IL. *Aerosols from Spray Cans and Trigger Sprays. Particle Size Distributions and Spreading in a Closed Environment.* 2004. TNO report PML 2004-C106.
30. Tuinman IL. *Particle size distributions of aerosols from spray cans and trigger sprays.* 2007. TNO report august 2007.
31. CIR Science and Support Committee of the Personal Care Products Council (CIR SSC). Comments on Draft Revised CIR Precedent - Aerosols Document/Submission of Aerosol Particle Size Data. Unpublished data submitted by the Personal Care Products Council. In:2018.
32. Steiling W, Almeida JF, Assaf VH, et al. Principles for the safety evaluation of cosmetic powders. *Toxicol Lett.* 2018;297:8-18.
33. Nazarenko Y, Zhen H, Han T, Lioy PJ, Mainelis G. Nanomaterial inhalation exposure from nanotechnology-based cosmetic powders: a quantitative assessment. *J Nanopart Res.* 2012;14(11).
34. Nazarenko Y. Exposure assessment of nanomaterial-containing aerosols from spray and powder products. Unpublished information presented at the 144th CIR Expert Panel Meeting, September 11, 2017. Washington D.C.

35. Oh H-J, Kim J. Characterization of inhalable aerosols from cosmetic powders and sustainability in cosmetic products. *Sustainability.* 2020;12(8187).
36. 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;120(6):885-892.
37. Tillett T. A compact exposure: estimating inhalation of engineered nanoparticles in cosmetic powders. *Environ Health Perspect.* 2012;120(6):A245.
38. Scientific Committee on Consumer Safety (SCCS). *Scientific advice on the safety assessment of nanomaterials in cosmetics.* 2021. SCCS/1618/20.
39. Laycock A, Wright MD, Romer I, Buckley A, Smith R. Characterisation of particles within and aerosols produced by nano-containing consumer spray products. *Atmos Environ X.* 2020;8:100079.
40. Nowack B, Bucheli TD. Occurrence, behavior and effects of nanoparticles in the environment. *Environ Pollut.* 2007;150(1):5-22.
41. U.S. Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition (CFSAN). Guidance for Industry Safety of Nanomaterialsin Cosmetic Products. In:2014.
42. Nazarenko Y, Han TW, Lioy PJ, Mainelis G. Potential for exposure to engineered nanoparticles from nanotechnology-based consumer spray products. *J Expo Sci Environ Epidemiol.* 2011;21(5):515-528.
43. Nazarenko Y, Lioy PJ, Mainelis G. Quantitative assessment of inhalation exposure and deposited dose of aerosol from nanotechnology-based consumer sprays. *Environ Sci Nano.* 2014;1(2):161-171.
44. Pearce K, Goldsmith WT, Greenwald R, Yang C, Mainelis G, Wright C. Characterization of an aerosol generation system to assess inhalation risks of aerosolized nano-enabled consumer products. *Inhal Toxicol.* 2019;31(9-10):357-367.
45. Pearce KM, Okon I, Watson-Wright C. Induction of Oxidative DNA Damage and Epithelial Mesenchymal Transitions in Small Airway Epithelial Cells Exposed to Cosmetic Aerosols. *Toxicol Sci.* 2020;177(1):248-262.
46. Park J, Ham S, Kim S, et al. Physicochemical characteristics of colloidal nanomaterial suspensions and aerosolized particulates from nano-enabled consumer spray products. *Indoor Air.* 2020;30(5):925-941.
47. Dreno B, Alexis A, Chuberre B, Marinovich M. Safety of titanium dioxide nanoparticles in cosmetics. *J Eur Acad Dermatol Venereol.* 2019;33 Suppl 7:34-46.
48. Lu PJ, Huang SC, Chen YP, Chiueh LC, Shih DY. Analysis of titanium dioxide and zinc oxide nanoparticles in cosmetics. *J Food Drug Anal.* 2015;23(3):587-594.
49. Borowska S, Brzoska MM. Metals in cosmetics: implications for human health. *J Appl Toxicol.* 2015;35(6):551-572.
50. Fytianos G, Rahdar A, Kyzas GZ. Nanomaterials in Cosmetics: Recent Updates. *Nanomaterials (Basel).* 2020;10(5).
51. Oh HJ, Han TT, Mainelis G. Potential consumer exposure to respirable particles and TiO2 due to the use of eyebrow powders. *J Expo Sci Environ Epidemiol.* 2020;31(6):1032-1046.
52. Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect.* 2005;113(7):823-839.
53. Scientific Committee on Consumer Safety (SCCS). *The SCCS's notes of guidance for the testing of cosmetic ingredients and their safety evaluation (11th Revision).* 2021. SCCS/1628/21.
54. Tha EL, Canavez A, Schuck DC, Gagosian VSC, Lorencini M, Leme DM. Beyond dermal exposure: The respiratory tract as a target organ in hazard assessments of cosmetic ingredients. *Regul Toxicol Pharmacol.* 2021;124:104976.
55. Scientific Committee on Emerging and Newly Identified Health Risk (SCENIHR). *Opinion on: The appropriateness of existing methodologies to assess the potential risk associated with engineered and adventitious products of nanotechnologies.* 2006.
56. Simeonova PP, Erdely A. Engineered nanoparticle respiratory exposure and potential risks for cardiovascular toxicity: predictive tests and biomarkers. *Inhal Toxicol.* 2009;21 Suppl 1:68-73.
57. Scientific Committee on Consumer Safety (SCCS). *Guidance on the safety assessment of nanomaterials in cosmetics.* 2019. SCCS/1611/19.

58. Mitrano DM, Motellier S, Clavaguera S, Nowack B. Review of nanomaterial aging and transformations through the life cycle of nano-enhanced products. *Environ Int.* 2015;77:132-147.
59. Choudhury T. The physical chemistry of cosmetic formulations. https://www.happi.com/contents/view_features/2008-02-29/the-physical-chemistry-of-cosmetic-formulatio/. Published 2008. Accessed 09/16/2021.
60. Chalbot MG, Pirela SV, Schifman L, et al. Synergistic effects of engineered nanoparticles and organics released from laser printers using nano-enabled toners: potential health implications from exposures to the emitted organic aerosol. *Environ Sci Nano.* 2017;4(11):2144-2156.
61. Bello D, Martin J, Santeufemio C, et al. Physicochemical and morphological characterisation of nanoparticles from photocopiers: implications for environmental health. *Nanotoxicology.* 2013;7(5):989-1003.
62. Kamiya H, Iijima M. Surface modification and characterization for dispersion stability of inorganic nanometer-scaled particles in liquid media. *Sci Technol Adv Mater.* 2010;11(4):044304.
63. Boxall A, Chaudhry Q, Sinclair C, et al. Current and future predicted exposure to engineered nanoparticles. Health Environ Res. In: Department for Environment FRA, ed. United Kingdom 2007.
64. Bermudez E, Mangum JB, Wong BA, et al. Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles. *Toxicol Sci.* 2004;77(2):347-357.
65. Quadros ME, Marr LC. Silver nanoparticles and total aerosols emitted by nanotechnology-related consumer spray products. *Environ Sci Technol.* 2011;45(24):10713-10719.
66. Calderon L, Yang L, Lee K, Mainelis G. Characterization of Airborne Particle Release from Nanotechnology-enabled Clothing Products. *J Nanopart Res.* 2018;20(12).
67. Losert S, von Goetz N, Bekker C, et al. Human exposure to conventional and nanoparticle--containing sprays-a critical review. *Environ Sci Technol.* 2014;48(10):5366-5378.
68. Bekker C, Brouwer DH, van Duuren-Stuurman B, Tuinman IL, Tromp P, Fransman W. Airborne manufactured nano-objects released from commercially available spray products: temporal and spatial influences. *J Expo Sci Environ Epidemiol.* 2014;24(1):74-81.
69. Myers TR. The science guiding selection of an aerosol delivery device. *Respir Care.* 2013;58(11):1963-1973.
70. Kim HJ, Jung MS, Shin JM, Hur YK. Verification of air brush effectiveness using cosmeceutical ingredients. *Biomedical Dermatology.* 2018;2(24).
71. U.S. Food and Drug Administration (FDA). Product Classification-Airbrush. https://www.accessdata.fda.gov/scripts/cdrh/Cfdocs/cfpcd/classification.cfm?id=1327. Updated 10/11/2021. Accessed 10-18-2021.
72. U.S. Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition (CFSAN). Adverse Event Reporting System (CAERS). https://www.fda.gov/food/compliance-enforcement-food/cfsan-adverse-event-reporting-system-caers. Updated 07/29/2020. Accessed 09/12/2021, .
73. Scientific Committee on Consumer Safety (SCCS). *Opinion on Titanium dioxide (TiO_2) used in cosmetic products that lead to exposure by inhalation.* 2020. SCCS/1617/20.
74. Scientific Committee on Consumer Safety (SCCS). *Opinion for clarification of the meaning of the term "sprayable applications/products" for the nano forms of carbon black CI 77266, titanium oxide and zinc oxide.* 2015. SCCS/1539/14.
75. Braunberger TL, Nahhas AF, Katz LM, Sadrieh N, Lim HW. Dihydroxyacetone: A Review. *J Drugs Dermatol.* 2018;17(4):387-391.
76. U.S. Food and Drug Administration (FDA). Tanning Products. https://www.fda.gov/radiation-emitting-products/tanning/tanning-products. Published 2019. Updated 04/26/2019. Accessed 08-26-2021.
77. Meadows M. Don't be in the dark about tanning. *FDA Consumer magazine.* 2003;37:16-17.
78. Fu JM, Dusza SW, Halpern AC. Sunless tanning. *J Am Acad Dermatol.* 2004;50(5):706-713.
79. Russell RS, Merz RD, Sherman WT, Sivertson JN. The determination of respirable particles in talcum powder. *Food Cosmet Toxicol.* 1979;17(2):117-122.
80. Singal M. Considerations for inhalation safety assessment: safety assessment approaches and application. Unpublished information presented at the 144th CIR Expert Panel Meeting, September 11, 2017. Washington D.C.
81. Steiling W, Buttgereit P, Hall B, et al. Skin exposure to deodorants/antiperspirants in aerosol form. *Food Chem Toxicol.* 2012;50(6):2206-2215.

82. Steiling W, Bascompta M, Carthew P, et al. Principle considerations for the risk assessment of sprayed consumer products. *Toxicol Lett.* 2014;227(1):41-49.
83. Schwarz K, Pappa G, Miertsch H, Scheel J, Koch W. A methodology for the assessment of inhalation exposure to aluminium from antiperspirant sprays. *Arch Toxicol.* 2018;92(4):1383-1392.
84. Loretz L, Api AM, Barraj L, et al. Exposure data for personal care products: hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. *Food Chem Toxicol.* 2006;44(12):2008-2018.
85. U.S. Environmental Protection Agency (EPA). *Exposure Factors Handbook 2011 Edition (Final Report).* Washington, DC. 2011. EPA/600/R-09/052F.
86. Behrsing H, Hill E, Raabe H, et al. 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.* 2017;45(3):117-158.
87. European Aerosol Federation (FEA). *Guide on Inhalation Safety Assessment for Spray Products.* Belgium. 2013.