

COSMETIC INGREDIENT REVIEW

CIR Precedents

Aerosols

9/2012

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

Sprays/Powders

Update 1/2012

BACKGROUND

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

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

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

The physical parameter most strongly associated with the deposition pattern of an aerosol in the respiratory tract is the aerodynamic equivalent diameter, d_{ae} .^{6,7} The d_{ae} of a droplet/particle is defined as the diameter of a hypothetical, smooth sphere of unit density (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.^{5,8}

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

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

Particle size distributions are product specific. Numerous factors determine the initial size distribution of droplets or particles released from a spray product, including the product formulation (e.g., volatile or nonvolatile solvent), propellant, can size, and differential pressure through the nozzle for propellant sprays, and formulation and nozzle characteristics for pump sprays.^{1,16} After release to the air,

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

Both pump sprays and propellant sprays (also called “aerosol sprays”) produce aerosols, but the aerosols from propellant sprays have larger fractions of respirable droplets/particles than aerosols from pump sprays.¹ For example, the median d_{ae} of the airborne droplets/particles of pump hair sprays range from $60 \mu\text{m}$ to $80 \mu\text{m}$.^{1,16,17} Typically, $<1\%$ of the airborne droplets/particles released from pump sprays are in the range considered to be respirable (i.e., $d_{ae} < 10 \mu\text{m}$).¹⁶ In comparison, the median d_{ae} of the airborne droplets/particles of propellant hair sprays range from $25 \mu\text{m}$ to $50 \mu\text{m}$.^{1,16,17} Usually, 1% to 2.5% but no more than 5% of the droplets/particles emitted from propellant hair sprays are within the respirable range.¹⁶

Further, different types of propellant-spray products may yield substantially different particle size distributions. For example, conservative estimates indicate that propellant hair-spray aerosols have a median d_{ae} of $35 \mu\text{m}$ with a coefficient of variation of 0.3 .^{12,17} Thus, the insoluble aerosol particles inhaled during hair-spray use will be deposited primarily in the nasopharyngeal and bronchial regions, where they can be trapped and cleared from the respiratory tract through mucociliary action. In contrast, analogous estimates indicate that the tested deodorant-spray aerosols have a median d_{ae} of $10 \mu\text{m}$ with a coefficient of variation of 0.3 , suggesting that half of these particles are within the range considered to be respirable.^{12,17}

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

The droplets/particles released from a propellant hair spray are distributed within a 1 to 2 m^3 space in the breathing zone during the first 2 minutes after spraying, which expands to form an homogenous 10-m^3 cloud (about the size of a bathroom) over the subsequent 18 minutes.^{1,16} Simulation studies revealed that all of the droplets/particles released from both pump sprays and propellant sprays settle quickly after spraying, including the respirable and inhalable fractions, which substantially reduces the overall potential for inhalation exposure.^{5,8,16-18} 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.¹⁶ The droplets/particles are likely to be undetectable in the breathing zone within 10 minutes after spraying.

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,²¹ although the mechanism(s) of overload-induced tumor formation is not completely understood.²¹⁻²⁴ The European Union’s current threshold for protecting workers from pulmonary overload during occupational exposure to respirable dust particles is 1.5 mg/m^3 8-hour time-weighted average. In comparison, inhalation exposures to aerosols from cosmetic sprays will be much lower than this threshold, primarily because of the much shorter exposure duration associated with cosmetic spray use (i.e., only a few minutes).^{1,16}

Industry can ensure that inhalation exposures to cosmetic sprays and powders are minimized.¹⁶ 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, in the formulations.²⁵ The binding materials foster the agglomeration of the ingredients and substantially increase their cohesivity. These measures increase the size of the particles in the product.

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

The CIR Expert Panel noted that, in practice, 95% to 99 % of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters greater than 10 μm . 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. However, some of the droplets/particles are respirable, including up to 5% of the particle size distribution during the use of some products. Such information should be included in each safety assessment for which the ingredient(s) may be used in a pump or propellant spray. Information will continue to be sought from suppliers and formulators to specifically identify such spray uses.

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

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

The Panel will continue to review all of the relevant inhalation toxicity, use, and other data to determine the safety of cosmetic ingredients. The Panel will evaluate the importance of the inhalation route for assessing the safety of an ingredient or group of ingredients, and evaluate data that may be available to estimate potential respiratory doses from aerosolized products. Factors to consider include whether or how much of the spray products enter the breathing zone, the likely droplet/particle size distributions in the breathing zone, and the exposure durations that can be expected during product use. The Panel agreed that, generally, inhalation exposure to ingredients in aerosolized cosmetic products is unlikely to be significant compared to the dermal or other exposure routes associated with the use of cosmetic products. For example, conservative estimates indicate that inhalation exposures for once-a-day application of a propellant deodorant spray, pump hair spray, or propellant hair spray containing 10%

of an ingredient would be no more than 3, 7, and 20 µg/kg/day.²⁶ These estimates were based on the following conservative assumptions:

- All of the spray enters the breathing zone (i.e., 100% is available for inhalation)
- Exposure duration: 20 minutes
- The droplets/particles:
 - Form a 1-m³ cloud in the first 2 minutes after spraying
 - Dissipate to fill 10-m³ space around the user in the next 18 minutes
- 25% of the inhaled droplets/particles are exhaled
- Breathing rate: 0.01 m³/minute
- Body weight: 60 kg
- Amount of product used: 1.43, 15.6 and 9.89 g/day deodorant, pump-hair, and propellant-hair spray, respectively²⁷
- Respirable fraction: 5%, 1%, 5% for deodorant, pump-hair, and propellant-hair spray, respectively

However, even such small inhalation exposures may be significant for an ingredient that has the potential to act as a potent systemic or local respiratory tract toxicant or to accumulate in the body.

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 aerodynamic equivalent diameter 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.

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

Precedent language for specific report sections:

Cosmetic Use Section

[INGREDIENT(S) *is OR are*] was/were reported to be used in [LIST TYPE(S) OF PRODUCT(S), e.g., *cosmetic sprays, including hair, deodorant, foot, and other propellant and pump spray products*], and could possibly be inhaled. [NOTE THE HIGHEST MAXIMUM USE CONCENTRATION OF THE INGREDIENT IN A SPRAY PRODUCT IF THIS INFORMATION IS AVAILABLE, e.g., *These ingredients are reportedly used at concentrations up to 4%*] In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm [IF PRODUCT(S) MAY INCLUDE BOTH PROPELLANT AND PUMP SPRAYS, ADD: *, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump sprays*]. (Rothe et al 2011, Bremmer et al 2006, Rothe 2011, Johnsen 2004).^{1,12,16,28} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount. Rothe et al 2011, Bremmer et al 2006).^{1,12} [IF PRODUCT(S) MAY INCLUDE DEODORANT SPRAY(S), ADD: *There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable (Bremmer et al 2006).*¹² However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.]

Discussion Section

For Tentative Reports

The Panel discussed the issue of incidental inhalation exposure from [LIST PERTINENT PRODUCT TYPES FOR THE INGREDIENT(S); *EXAMPLE: body and hand sprays, hair color sprays, fragrance preparations and foot powders.*] [IF APPROPRIATE, ADD: *There were no inhalation toxicity data available.*] The Panel considered pertinent data indicating that incidental inhalation exposures to [*this ingredient OR these ingredients OR some of these ingredients*] in such cosmetic products would not cause adverse health effects, including [BRIEFLY LIST WHATEVER DATA THE PANEL DEEMED TO SUPPORT THE CONCLUSION; THIS WILL VARY FROM INGREDIENT (GROUP) TO INGREDIENT (GROUP); *EXAMPLE: data characterizing the potential for [INGREDIENT(S)] to cause systemic toxicity, ocular or dermal irritation or sensitization, and other effects*]. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs; In principle, Inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <http://www.cir-safety.org/cir-findings>.

For Final Reports and Re-Review Summaries

The Panel discussed the issue of incidental inhalation exposure from [LIST PERTINENT PRODUCT TYPES FOR THE INGREDIENT(S); *Example: ...body and hand sprays, hair color sprays, fragrance preparations and foot powders.*]

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

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

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

[ADDRESS PARTICLE SIZES IN COSMETICS, **IF POSSIBLE**; EXAMPLES: (1) The Expert Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. Thus, the adverse effects reported using high doses of respirable particles in the inhalation studies do not indicate risks posed by use in cosmetics OR (2) The particle sizes of these ingredients was reported to range from 50 nm – 1000 μm with the largest portion being in the 50 – 300 μm range. The Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation OR (3) Several of these ingredients are used to increase viscosity, indicating that they tend to swell and aggregate in water and other solvents and would, thus, be too large to be inhaled or respired.]

[NOTE MAXIMUM USE CONCENTRATIONS IN SPRAYS AND/OR LOOSE POWDERS; EXAMPLES: (1) These ingredients are reportedly used at concentrations up to 4% in cosmetic products that may be aerosolized and up to 97% in other products that may become airborne OR (2) These ingredients are reportedly used at concentrations up to 0.01% in cosmetic products that may be aerosolized.]

The Panel noted that 95% – 99% of droplets/particles would not be respirable to any appreciable amount.

[ADDRESS POTENTIAL EXPOSURES TO UPPER AND MID RESPIRATORY TRACT, **AS APPROPRIATE**; EXAMPLES: (1) Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of this ingredient OR (2) Furthermore, these ingredients are not likely to cause any direct toxic effects in the upper respiratory tract, based on the properties of the [INGREDIENT(S)] and on data that shows that these ingredients are not irritants OR (3) The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs; In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties.]

Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects.

The Panel considered other data available to characterize the potential for [INGREDIENT(S)] to cause [LIST PERTINENT TOXICITIES EVALUATED; EXAMPLES: (1) irritation and sensitization

OR (2) systemic toxicity, irritation, sensitization, reproductive and developmental toxicity, and genotoxicity.]

[SUM UP PERTINENT TOXICOLOGY RESULTS; EXAMPLES: (1) They noted the lack of systemic toxicity at high doses in several acute and subchronic oral exposure studies and one chronic oral exposure study, little or no irritation or sensitization in multiple tests of dermal and ocular exposure, the absence of genotoxicity in multiple Ames tests and a Chinese hamster ovary test, and lack of carcinogenicity in a lifetime oral exposure study OR (2) They noted the lack of irritation or sensitization in tests of dermal exposure, no systemic toxicity at 5000 mg/kg, and the absence of genotoxicity in an Ames test of a related chemical.]

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

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

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