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RESEARCH PAPER

Nanomaterial inhalation exposure from nanotechnology-based cosmetic powders: a quantitative assessment

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Abstract In this study we quantified exposures to airborne particles ranging from 14 nm to 20 μm due to the use of nanotechnology-based cosmetic powders. Three nanotechnology-based and three regular cosmetic powders were realistically applied to a mannequin's face while measuring the concentration and size distribution of inhaled aerosol particles. Using these data we calculated that the highest inhaled particle mass was in the coarse aerosol fraction (2.5–10 μm), while particles <100 nm made minimal contribution to the inhaled particle mass. For all powders, 85–93 % of aerosol deposition occurred in the head airways, while <10 % deposited in the alveolar and <5 % in the tracheobronchial regions. Electron microscopy data suggest that nanomaterials were likely distributed as agglomerates across the entire investigated aerosol size range (14 nm–20 μm). Thus, investigation of nanoparticle health effects should consider not only the alveolar region, but also other respiratory system regions where substantial nanomaterial deposition during the actual nanotechnology-based product use would occur.

Keywords Nanoaerosol · Consumer products · Nanoparticles · Personal exposure · Safety of nanotechnology

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Introduction

Use of nanomaterials in consumer products has now become a widespread industry practice (Chuankrerkkul and Sangsuk 2008; Gleiche et al. 2006; Lloyd's 2007; Mihranyan et al. 2012), including extensive application of nanomaterials in cosmetics and other products (Fender 2008; Mihranyan et al. 2012; Mu and Sprando 2010; Nohynek et al. 2008). While it has now been recognized that human exposure to nanomaterials resulting from the use of certain consumer products is possible (Benn et al. 2010; Donaldson et al. 1998; Hagendorfer et al. 2010; Nazarenko et al. 2011, 2012), the extent of this exposure and the associated risks are still unknown (Bradford et al. 2009; Keenan et al. 2009; Lioy et al. 2010) and need to be investigated in depth. Since the market of nanotechnology-based consumer products is expanding (Bradford et al. 2009; Maynard

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2007; Woodrow Wilson International Center for Scholars 2011b), the prevalence of possible human exposures to nanomaterials in such products and related health risks are likely to be increasing as well. Toxicology of pure nanomaterials has been a subject of research for a number of years (Ostrowski et al. 2009). However, when it comes to nanotechnology-based consumer products where these nanomaterials are incorporated, the research community is still far from drawing substantiated conclusions about the potential associated health effects. This lack of quantitative exposure data is one of the reasons why the development of regulations and safety guidelines for nanotechnology-based consumer products is currently delayed (Maynard et al. 2006; Oberdörster et al. 2005b; Paull and Lyons 2008). This study provides a pioneering insight by quantitative assessing of inhalation exposure, which is the first step toward determining potential health effects.

Among the different kinds of nanotechnology-based consumer products, two categories—sprays and cosmetic powders—present a special concern as sources of potentially the strongest nanomaterial inhalation exposure (Hagendorfer et al. 2010; Shimada et al. 2009). When a person uses a cosmetic powder or a consumer spray, airborne particles from the generated aerosol could be inhaled and enter the respiratory system. If the products are nanotechnology-based, these inhaled airborne particles are likely to carry nanomaterials, which could be in the form of free nanoparticles and their agglomerates or nanoparticles attached or incorporated into larger particles. Our previous research on the potential of nanomaterial inhalation exposure from nanotechnology-based cosmetic powders has shown that particles ranging from 14 nm to 20 μm are aerosolized during cosmetic powder application and are likely to be inhaled thus resulting in exposure to nanomaterials (Nazarenko et al. 2012). However, the fraction and size of aerosolized particles carrying nanomaterials that would deposit in a particular region of the respiratory system remained unknown. Information about the sizes of deposited particles as well as their deposition sites in the human respiratory system is important, because chemically the same substance may have substantially different toxicity and associated biological and health effects depending on its size and structural state as well as deposition site following inhalation (Brunekreef and Holgate 2002; Lee 2011; Nel et al. 2006; Oberdörster et al. 2005a; Tsuji et al. 2009; Wardak et al. 2008). These differences can be profound even for small variations in particle size, including within the 1–100 nm range (Bermudez et al. 2004; Carlson et al. 2008; Grassian et al. 2007; Hussain et al. 2005; Quadros and Marr 2011).

In our earlier study, we measured number concentration of aerosol particles that would be released and inhaled during simulated application of cosmetic powders (Nazarenko et al. 2012). Here, we used those data to calculate the mass of various aerosol size fractions inhaled and deposited in different regions of the human respiratory system as a result of using nanotechnology-based cosmetic powders. For comparison, regular powders (not based on nanotechnology) were investigated as well.

To the best of our knowledge, these are the first quantitative data on nanomaterial inhalation exposure due to the use of nanotechnology-based consumer products, specifically cosmetic powders. It is hoped that these inhalation and deposition exposure data will be useful in future studies investigating health effects due to the use of nanotechnology-based consumer products.

Materials and methods

Summary

The size characteristics of the tested nanotechnology-based and regular cosmetic powders were investigated using transmission electron microscopy (TEM). The powders were then realistically applied to the face of a human mannequin head. The particles released as a result of this application were sampled through the nostrils of the mannequin head and their sizes and concentrations were determined. These data were then used to determine the inhaled and deposited dose based on particle mass.

Investigated products

The quantitative inhalation exposure assessment was performed for three nanotechnology-based and three regular cosmetic powders. The three nanotechnology-based cosmetic powders were selected from The Woodrow Wilson Nanotechnology Consumer Products Inventory (Woodrow Wilson International Center for Scholars 2011a). The method used to construct The

Table 1 Investigated cosmetic powders

Product[a]	Purpose[b]	Composition[b]
Nanopowder M[a]	Moisturizer	Water, butylene glycol, sodium ascorbyl phosphate, glycerin, betain, silica, dimethicone, citric acid, polymethyl metacrylate, squalane, sodium hydroxide, sodium metabisulfite, capryloyl glycine, sodium hyaluronate, marus alba root extract, romaines officinalis (Rosemary) leaf extract, olea europaea (Olive) leaf extract
Nanopowder D[a]	Blusher	Mica, talc, dimethicone/vinyl dimethicone crosspolymer, hydrogenated C6–14 olefin polymers, petrolatum, dimethicone, polysilicone-2, aluminum stearate, HDI/trimethylol hexyllactone crosspolymer, sorbitan sesquisostearate, aluminum hydroxide, methicone, tocopherol, silica, triisostearin, trimethylolpropane trioctanoate, ethylparaben, butylparaben, Parfum, CI 77492, CI 77947, CI 77891, CI 77491, CI 77499
Nanopowder K[a]	Sunscreen	Active ingredients: titanium dioxide—25 %, zinc oxide—20 %
Powder F	Blot powder	Dimethicone, silica, kaolin, water, hydrolyzed soy protein, caprylyl glycol, hexylene glycol, methicone, coconut acid, phenoxyethanol, ± mica, iron oxides (CI 77491, CI 77492, CI 77499), ILN31255
Powder G	Blot powder	Talc, C12-15 alkyl benzoate, kaolin, silica silylate, ±mica, iron oxides (CI 77491, CI 77492, CI 77499)
Powder E	Cosmetic powder	Silica

[a] Nanoproduct as per the Woodrow Wilson Nanotechnology Consumer Products Inventory

[b] As per manufacturer

Inventory is based on information provided by manufacturers as part of product marketing. The three regular cosmetic powders with a similar purpose of use as the nanopowders were selected randomly. Table 1 lists the investigated nanotechnology-based and regular cosmetic powders alongside their purpose of use and chemical compositions as reported by the manufacturers. We tested all of the cosmetic powders in their original state without any pre-treatment, deagglomeration, or dilution. The brand names of the investigated cosmetic powders were replaced by letter codes. Additionally, the cosmetic powders were identified by their purpose of application.

TEM characterization of cosmetic powders

All of the cosmetic powders were examined in their original state using a transmission electron microscope (2010F, JEOL Ltd, Tokyo, Japan). A minute quantity of each cosmetic powder was placed on a HC300-Cu TEM grid (Electron Microscopy Sciences, Hatfield, PA, USA) and a number of representative digital micrographs at different magnifications were taken for each specimen. Particle diameters, shape, and the degree of agglomeration in each cosmetic powder were assessed visually using the automatically inserted scale bars on the micrographs.

Simulated application

The experiment to measure the number concentration of the released and inhaled particles was designed to simulate a realistic exposure scenario when cosmetic powders are used by a consumer. The cosmetic powder application and aerosol sampling and measurement process have been described in detail elsewhere (Nazarenko et al. 2012). Briefly, as shown in Fig. 1, a human mannequin head was placed inside a glove box located within a Level II Biosafety cabinet (NUAIRE, Inc., Plymouth, MN, USA). Two stainless steel tubes were installed into the nostrils of the mannequin head to allow for sampling of particles that would be inhaled during the real life application of the powders. The two aerosol streams drawn through the mannequin's nostrils were combined into one at the mannequin's nape using a stainless steel Y-connector, and then drawn into a Scanning Mobility Particle Sizer (SMPS) (module combination 3080/3786, TSI, Inc., Shoreview, MN, USA) and an Aerodynamic Particle Sizer (APS) (model 3321, TSI, Inc.) via electrically conductive tubing. The SMPS and the APS instruments provided aerosol concentrations and size distributions in the range between 14.1 nm and 20 μm.

All the connectors and sampling lines were made as short as possible and of conductive material to

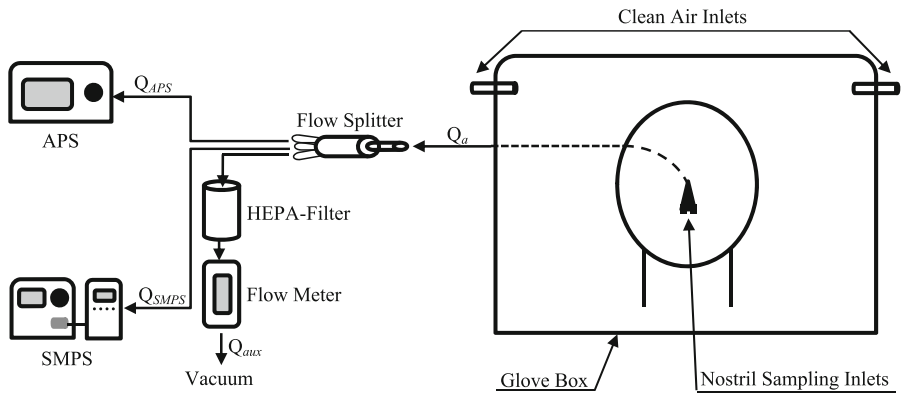

Fig. 1 Setup for exposure measurement of airborne particulate matter resulting from simulated cosmetic powder application

minimize potential particle losses due to the electrostatic effects, diffusion, and gravitational settling. Each test powder was continuously and, to our ability, uniformly applied to the face of the mannequin head during each measurement period. The applicators (brushes or pads) included with the products by the manufacturers were used. No applicators were supplied with Nanopowder M and Regular Powder E, so we used identical kabuki brushes (Sephora USA, Inc., San Francisco, CA, USA) for their application. Another clean kabuki brush was used without any cosmetic powder for comparison. Three measurement repeats were performed for each cosmetic powder. The background particle concentrations were subtracted from the SMPS and the APS measurements.

The total sampling flow rate was $Q_a = 11.0$ L/min corresponding to the breathing rate recommended for assessing short-term exposures for a 18–60 year-old female performing light activity (Yang et al. 2008). This total sampling flow rate was achieved by combining the sampling flow rates of the SMPS–$Q_{a(SMPS)}$ (0.3 L/min) and of the APS–$Q_{a(APS)}$ (4.7 L/min) with an auxiliary aspiration rate—Q_{aux} (6.0 L/min) provided by an additional pump.

Since we sampled through the nostrils of a human mannequin head, we assumed that the measured aerosol size distribution is approximately that of cosmetic powders aspirated into the human nasal airways during the real world cosmetic powder application.

Quantitative exposure assessment

Based on the SMPS and APS measurements, we calculated both the "inhaled dose" and the "deposited dose." By "inhaled dose" we mean the mass of airborne particulate matter that enters the human respiratory system. By "deposited dose" we mean the mass of particulate matter that deposits either in the entire respiratory system or in a specific region of the respiratory system: the head airways (HA), the tracheobronchial region (TB), and the alveolar region (AL).

Inhaled dose

In order to calculate the inhalation exposure, we used the concentration of aerosol released during the simulated application of cosmetic powders as an input for the inhalation model based on the work by Hansen and colleagues (Hansen et al. 2008). While the original Hansen's calculations assumed a hypothetical inhalable fraction of the aerosol not considering particle size, we, on the other hand, used the size-resolved concentrations of airborne particles released during the realistic cosmetic powder applications accounting for the inhalability. The following equation was used (based on Hansen et al. (2008)) and assumptions about each variable are provided below:

$$ID = f_{\text{nano}} \cdot C_{\text{inh}} \cdot Q_{\text{inh}} \cdot T_{\text{contact}}/Bw, \quad (1)$$

where ID, inhaled dose of particulate matter per powder application (ng/kg bw/application); C_{inh}, mass concentration of particulate matter in inhaled air (ng/L); Q_{inh}, inhalation flow rate for a given gender/activity scenario (L/min); T_{contact}, duration of contact per application (min); Bw, body weight (kg), and f_{nano}, mass fraction of nanomaterial(s) in the inhaled aerosol.

We assumed the duration of each application of a cosmetic powder $T_{\text{contact}} = 1$ min. A different T_{contact} can be used to recalculate for different scenarios of cosmetic powder use.

We were not able to determine the fraction of nanomaterials in each investigated product (f_{nano}).

This information was not provided by the manufacturers either, despite our requests. Therefore, we decided to present the worst case scenario by assuming that the powders are completely made up of nanomaterial(s) and the released and inhaled aerosol particles would be completely made of nanomaterials, i.e., $f_{\text{nano}} = 1$. If and when the information on nanomaterial content in the investigated products becomes available, the doses presented here could be easily recalculated using a new f_{nano}.

Mass concentration of particulate matter in the inhaled air (C_{inh}) used in Eq. (1) can be described as:

$$C_{\text{inh}} = IF \cdot C_{\text{air}}, \tag{2}$$

where C_{air} is mass concentration of aerosol particulate matter in the personal breathing cloud. Inhalability fraction (IF) used in Eq. (2) represents the fraction of particulate matter in the personal breathing cloud that is actually inhaled into the respiratory system and is described by Hinds (1999) as:

$$IF = 1 - 0.5\left(1 - \frac{1}{1 + 0.00076 d_{\text{p}}^{2.8}}\right), \tag{3}$$

where d_{p} is particle diameter. This equation is applied for particles up to 100 μm in diameter. Since we used a human mannequin head and sampled through its nostrils at a realistic sampling flow rate, we assumed that the particle aspiration efficiency through the mannequin's nostrils approximately matches inhalability fraction IF for the investigated particle size range of 14.1 nm–20 μm. Therefore, C_{inh} can be obtained directly from the SMPS and APS measurements, which were performed in our previous study (Nazarenko et al. 2012).

The SMPS and APS devices measure the number concentration and size distribution of the particles, and the Aerosol Instrument Manager software (TSI, Inc.) can convert the data into particle mass concentration using user-provided particle density and assuming that particles are spherical.

Both SMPS and APS report aerosol size distributions by particle number and the data are presented in multiple size channels, which are defined by their midpoint. The SMPS aerosol particle concentrations in 108 size channels in the size range of 14.1–661.2 nm were used, while for the APS, aerosol particle concentrations in 48 size channels ranging from 673 nm to 19.81 μm were used. The Aerosol Instrument Manager software (TSI, Inc.) then converts concentration data from each size channel into particle mass concentration using the channel midpoint diameter (assuming that particles are spherical) and user-provided particle density. Since cosmetic powders are generally mixtures of multiple, both inorganic and organic substances, and are usually composites of multiple materials mixed in mostly unknown proportions, we made an assumption of the particle density to be 1.0 g/cm^3. The final exposure data can easily be recalculated for different densities of particles.

The mass concentrations from individual channels could be summed up to determine the total inhaled particle mass or the mass from several channels could be grouped into fractions based on aerosol particle size. Since particles of different sizes may present different potential health impacts and have different penetration and deposition characteristics in the respiratory system, the entire investigated size range was divided into several particulate matter (PM) size fractions of interest: $PM_{0.1-0.014}$ (particles between 14 and 100 nm, or nanoparticle aerosol fraction), $PM_{1-0.1}$ (fine particles between 0.1 and 1 μm, or submicron fraction of fine particles), $PM_{2.5-1}$ (fine particles between 1 and 2.5 μm, or micron fraction of fine particles), $PM_{10-2.5}$ (particles between 2.5 and 10 μm, or coarse particles), and finally PM_{20-10} (particles between 10 and 20 μm, or supercoarse aerosol fraction). The supercoarse fraction was described by Lioy et al. (2006). For the $PM_{0.1-0.014}$ fraction, the lower limit of 14 nm represents the limit of our instruments. The inhaled particle mass was calculated for each one of these size fractions by adding the mass of particles in individual size channels within that fraction.

The body weight, Bw, and inhalation flow rate, Q_{inh}, were assumed to be those of an adult female (60 kg Bw) performing light activity level. This scenario was assumed to be the most typical for the application of cosmetic powders. For this scenario, the US EPA 2011 Exposure Factors Handbook recommends using 11.0 L/min inhalation flow rate specifically for short-term exposure studies (Table 6–49 in the US EPA 2011 Exposure Factors Handbook) (Yang et al. 2008).

The inhalation flow rate associated with light activity (11 L/min) slightly exceeds the inhalation flow rates referenced in the ICRP Publication 66 (International Commission on Radiological Protection 1994) and the US EPA 2011 Exposure Factors Handbook for sedentary activity defined as sitting

and standing and as car driving and riding. However, since the powder application not only involves passive sitting or standing, but also involves the physical activity required to apply a cosmetic powder, we feel that selection of a slightly higher inhalation flow rate is justified. Moreover, in many cases cosmetic products are applied while visiting a public bathroom or a similar place of retreat following light activity (walking), thus resulting in a higher breathing rate than would result from simply standing or sitting.

Deposited dose

We defined the deposited dose, DD_i, as a product of inhaled dose, ID, and the deposition fraction, DF_i, integrated over a particle size range, d_p:

$$DD_i = \int_{d_p} DF_i(d_p) ID(d_p), \tag{4}$$

where i represents a particular region of the respiratory system: head airways, tracheobronchial region, alveolar region, or the entire respiratory system. The deposition fraction DF_i is a fraction of inhaled airborne particulate matter that is removed from the air within a particular region or the entire respiratory system. Deposition fractions for different regions of the respiratory system were calculated using equations fitted to the ICRP (International Commission on Radiological Protection 1994) model for monodisperse spheres of standard density at standard conditions (Hinds 1999). The equations were modified to exclude the inhalability fraction IF because, as discussed above, we assumed that it already is taken into account due to sampling through the nostrils of the human mannequin head (see Eq. 2). The modified equations for DF_i as a function of particle diameter are:

$$DF_{\mathrm{HA}}(d\mathrm{p}) = \left(\frac{1}{1+\exp(6.84+1.183\ln d\mathrm{p})} + \frac{1}{1+\exp(0.924-1.885\ln d\mathrm{p})}\right), \tag{5}$$

$$DF_{\mathrm{TB}}(d\mathrm{p}) = \frac{\left(\frac{0.00352}{d\mathrm{p}}\right)\left[\exp\left(-0.234(\ln d\mathrm{p}+3.40)^2\right) + 63.9\exp\left(-0.819(\ln d\mathrm{p}-1.61)^2\right)\right]}{1-0.5\left(1-\frac{1}{1+0.00076 d\mathrm{p}^{2.8}}\right)}, \tag{6}$$

$$DF_{\mathrm{AL}}(d\mathrm{p}) = \frac{\left(\frac{0.0155}{d\mathrm{p}}\right)\left[\exp\left(-0.416(\ln d\mathrm{p}+2.84)^2\right) + 19.11\exp\left(-0.482(\ln d\mathrm{p}-1.362)^2\right)\right]}{1-0.5\left(1-\frac{1}{1+0.00076 d\mathrm{p}^{2.8}}\right)}, \tag{7}$$

$$DF_{\mathrm{T}}(d\mathrm{p}) = \left(0.0587 + \frac{0.911}{1+\exp(4.77+1.485\ln d\mathrm{p})} + \frac{0.943}{1+\exp(0.508-2.58\ln d\mathrm{p})}\right), \tag{8}$$

where DF_{HA}, deposition fraction for the head airways; DF_{TB}, deposition fraction for the tracheobronchial region; DF_{AL}, deposition fraction for the alveolar region; DF_T, total deposition fraction, equal to the sum of DF_{HA}, DF_{TB}, and DF_{AL}.

Based on our experimental data, d_p corresponded to a midpoint diameter of an SMPS or APS size channel (μm) and the deposited dose in each region of the respiratory system or the total deposition was calculated as a sum of deposited doses for each measurement channel:

$$DD_i = \sum_{d_p} DF_i(d\mathrm{p})ID(d\mathrm{p}), \quad (9)$$

Thus, the deposited dose was calculated as mass of particulate matter deposited in a given region of the respiratory system per 1-minute cosmetic powder application per 1 kg of body weight.

Additionally, we calculated the deposited dose for each human respiratory system region as percentage of the total deposited dose to better showcase the region of the respiratory tract with the greatest deposition of inhaled particulate matter.

The assumptions used to calculate the deposited dose were the same as discussed above when calculating inhaled dose. For both the inhaled and the deposited dose, we considered particle losses in the sampling lines to be negligible.

Results

TEM characterization of cosmetic powders

During the TEM characterization of the cosmetic powders, we did not observe the electron beam to affect the integrity of particles in any of the cosmetic powders as was the case with particles in certain spray-type consumer products investigated previously (Nazarenko et al. 2011). This means that the chemical nature of the particles is likely inorganic (Egerton et al. 2004).

We observed Nanopowder M (Fig. 2a) to contain only nanoparticles (<50 nm), spheroidal in shape, and in a highly agglomerated state. Nanopowder D (Fig. 2b) did not contain any nanoparticles visible using TEM, but seemed to contain only very large irregularly shaped (>5 μm) individual non-agglomerated particles. The majority of particles in Nanopowder K (Fig. 2c) were nanoscale along with larger particles (>3 μm), angular or rod-like, all of which were highly agglomerated.

In the Regular Powder F (Fig. 2d), we observed no individual or agglomerated nanoparticles, but there were nanosized electron-contrast inclusions within the larger particles if viewed at higher magnifications. Similar to Nanopowder D, Regular Powder F contained large (>1 μm) and very large (>5 μm) irregularly shaped individual non-agglomerated particles. There were a few small nanosized structures observed in the Regular Powder G (Fig. 2e); however, we mostly observed 5–10 μm and larger irregularly shaped particles that were either agglomerated or individual. In the Regular Powder E (Fig. 2f), we found both agglomerated and individual spherical particles of a very wide range of sizes up to >10 μm, and also many nanoparticles, all of which were attached to the surface of larger particles.

In summary, nanoparticles dominated in two out of three nanopowders (Nanopowder M and Nanopowder K) and constituted a considerable fraction in the Regular Powder E.

Quantitative exposure assessment

The inhaled dose, calculated as mass of inhaled particulate matter per kilogram of body weight for 1-minute application of each cosmetic powder is shown in Fig. 3. Additionally, we show the inhaled dose calculated for simulated application with a clean kabuki brush, where no powder was used. Here, the particles were produced due to shedding of the brush. Inhaled dose is presented for the five different aerosol size fractions defined above: $PM_{0.1-0.014}$, $PM_{1-0.1}$, $PM_{2.5-1}$, $PM_{10-2.5}$, and PM_{20-10}.

In the $PM_{0.1-0.014}$ aerosol size fraction, inhaled particle dose significantly higher than the background was observed only for Nanopowder M (6×10^{-5} ng/kg bw/application) and Regular Powder E (6×10^{-3} ng/kg bw/application). Since the background aerosol concentration was subtracted from each measurement, the values above indicate the presence of particles higher than the background level.

Use of nanopowders D and K and Regular Powder E resulted in the highest inhaled dose of the $PM_{1-0.1}$ aerosol fraction, close to ~60 ng/kg bw/application for these two nanopowders and about 350 ng/kg bw/application for Regular Powder E. For the remaining products, the inhalation exposure was around 0.1 ng/

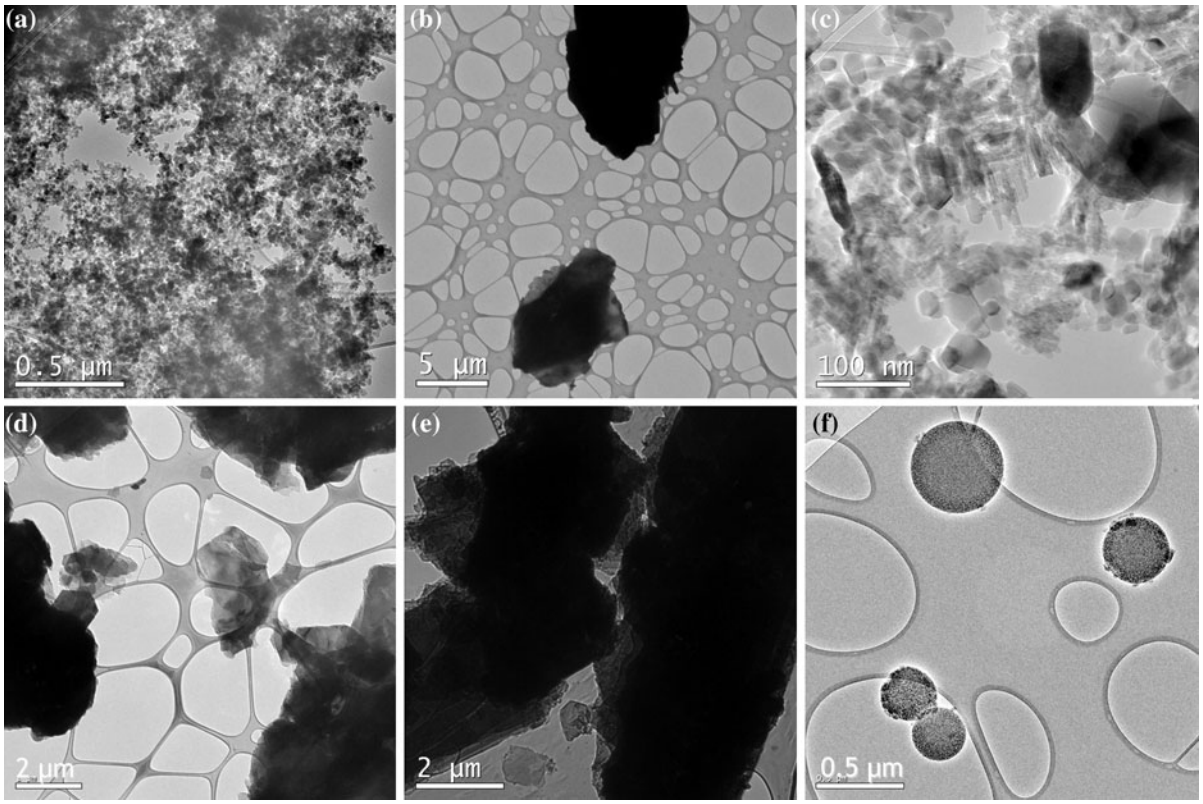

Fig. 2 Transmission electron micrographs of the tested cosmetic nano- and regular powders: **a** Nanopowder M (0.5 µm *scale bar*), **b** Nanopowder D (5 µm *scale bar*), **c** Nanopowder K (100 nm *scale bar*), **d** Regular Powder F (2 µm *scale bar*), **e** Regular Powder G (2 µm *scale bar*), **f** Regular Powder E (0.5 µm *scale bar*)

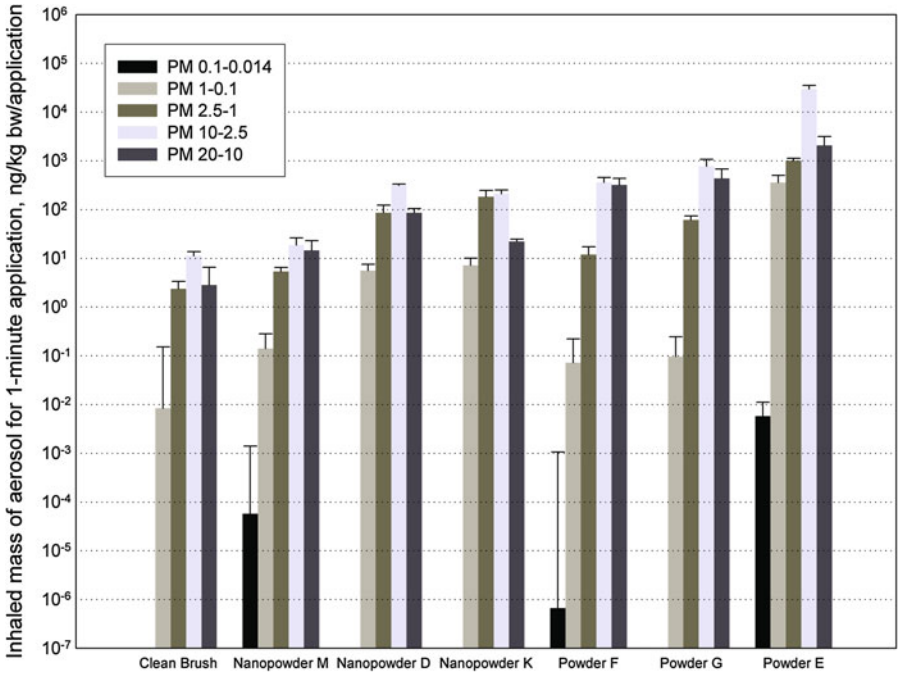

Fig. 3 Inhaled dose of particulate matter during the use of cosmetic powders. Based on mass concentration of particulate matter in different aerosol particle size fractions as sampled with the mannequin head sampler during simulated product application. The data represent averages of three repeats. The *error bars* represent one standard deviation

kg bw/application—about an order of magnitude higher than inhaled dose from the use of a clean kabuki brush.

For nanopowders D and K and Regular Powder G, the inhaled dose in the $PM_{2.5-1}$ fraction was on the order of 10^3 ng/kg bw/application while for Nanopowder M and Regular Powder F—about an order of magnitude lower (~50–100 ng/kg bw/application)—close to the level for the clean kabuki brush (~25 ng/kg bw/application). Regular Powder E showed the highest inhaled dose for the $PM_{2.5-1}$ fraction: $\sim 1 \times 10^4$ ng/kg bw/application.

The highest inhaled dose of the $PM_{10-2.5}$ aerosol size fraction also resulted from the use of Regular Powder E ($\sim 3 \times 10^4$ ng/kg bw/application). Nanopowders D and K and regular powders F and G showed inhaled dose levels two orders of magnitude lower in the range 200–775 ng/kg bw/application while Nanopowder M only produced a relatively low exposure to this aerosol size fraction at 19 ng/kg bw/application, which was close to the level for the clean kabuki brush (11 ng/kg bw/application).

For the supercoarse size fraction (PM_{20-10}), the highest exposure ($\sim 2 \times 10^3$ ng/kg bw/application) was created by the use of Regular Powder E. This level of inhaled dose was about an order of magnitude higher than for the other two regular powders (F—322 ng/kg bw/application and G—437 ng/kg bw/application). For all of the tested nanopowders compared to the regular powders, the simulated application resulted in much lower inhaled doses of the PM_{20-10} aerosol size fraction (in the range 15–86 ng/kg bw/application).

The deposited dose for each cosmetic powder as well as for the clean kabuki brush is shown in Fig. 4. The dose is expressed as mass of inhaled particulate matter per kilogram of body weight that would deposit in the head airways (HA), the tracheobronchial region (TB), the alveolar region (AL), as well as the total respiratory system deposition during a 1-minute application of cosmetic powders.

As can be seen in Fig. 4, the highest deposited mass in all three respiratory system regions resulted from the application of Regular Powder E with the total deposited dose of 3.2×10^4 ng/kg bw/application, which was 1–3 orders of magnitude higher than for the other cosmetic powders. The total deposited dose for Nanopowder M was the lowest of all the products: 37 ng/kg bw/application, only about twice as high as the use of the clean kabuki brush (15 ng/kg bw/application). The other two nanopowders (D and K) produced deposited doses around 400 ng/kg bw/application, and regular powders F and G produced doses of 684 and 1.2×10^3 ng/kg bw/application, respectively.

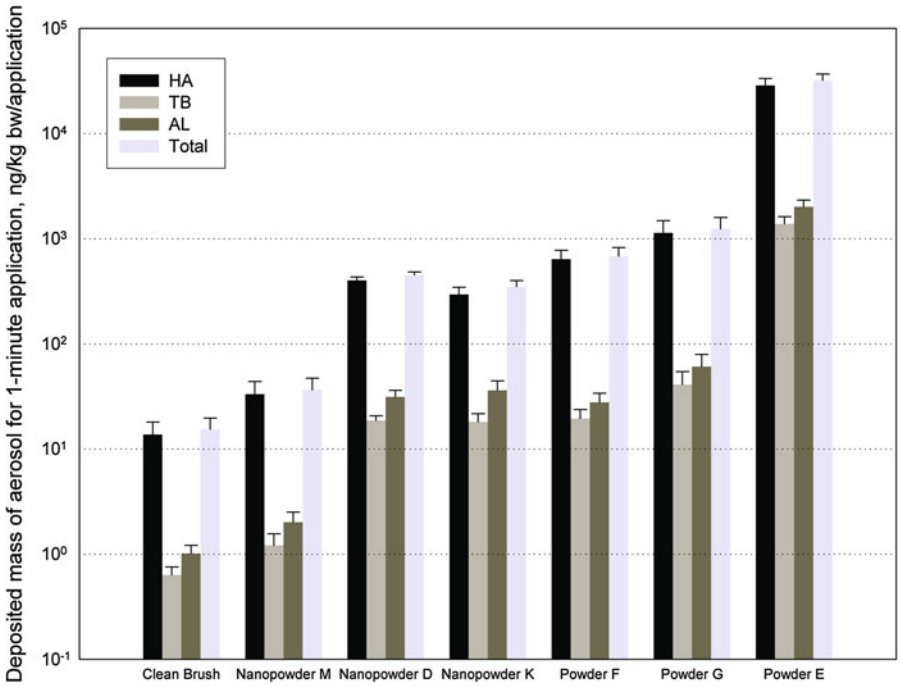

Fig. 4 Dose of particulate matter deposited in different regions of the respiratory system during simulated application of cosmetic powders. Deposited mass was calculated for the head airways (HA), the tracheobronchial (TB), the alveolar (AL) regions, and the total respiratory system deposition (Total). The data represent averages of three repeats. The *error bars* represent one standard deviation

For all the nano and regular cosmetic powders, the mass deposited in alveolar region was by a factor of 1.5–2 higher compared to the tracheobronchial deposition for the same powders. Regular powder E stood out with the highest AL and TB deposited doses (2×10^3 and 1.4×10^3 ng/kg bw/application, respectively). Nanopowder M showed very low levels: 2 ng/kg bw/application for AL and 1.2 ng/kg bw/application for TB. The other four cosmetic powders were in-between: the AL ranged from 31 to 61 ng/kg bw/application and the TB—from 19 to 41 ng/kg bw/application.

For all the powders, the distribution of mass deposition in the head airways was similar to that in the two other regions of the respiratory system. The dose deposited in HA due to the use of Regular Powder E was 1–3 orders of magnitude higher (2.9×10^4 ng/kg bw/application) compared to nanopowders D and K and regular powders F and G. For the latter four cosmetic powders, the HA deposited dose ranged from 295 to 1.1×10^3 ng/kg bw/application. For Nanopowder M, it was the lowest— $\sim$ 33 ng/kg bw/application, which was consistent with the generally lower deposited dose from this product in the other two respiratory system regions.

The comparison of deposited dose in different regions of the respiratory system is shown in Fig. 5. As could be seen, the dose deposited in the head airways constituted the dominant portion of the total deposited dose; between 85 and 93 % of the total deposition of inhaled particulate matter occurred in the HA region of the human respiratory system.

Discussion

The most important outcome of this study is that for all of the tested cosmetic powders, the coarse aerosol fraction ($PM_{10-2.5}$ in Fig. 3) was responsible for the highest inhaled dose. It is also notable that while the TEM showed a very high abundance of nanoparticles in nanopowders M and K and the Regular Powder E, the inhaled dose of individual nanoparticles and/or nanoagglomerates, represented by the $PM_{0.1-0.014}$ aerosol fraction in Fig. 3, was either very low (nanopowders M and E) or insignificant (Regular Powder K) compared to the background. If engineered nanomaterials are added to a cosmetic powder, when the powder is applied, the nanomaterials are unlikely to become dispersed as nanosized airborne particles due to insufficiency of energy needed for deagglomeration (Seekkuarachchi and Kumazawa 2008). Instead, the majority of nanomaterials should be distributed in larger size fractions due to particle

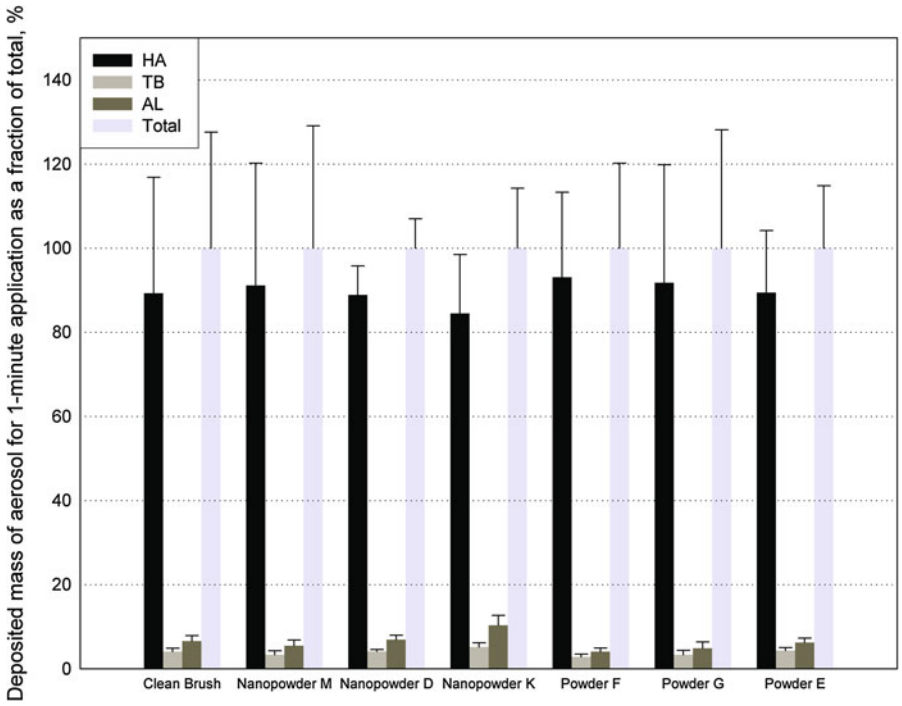

Fig. 5 Percent distribution of particulate matter deposited in different regions of the respiratory system during simulated application of cosmetic powders. Percent deposition was calculated for the head airways (HA), the tracheobronchial (TB), and the alveolar (AL) regions. The total deposition represents the sum from the three regions. The data represent averages of three repeats. The *error bars* represent one standard deviation

agglomeration. Therefore, engineered nanomaterials can be effectively delivered into all regions of the human respiratory system in the form of agglomerates of various sizes. The quantities of these nanomaterials entering the respiratory system would be proportional to the total aerosol mass in each size fraction and the fraction of nanomaterial in it.

Since coarse particles are responsible for the highest fraction of inhaled dose, it came as no surprise that the overwhelming deposition of particulate matter was shown to occur in the head airways (Figs. 4, 5). The alveolar region was the second most exposed region of the respiratory system; however, the deposited mass was only $\sim 1/20$ of that deposited in the head airways. Deposition levels in the tracheobronchial region were lower than that in the AL by a factor of 1.5–2. Although the absolute deposited dose levels differed from product to product, the above-mentioned proportion of particulate matter deposition between the HA, TB, and AL human respiratory system regions was similar for all tested cosmetic powders.

There is an active debate regarding the best particle metric to use when analyzing nanomaterial exposures: particle number, surface area, or mass (Dhawan et al. 2009). Although the surface area and number of nanoparticles deposited in the respiratory system have been shown to correlate well with toxic effects for some nanoaerosols like nanoparticulate quartz, metallic cobalt and nickel, and elemental carbon ^{13}C (Duffin et al. 2002; Oberdörster et al. 2004), this was not the case with many other materials like nanoparticulate TiO_2, carbon black, polystyrene beads, and surface-modified quartz (Duffin et al. 2007; U.S.EPA 2011; Wittmaack 2007). The existing measurement techniques are still limited when it comes to the measurement of number and surface area concentration of agglomerated nanoparticles and nanoparticles in composites with larger particles, which is the case of cosmetic powders. In this study, we chose to use the mass metric because here we deal with a nanomaterial-containing aerosol where nanomaterials are distributed across all aerosol size fractions in the form of agglomerates. Hence, much greater mass of nanomaterials is delivered into the respiratory system in the form of nanomaterial-containing agglomerates and composites compared with nanomaterials in the form of nanosized particles (Nazarenko et al. 2012). The particle number metric would count each individual agglomerate containing multiple nanoparticles as a single particle while the surface area may not be accurately measured for multi-ingredient products where particulate matter is often embedded in a matrix of organic and other components.

Nanotechnology-based consumer products differ from pure nanomaterials because they usually contain many other ingredients. The presence of ingredients other than the nanomaterial component is likely to affect particle agglomeration and therefore plays a major role in determining the distribution of nanomaterials across different size fractions once the product is aerosolized. Consequently, during inhalation exposure, the multi-ingredient composition and agglomeration of particles released from a nanotechnology-based consumer product would lead to a different deposition of nanomaterial(s) and other essential materials across the human respiratory system compared to tests with pure nanomaterials. Nanomaterials may become substantially altered by their inclusion in a product matrix composed of other ingredients, and the aerosol generated during a multi-ingredient nanoproduct's use may be substantially different from the aerosol generated from a pure nanomaterial composed of the same primary nanoparticles. Hence, we suggest that the exposure and toxicology studies of pure nanomaterials should be conducted in parallel to similar studies of actual products and exposures that use nanomaterials. This parallel approach will provide the relevant data, and conclusions can be drawn about the exposure and potential health effects resulting from the use of nanotechnology-based consumer products.

Our investigation with the TEM showed that two out of the three tested nanopowders–Nanopowder M and Nanopowder K—contained exclusively (in Nanopowder M) or predominantly (in Nanopowder K) nanosized particulate matter. Regular Powder E contained a high number of nanoparticles along with larger particles. This observation indicates that when particles from these products are aerosolized during product use, there can be exposure to actual nanomaterials. At the same time, however, the third nanopowder (D) did not contain any nanoparticles that could be detected using TEM, and particles below 100 nm were virtually not detected in the air (Fig. 3). These findings illustrate that manufacturers' claims regarding the inclusion of nanomaterials in their products need to be verified. Due to the current absence of any regulations mandating the reporting of

nanotechnology-based ingredients in cosmetics or other consumer product types, a manufacturer's statement about the nano status of their product is not a guarantee that the product, marketed or not marketed as nanotechnology-based, contains engineered nanomaterial(s) (Hansen et al. 2008). Therefore, conducting specific analyses to detect and characterize nanomaterials in such products is essential to estimate potential of exposure to nanoparticles from such products, as well as, the exposure to agglomerates during use.

Regular Powder F presented a special case where TEM showed no separate nanoparticles, but nanosized inclusions within the larger particles were noticed. We think that in this case, the exposure and risk of nanoparticle-related effects would be minimal if nanoparticles were not released from the larger particles. However, disintegration of such larger particles and the potential release of nanoparticles from them in vivo cannot be completely ruled out and such a phenomenon should be a subject of future investigations.

Conclusions

We found that the levels of inhalation exposure to particulate matter associated with different aerosol size fractions varied substantially depending on the product used. Mass-based inhalation exposure to individual nanoparticles or their agglomerates smaller than 100 nm was found to be minimal compared to the inhalation exposure to larger particles. The highest mass of inhaled particles was found in the coarse aerosol fraction ($PM_{10-2.5}$) for all products. Since electron microscopy showed the presence of nanosized particles in nanopowders M and K and Regular Powder E, it is likely that particles in the entire investigated aerosol size range contained nanoparticle agglomerates or nanoparticles attached to other particles.

Our data show that the vast bulk of inhaled cosmetic powders by mass, including particles containing nanomaterials, would deposit in the head airways (more than 80 %), while less than 10 % of deposition would occur in the alveolar region. It is, therefore, necessary to reconsider the current research overemphasis on the alveolar region for the study of nanomaterial effects. Instead, efforts must be directed to investigate those regions of the human respiratory system where majority of nanomaterial deposition during the actual product use would occur.

The methodological approach used in this study emphasizes realistic simulation of product application to determine inhalation exposures. It can serve as a model for future quantitative inhalation exposure assessments. Such assessments will be required to obtain quantitative exposure data for a wide variety of nanotechnology-based consumer products and are necessary for the ongoing development of safety guidelines and potential regulations.

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Conflict of interest The authors declare no conflict of interest.

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