This document is a compilation of issues discussed by the CIR Expert Panel. This is intended to provide
background on issues and serve as a reference explaining the reasoning behind Panel decisions.
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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 formulation. It should also be noted that droplet/particle size data generated under experimental conditions may be different from droplet/particle size in actual consumer exposures. Other exposure factors are key in assessing inhalation safety, such as temperature, humidity, spray distance, spray time, container fullness, the amount of pressure on the actuator, etc.

Pulmonary overload is a condition in which the accumulation of any inert, poorly soluble particulate material in the lungs overwhelms the capacity of the alveolar macrophages to clear the material from the lungs. Chronic pulmonary overload can cause persistent inflammatory responses, fibrosis and tumors,6 although the mechanism(s) of overload-induced tumor formation is not completely understood.6-9 The European Union’s current threshold for protecting workers from pulmonary overload during occupational exposure to respirable dust particles is 1.5 mg/m3 8 hour time-weighted average. In comparison, inhalation exposures to aerosols from cosmetic sprays will be much lower than this threshold, primarily because of the much shorter exposure duration associated with cosmetic spray use (i.e., only a few minutes).1,10

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

Regional Particle Deposition

The physical parameter most strongly associated with the deposition pattern of an aerosol in the respiratory tract is the aerodynamic equivalent diameter ($d_{ae}$).12,13 The $d_{ae}$ of a droplet/particle is defined as the diameter of a hypothetical, smooth sphere of unit density (e.g., 1 g/cm3) that has the same gravitational settling velocity as the droplet/particle in calm air, regardless of its actual geometric size, shape and density.5,14

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
dae ~ 100 µm), which can enter the nasopharyngeal region through the nose or mouth, the bronchial fraction (median dae ~ 10 µm), which can pass through the larynx to enter the trachea, bronchi and bronchioles, and the respirable fraction (median dae ~ 4 µm), which can enter the alveolar region of the lungs. 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. 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 dae > 10 µm into the pulmonary region is essentially zero. Thus, only droplets/particles with dae ≤ 10 µm are considered to be respirable. This is a conservative assumption because a dae of 5 µm or less is often reported in the scientific literature as the threshold below which droplets/particles can reach the alveoli. In addition, there is consensus that droplets/particles with dae > 15 µm are deposited almost exclusively in the nasopharyngeal and bronchial regions of the respiratory tract, and that healthy people will clear particles with dae > 7 µm from these regions within 24 hours through mucociliary action.

**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. After release to the air, the particle size distribution can change rapidly through aggregation, agglomeration, sedimentation, evaporation of volatile components, or hygroscopic absorption of water. For example, all of the water and other volatile solvents and propellants in droplets with dae < 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.

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

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 dae of 35 µm with a coefficient of variation of 0.3. 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 dae 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.
Measurement of Particle Size Distribution

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

The droplets/particles released from a propellant hair spray are distributed within a 1 to 2 m³ space in the breathing zone during the first 2 minutes after spraying, which expands to form an homogenous 10 m³ cloud (about the size of a bathroom) over the subsequent 18 minutes.1,10 Simulation studies revealed that all of the droplets/particles released from both pump sprays and propellant sprays settle quickly after spraying, including the respirable and inhalable fractions, which substantially reduces the overall potential for inhalation exposure.5,10,14,23,24 Specifically, about 35% of the airborne droplets/particles drop away from the breathing zone in the first minute, 60% in the second minute, 90% in six minutes, and 95% in eight minutes after spraying.10 The droplets/particles are likely to be undetectable in the breathing zone within 10 minutes after spraying.

Due to the compressed format and low usage amounts, inhalation exposure to compact powders is not expected at use conditions.27 In contrast, loose powders, which lack the particle cohesion, have the potential to generate airborne particles, with which there is potential for inhalation exposure. Most of the mass (85% to 93%) of inhaled airborne particles released from cosmetic powders is deposited in the head airways.28,29 The current weight-of-evidence suggests that particles from cosmetic powders are predominately large, and only small amounts of powder deposit in the lower regions of the respiratory system (pulmonary region). Further reduction of incidental inhalation exposures to respirable particles from cosmetic products can be accomplished, however, by utilizing use devices, ingredients, and formulations that enable minimized aerosol generation, and/or skew the size distributions, of the particles released from these products, outside of the respirable range.28

One industry survey provides volume weighted particle size distribution data, measured using laser diffraction, for propellant hair sprays and propellant deodorant/antiperspirant sprays.30 Data are reported as volume diameter defined by 10%, 50% (volume median), and 90% of the cumulative volume undersize (Dv10, Dv50, and Dv90, respectively). The 90% particle sizes (Dv90) of droplets/particles released from propellant hair sprays are distributed within the size range of 23.5 – 409 μm, whereas the mean (SD) values of Dv50 and Dv10 are 70.5 (36.3) and 32.7(18.2) μm, respectively. Propellant deodorant/antiperspirant sprays have consistently smaller median particle/droplet size than propellant hair sprays. The mean (SD) values of Dv90, Dv50 and Dv10 of droplets/particles released from propellant deodorant/antiperspirant sprays are 4.1 (2.6), 23 (33.2), and 35.3 (7.6) μm, respectively. In addition, the percentage of respirable particles/droplets (% < 10 μm) is 3.24 ± 4.48 and 26.6 ± 13.4 (mean ± SD) for propellant hair sprays and deodorant/antiperspirant sprays, respectively. Hairsprays have consistently larger median droplet/particle size than deodorant/antiperspirant.

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

Characterizing the particle size distributions released from finished powder products under use conditions is difficult. This is because the methods used to measure the particle sizes of powder products involve dispersing the powder in a solvent or applying a pressure differential to break up the agglomerated particles. Thus, these measurements may not correlate well with the size distributions of the particles released from the product under consumer use conditions. Some photographic methods are being developed to characterize the actual sizes and shapes of the particles released from powder products during use, such as scanning mobility particle sizer (SMPS) and aerodynamic particle sizer (APS). These sampling devices provide airborne particle concentrations and size distributions in the range between 14.1 nm and 20 µm, which does not cover the full spectrum of particle sizes typically released from cosmetic sprays (with the largest portion being in the 50 – 300 µm range). In addition, SMPS requires at least 3 minutes of application period to scan the entire particle size, which represents an exaggerated estimate of duration per aerosol spray application, compared to customary cosmetic use conditions. Organic particles or a more complex mixture are hard to detect using electron microscopy. 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. 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.

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

The CIR Expert Panel has previously noted that in practice, 95% to 99% of the droplets/particles released from cosmetic pump and propellant hair sprays have aerodynamic equivalent diameters greater than 10 µm. While a larger fraction of respirable particles would release from propellant deodorant sprays, the realistic consumer exposure is generally many times lower compared to the amount calculated with the in silico models. Thus, most aerosol droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions of the respiratory tract and would not be respirable to any appreciable amount. Unintentional exposure to an ingredient by inhalation during the application of cosmetic sprays will be very low to negligible.

Tiered Approach for Inhalation Safety Evaluation

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

- 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 m³ for cosmetics sprayed towards
the body). This simple, very conservative exposure assessment value is then compared to a systemic threshold and if the outcome is acceptable, no additional work is needed.

- **Tier II** 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, for example, one-box and two-box models, which vary in the number of assumed zones in which the emitted material is homogeneously dispersed. More sophisticated models may incorporate factors to determine how much of a spray/chemical is actually inhaled, exhaled, is reaching the deeper lung, or is deposited.

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

In practice, exposure to 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.

**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.

The Panel recognized that aerosols from propellant sprays are distinct from aerosols from pump sprays. For each ingredient or ingredient group assessed, the Panel would like to know whether the current practices of use include propellant sprays, pump sprays, or both. Identifying the use of ingredients in deodorant spray products may be especially important, because they potentially release the largest amount of respirable droplets/particulates among the products evaluated. However, better information about particle size distributions and their variability (within and across product types) that can be reasonably expected, generally, from a broad range of products (e.g., hair, sunscreen, indoor suntanning, foot and deodorant sprays, and loose powders) would substantially increase confidence in safety assessments of ingredients in products that may be aerosolized.

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

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

On the other hand, the Panel noted that inhalation toxicity studies on test animals are often conducted using high concentrations of droplets/particles with size distributions well within the respirable range and long exposure durations to ensure that the potential for pulmonary or systemic toxicity will be detected. In contrast, the concentrations of respirable droplets/particles and the inhalation exposure durations from the use of cosmetic products will be much less than those of the animal studies. Thus, the adverse effects reported in such studies may have little or no relevance for evaluating the inhalation safety of cosmetic ingredients.

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

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

References


30. Worldwide MI. A basic guide to particle characterization. 2015.  


