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Modeling Population Exposures to Silver Nanoparticles Present in Consumer Products

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Abstract

Exposures of the general population to manufactured nanoparticles (MNPs) are expected to keep rising due to increasing use of MNPs in common consumer products (PEN 2014). The present study focuses on characterizing ambient and indoor population exposures to silver MNPs (nAg). For situations where detailed, case-specific exposure-related data are not available, as in the present study, a novel tiered modeling system, Prioritization/Ranking of Toxic Exposures with GIS (Geographic Information System) Extension (PRoTEGE), has been developed: it employs a product Life Cycle Analysis (LCA) approach coupled with basic human Life Stage Analysis (LSA) to characterize potential exposures to chemicals of current and emerging concern. The PRoTEGE system has been implemented for ambient and indoor environments, utilizing available MNP production, usage, and properties databases, along with laboratory measurements of potential personal exposures from consumer spray products containing nAg. Modeling of environmental and microenvironmental levels of MNPs employs Probabilistic Material Flow Analysis combined with product LCA to account for releases during manufacturing, transport, usage, disposal, etc. Human exposure and dose characterization further employs screening Microenvironmental Modeling and Intake Fraction methods combined with LSA for potentially exposed populations, to assess differences associated with gender, age, and demographics. Population distributions of intakes, estimated using the PRoTEGE framework, are consistent with

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published individual-based intake estimates, demonstrating that PRoTEGE is capable of capturing realistic exposure scenarios for the US population. Distributions of intakes are also used to calculate biologically-relevant population distributions of uptakes and target tissue doses through human airway dosimetry modeling that takes into account product MNP size distributions and age-relevant physiological parameters.

Keywords

manufactured nanoparticles; engineered nanomaterials; silver nanoparticles; consumer products; life cycle analysis; life stage analysis; PRoTEGE

INTRODUCTION AND BACKGROUND

Worldwide use of Manufactured Nanoparticles (MNPs) has risen significantly in the past five years, as reflected by the rapid increase in the number of consumer products containing MNPs. Data from the US based Project for Emerging Nanotechnologies (PEN 2014) and the Netherlands National Institute for Public Health and the Environment (RIVM 2014) show that silver, titanium, and carbon-based ENMs are the major MNPs associated with consumer products (Yang and Westerhoff 2014). Silver nanoparticles (nAg) are in fact the most common MNPs used in consumer products and the number of such products containing nAg, that are available in the US and listed in PEN, increased from 23 in 2006 to 410 in 2014 (see Fig. 1). Silver nanoparticles can be found in a very wide variety of products that include textiles (used primarily for items such as socks, underwear and shirts) (Quadros et al. 2013), surfaces of hair care appliances (e.g. flat irons) and tableware, shoe soles, pesticides, detergents, disinfectants, soaps, cosmetic powders, face creams, toothpastes, and even dietary supplements. Due to the variety of products and their uses, exposure to MNPs becomes a function of the nature, frequency, and extent of contact with the particular consumer product (as shown for textiles containing nanosilver by Quadros et al. (2013)).

MNPs have been shown to have adverse effects in mammals, especially on the pulmonary and cardiovascular systems (Roberts et al. 2013).The increased presence of MNPs in consumer products has resulted in an urgent need to address gaps in assessments of exposures to these particles (Thomas et al. 2009) and associated environmental and human health risks. Substantial efforts focusing on nAg have been ongoing in both Europe (Schafer et al. 2013) and the US. A case study conducted by the USEPA (USEPA 2012), selected nAg “to understand the scientific issues and information gaps for prioritizing research that would support future assessment efforts.” In particular this study identified nAg in disinfectant sprays as “the best application to focus thinking about the types of information that could inform future assessments of the potential ecological and health implications of nAg” (USEPA 2012).

Analysis of potential risks associated with MNPs is hindered by the fact that, unlike traditional chemicals, MNPs have highly variable physicochemical properties, such as shape, size distribution, surface coatings, etc., that influence their transport and fate, and consequently the potential for human exposures (Oberdorster 2010; Stark 2011). Therefore, traditional hazard identification procedures involving “standardized” materials and high-

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dose toxicological studies would fail to capture the levels and types of risks associated with real world exposures (NNI 2011). Characterizing exposures to MNPs in principle requires detailed characterization of the structure and form of the MNP at the point of exposure and through the entire duration of the exposure. For example, Chen et al. (2010) demonstrated the temporal and spatial variation of nanoparticle characteristics resulting from a wet spray. Exposure assessment further requires a complete Life Cycle Analysis (LCA) of products containing MNPs, from production to use and disposal, as well as tracking physicochemical changes of the particles across their Life Cycles. The potential for human exposures to MNPs present in consumer products, under realistic use scenarios, is not well characterized and, given the variety of such products in the market, systematic approaches are required to determine MNP properties critical for evaluating potential consumer risks (Thomas et al. 2009). LCA has been used by environmental agencies and regulators to assess effects of chemicals to ecosystems and human populations and the ISO 14040 and 14044 standards have established guidelines for utilization of LCA in fate and impact assessments (ISO 2006a; ISO 2006b). However, without detailed knowledge regarding production, use, and disposal of MNPs and of products that incorporate them, LCA analyses suffer from large uncertainties that are also reflected in subsequent exposure estimates (USEPA 2007). LCA of nanoparticles in the environment has been considered by Mueller and Nowack (2008), and the same approach was refined by Gottschalk et al. (2010; 2009) using a Probabilistic Material Flow Analysis (PMFA) to estimate distributions of nanoparticle concentrations in environmental media. Hischier and Walser (2012) compiled a comprehensive review of LCA efforts for engineered nanomaterials and pointed out that the lack of characterization of nanoparticle releases both indoors and outdoors makes the assessment of exposures to engineered nanomaterials incomplete. This article combines available LCA estimates for silver MNPs and presents a population-wide exposure model for the contiguous US across multiple age-groups, considering relevant activity-patterns and actual product-specific characterization at the point of contact.

METHODS

The present work presents and applies a new modeling framework that aims to advance current exposure characterizations of MNPs, utilizing a combination of customized computational tools in conjunction with extant as well as newly available data. The PRoTEGE framework, that is utilized in the present work, is based on the Modeling ENvironment for TOtal Risk studies (MENTOR), developed by Georgopoulos and Lioy (2006) (see also Georgopoulos 2008; Georgopoulos et al. 2009; Georgopoulos et al. 2008; Georgopoulos et al. 2005), which provides tools for comprehensive source-to-dose analyses of chemicals of concern, including considerations of mixtures and multiple media, and various indoor, outdoor, and occupational exposure pathways. Employing simplified components of MENTOR in conjunction with extant databases (see Table 1) Georgopoulos *et al*. (Georgopoulos et al. 2014; Mitchell et al. 2013) have developed the tiered Prioritization/Ranking of Toxic Exposures with GIS Extension (PRoTEGE) system, which couples the LCA approach with basic human Life Stage Analysis (LSA) to identify and quantify potential exposures to chemicals of current and emerging concern, such as MNPs, for which significant information gaps may exist. In the present study, the PRoTEGE system

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(shown schematically in Fig. 2) has been implemented for silver nanoparticles (nAg) from representative consumer products, using new data from laboratory studies employing simulated exposure conditions involving nAg cleaning, cosmetic, etc. products, to characterize potential exposures for the population of the contiguous US (CONUS). The model implementation considers explicitly size distributions and source characterization for nAg from "near field" exposure sources (considering specifically spray products) and takes into account exposures from both indoor "near field" sources (associated with the use of cleaning products containing nAg) and from outdoor "far field" sources (associated with estimated total "presence" and disposal of nAg in its Life Cycle compartments across the CONUS). The present work also develops distributional estimates of inhalation uptakes from nAg exposures for different age groups in the US population, considering variability in age-dependent physiological (respiratory) and activity parameters.

"Tier 1" PRoTEGE Characterization of nAg Exposures

The schematic overview of the PRoTEGE framework (Georgopoulos et al. 2014), in Fig. 2, identifies the product Life Cycle "compartments" that are considered in the present study. The PRoTEGE system has been designed to allow for multiple tiers of analysis, depending on (a) the type of questions considered for particular exposure/risk scenarios and (b) the availability of information regarding production, usage, releases, etc. of the chemicals considered. Tier 1 applications of this system involve development of semi-quantitative metrics characterizing magnitude, frequency, and efficacy of potential exposures to "chemicals of concern," in this case nAg. These metrics are based on a combination of available quantitative information on releases and concentrations, qualitative information on routes and pathways of potential and actual exposures reported in the literature, and expert judgment on various facets of these exposures. The four exposure-relevant metrics considered in the PRoTEGE system are:

- Pervasiveness - expressing how widespread the exposures are (or can potentially be) within the general population

  – Factors considered: percentage of locations (e.g. US counties) reporting releases of chemicals, reporting usage of the chemical, percentage of measured ambient concentrations above a threshold, etc.

- Persistence - reflecting the temporal frequency and/or duration of exposures

  – Factors considered: temporal patterns of emissions, releases, contacts, etc.

- Severity – representing the potential for high levels of exposures

  – Factors considered: frequency and localization of high releases, etc.

- Efficacy – characterizing the potential of the contact with the chemical to result in intake, and to potentially biologically relevant uptake

  – Factors considered: physicochemical properties such as partition coefficients affecting bioavailability, tissue penetration, etc.

The "four metric" approach for exposure characterization utilizes and expands the approach of Hansen et al. (2013) for characterization of exposure potentials and hazards of

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nanomaterials., Exposure efficacy is higher when the nanomaterials are not fixed or embedded in a solid, e.g as in products which contain “nanoparticles suspended in liquids” or that result in “airborne nanoparticles” during product usage. Exposure efficacy is lower for “surface-bound nanoparticles,” unless product usage involves processes that degrade the surface (e.g. sanding). As noted by Hansen et al. (2013), “release of nanoparticles from a matrix cannot be excluded per default, especially from paints with low strength matrices, poor quality, high energy paint removal, or if subjected to weathering.” If the products contain nanoparticles “embedded” in a solid, exposure efficacy is expected to be low.

The above four exposure metrics are assigned integer values from 1 to 5, corresponding to very low (1), low (2), moderate (3), high (4) and very high (5) levels of the corresponding metric, based on the information available in the databases accessed and “mined” by PRoTEGE. (A representative subset of these databases is provided in Table 1.) Fig. 3 summarizes the PRoTEGE estimates of these metrics, employing data relevant to potential population exposures to nAg in the contiguous United States (CONUS). Based on the information available in these databases, inhalation exposures, followed by dermal exposures, represent the two most important exposure routes for nAg. Ingestion is, in general, expected to be a minor exposure route, except for selected sup-populations who use products such as dietary supplements or even toothpastes containing nAg, etc. (Reed et al. 2014; Yang and Westerhoff 2014).

Unfortunately, the most comprehensive databases on chemical usage, transport, and release – even databases on consumer product properties and usage (Goldsmith et al. 2014) – do not provide information specific to any nanomaterials these products (may) contain. So, information on production, usage, etc. of products containing MNPs is derived primarily from specialized “nanoinformatics” databases (Panneerselvam and Choi 2014), such as PEN (2014) and RIVM (2014), that, however, rely primarily on self-reported information from manufacturers that varies widely in quality.

“Tier 2” PRoTEGE Characterization of nAg Exposures

Characterization of population exposure factors—In order to conduct a “Tier 2”assessment of population exposures to silver MNPs, multiple exposure-relevant attributes of the general population, such as age, gender, and behavior/activity patterns, including time spent indoors/outdoors, are utilized in conjunction with the PRoTEGE system. Inter-individual variability is incorporated through Monte Carlo sampling of exposure attributes for individuals within the population of concern, structured by age and gender groups. A “virtual representation” of the population of the CONUS is constructed using US Census demographics data (USCB 2012), so as to reflect the actual age and gender composition of the true population. The virtual population *S* is constructed by selecting a “sample” consisting of one million “virtual individuals” drawn from the “actual” population distribution, denoted as *P*(age, gender) , and parameterized by age and gender.

$$SP\,(\text{age}, \text{gender}) \quad (1)$$

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The modeling scheme used (shown in Fig. 4) requires individual-specific exposure factors, such as inhalation rate for outdoor and indoor activities, that depend on physiological attributes (age, gender, activity level) for the members of the virtual population *S*. These factors are parameterized in a manner generally consistent with the recommendations and values contained in the USEPA's Exposure Factors Handbook (EFH) (USEPA 2011). EFH provides data on inhalation rates for different activity levels (e.g., resting and light, moderate, or heavy activity) for fourteen (14) population groups and two (2) gender classifications along with information regarding activity microenvironments (indoor/outdoor) for the general population. Based on these statistics, $R_{\text{inh},i}$, the inhalation rate of the ith virtual individual was calculated considering activity levels (resting, light, moderate, or heavy activities) and activity microenvironments (indoor and outdoor, residential and public), utilizing activity pattern data consistent with EFH recommendations. In this analysis, the individual inhalation rates for time spent indoors and outdoors are calculated using inhalation rates for different activity levels and fraction of time spent while resting or engaged in light, moderate, or heavy activity. Activities for each individual were associated with their respective indoor and outdoor microenvironments, based on the "assignment" of time spent outdoors, $T_{\text{indoor},i}$, for that virtual individual, *i*, and considering $T_{\text{indoor},i}$ as 24 hours minus $T_{\text{outdoor},i}$.

nAg production, manufacturing, consumption, and disposal—In the absence of actual production, consumption, and disposal estimates of nAg in the CONUS, the Production-Manufacturing-Consumption (PMC) metric employed by Gottschalk et al. (2009), was used and is denoted by M_{PMC} in the present study. Gottschalk et al. (2009) estimated worldwide production volumes of nanomaterials based on values obtained from published articles. These values were then scaled to regional production volumes based on the region's population size, and these scaled values were fitted to a lognormal distribution (Gottschalk et al. 2009). Since the CONUS inventory of nAg was scaled down from the estimated global amount, the inventory data are thus reflecting a "top-down" approach.

$$M_{PMC,\text{t-d}} \sim logN\left(\mu, \sigma^2\right) \quad (2)$$

Hendren et al. (2011) estimated the CONUS production volume of nAg based on information from companies in the CONUS that produce nAg. Based on production capacity data from individual companies, the authors estimated the lower and upper bounds of the CONUS production volumes, developing an inventory that reflects a "bottom-up" approach. A uniform distribution (denoted by $U(a, b)$) was constructed, conforming with the lower and upper bounds of the estimated CONUS production volumes:

$$M_{PMC,\text{b-u}} \sim U(a, b) \quad (3)$$

For the present study, "alternative" production/usage volumes of nAg in the CONUS, M_{PMC}, were estimated separately using each inventory development approach (top-down and bottom-up).

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nAg in spray products—Fig. 5 shows the probability densities of nAg concentrations in environmental media calculated through a probabilistic computational material flow analysis approach used for "far field" sources of "ambient contamination" in PRoTEGE, which is methodologically similar to the approach employed by Gottschalk et al. (2010; 2009). For each LCA compartment, two estimated probabilistic distributions of concentrations are shown, corresponding to model predictions for the two "alternative" nAg inventories developed through the bottom-up and top-down approaches. The probability densities of nAg concentrations in ambient air shown in Fig. 5(a) were used in the calculation of population intakes of ambient nAg presented in the Results Section.

While levels of nAg in ambient environmental media reflect total production/usage, consideration of indoor exposures in the present study focused on consumer spray products used for cleaning and cosmetic purposes, following the rationale of USEPA (2012). The amount of nAg used in consumer spray products in the CONUS was calculated using estimated total nAg production volumes (described in the previous section) and estimates of fractional allocation of nAg to product categories. Piccinno et al. (2012) estimated the worldwide allocation of nAg to the "paints, coatings and cleaning" and "cosmetic" product categories based on survey responses received from companies producing and using nAg, and the allocation was estimated to be between 10% and 30% for the former and 20% for the latter. Due to lack of more detailed data, exposures were assessed based on the assumption that all of the nAg contained in these two product categories is emitted through spraying, corresponding to a worst-case scenario. Accordingly, the randomized estimate of the fraction of total nAg in cleaning sprays was sampled uniformly from the interval [0.1, 0.3] and that for nAg in cosmetic sprays was taken as 0.2. So, the respective "distributions" $M_{\mathrm{PMC,clean}}$ and $M_{\mathrm{PMC,cosm}}$ are approximated by:

$$M_{\mathrm{PMC,clean}} \tilde{} M_{\mathrm{PMC}} \cdot U\left(0.1, 0.3\right) \quad (4)$$

$$M_{\mathrm{PMC,cosm}} \tilde{} M_{\mathrm{PMC}} \cdot \left(0.2\right) \quad (5)$$

Population exposures—Production/usage metrics of nAg spray products, $M_{\mathrm{PMC,clean}}$, and $M_{\mathrm{PMC,cosm}}$, are used to characterize nAg exposures for each of the one million virtual individuals in the simulations. The following assumptions are made in developing the exposure estimates:

(i) 25% of the total amount nAg in cleaning sprays is assumed to be used in indoor residential settings, f_{res}, and 75% in indoor non-residential settings, $f_{\mathrm{non\text{-}res}}$; (ii) all of nAg in cosmetic spray products is assumed to be used in indoor residential settings (i.e. f_{res} = 100%); (iii) market penetration levels, f_{MP}, of both types of nAg spray products are assumed to be either 25% or 50% in two alternative scenarios. Then, $M_{\mathrm{E,p,r}}$, the potential emitted amount "corresponding" to an individual in the virtual population, for a product category p in an indoor environment r (residential or non-residential), can be calculated as:

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$$M_{\mathrm{E,p,r}} \sim \frac{M_{\mathrm{PMC,p}} \cdot f_{\mathrm{r}}}{N \cdot f_{\mathrm{MP}}} \cdot U_p \cdot \mathbb{I}_{f_{\mathrm{MP}}}(x), \quad (6)$$

where N is the size of the CONUS population, f_{MP} is the market penetration of nAg spray products, U_p is the distribution accounting for variability in usage of product category p, and $\mathbb{I}_{f_{MP}}(x)$ is an indicator function applied on x, a uniform random variable on [0, 1] as:

$$\mathbb{I}_{f_{\mathrm{MP}}}(x) = \begin{cases} 1, & \text{if} \quad x \leq f_{MP} \\ 0, & \text{if} \quad x > f_{\mathrm{MP}} \end{cases} \quad (7)$$

The variability in U_p, the usage of spray products across the CONUS population, was quantified using census tract-level consumer expenditure data (Bureau of Labor Statistics 2014), (corresponding to panels (c) and (d) of Fig. 6) using ESRI Business Analyst® (Esri 2014). The maps in Fig. 6 a and b present Spending Potential Index (SPI) data aggregated to county-level, which represents the "default" spatial resolution employed in the PRoTEGE system. SPI is "household-based, and represents the amount spent for a product or service relative to a national average of 100, estimated based on the latest Consumer Expenditure Surveys (CEX) from the Bureau of Labor Statistics." The distribution of product usage, U_p, was assumed to be similar to the distribution of SPI across CONUS counties.

Population intakes—For "Tier 2" modeling within the PRoTEGE framework, the estimates of nAg emissions, that were calculated in the previous section, are linked to population intakes based on the concept of intake fractions. Intake fraction is the "attributable pollutant mass taken in by an exposed population per unit mass emitted from a source" (Nazaroff 2008), and can be expressed as the ratio of intake amount, $M_{\mathrm{I,i}}$, over emitted amount, $M_{\mathrm{E,i}}$:

$$f_{\mathrm{IF,i}} = \frac{M_{\mathrm{I,i}}}{M_{\mathrm{E,i}}} \quad (8)$$

where $f_{\mathrm{IF,i}}$ represents the intake fraction for the individual i. If one assumes that nAg is emitted in a well-mixed indoor environment, then the intake fraction can also be quantified as the ratio of inhalation rate over building ventilation rate (Nazaroff 2008). The residential ventilation rate per person, $R_{\mathrm{vent,res},i}$, was sampled from a lognormal distribution specified by Nazaroff (2008). The non-residential ventilation rate per person, $R_{\mathrm{vent,non\text{-}res},i}$, was sampled from a non-parametric distribution constructed according to the Commercial Buildings Energy Consumption Survey (CBECS) data (CBECS 2003). Then the intake of nAg, $M_{\mathrm{I,p},i}$, from product category p, by the ith individual can be expressed as:

$$M_{\mathrm{I,p},i} = \sum_{\substack{\mathrm{r=res,} \\ \mathrm{non-res}}} f_{IF,\mathrm{r},i} \cdot M_{\mathrm{E,p,r},i} \cdot f_{\mathrm{T,r},i} = \sum_{\substack{\mathrm{r=res,} \\ \mathrm{non-res}}} \frac{R_{\mathrm{inh,indoor},i}}{R_{\mathrm{vent},r,i}} \cdot M_{\mathrm{E,p,r},i} \cdot f_{\mathrm{T,r},i}, \quad (9)$$

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where $f_{T,r,i}$ is the fraction of time in a day spent in residential/non-residential setting by the ith individual, calculated for all virtual individuals employing data retrieved from the Consolidated Human Activity Database (CHAD) (Stallings et al. 2002).

Measurements from spray product applications—Measurements from applications of two (2) types of spray products (cosmetics and cleaning) were conducted in a laboratory. A specially designed 124 cm^3 glove box was used as a spraying chamber. The inner walls of the box were covered with conductive material. A conductive sampling port was installed on one side of the box and connected to aerosol instruments. Two conductive inlets were installed on one side of the box and perpendicular to the sampling inlet to let in the air removed by the aerosol instruments. A Scanning Mobility Particle Sizer 3986 (SMPS) and an Aerodynamic Particle Sizer 3321 (APS) (TSI, Inc., Shoreview, MN) were used to measure airborne particle size distribution and concentration in the combined size range of 14 nm to 20,000 nm. During the tests, the glove box with its cover removed was placed inside an operating Class II Type A2 biological safety cabinet (NuAire®, Plymouth, MN, USA) to control particle background concentration. Once the total background concentration inside the box was below 3 particles/cm^3, the product was positioned inside the box and its lid was closed. The product was aerosolized manually using gloves built-in in the box, by spraying the product five times before starting the measurement to achieve a steady airborne particle concentration inside the glove box. Once the aerosol measurements were started the spray was activated approximately every three seconds to maintain constant aerosol concentration inside the chamber. Each measurement lasted at least 3.5 minutes, a minimum time needed by the SMPS to complete a full scan. After each measurement, the box was open and cleaned with alcohol and kimwipes™. A minimum of three repeats was completed for each product.

Quantification of nAg retention and clearance for the exposed population depends on the size distribution of aerosol droplets released from spray products. For simplicity, and considering all other uncertainties, the fraction of nAg in the aerosol is assumed to be the same for all droplet sizes in the present analysis. Table 2 presents the spray products selected from the simulated exposure experiment; three of these were classified as cleaning sprays and five were classified as cosmetic sprays. The measured size distributions of the aerosolized particles from the spray products are used in the current modeling application by averaging over products of the same category. Fig. 7 shows the relative size distributions based on mass fraction, M^*, which were obtained from averaging the size measurements of spray products of the same category, (cosmetics and cleaning products) as obtained from the laboratory-based simulated exposure study. Then, the size distribution by mass of $M_{I,p,i}$ can be characterized using $f_{m,p}(D_j)$, the fractional mass corresponding to diameter D_j . $f_{m,p}(D_j)$ corresponds to M^* in the particle size distribution shown in Fig. 7. Then, the size distribution by mass of product-associated nAg intakes for individual i can be expressed as:

$$M_{\mathrm{I,p},i}(D_j) = M_{\mathrm{I,p},i} \cdot f_{m,p}(D_j), \quad \text{for} \quad \text{all} \quad D_j \qquad (10)$$

Ambient air inhalation exposure—As described earlier, probabilities of ambient air concentrations of nAg are modeled employing an extension of the Probabilistic Material

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Flow Analysis (PMFA) approach described in Gottschalk et al. (2010; 2009). Environmental releases of nAg are quantified based on the production, usage, and disposal – from cradle-to-grave – of products containing nAg. In the network of environmental and disposal compartments illustrated in Fig. 2, the material flows beginning from the production-processing-usage compartment are modeled based on the LCA of these product categories. The amount of nAg accumulating in the ambient outdoor air compartment is modeled for both top-down and bottom-up estimates of nAg production volume in the CONUS, and the resulting ambient air concentrations of nAg, M_{E}^{out}, are calculated considering an atmospheric layer of 1 km depth extending over the surface of the CONUS, similar to the approach employed by Gottschalk et al. (2010; 2009). Then the distributions of population intake amounts of ambient nAg are calculated as:

$$M_{\mathrm{I}}^{out} = M_{\mathrm{E}}^{\mathrm{out}} \cdot T_{\mathrm{outdoor},i} \cdot R_{\mathrm{inh,outdoor},i} \quad (11)$$

Population uptakes—The Multiple-Path Particle Dosimetry Model (MPPD) v2.11 (ARA 2014) was employed to calculate uptakes of the inhaled nanoparticles in the respiratory airways. MPPD has been a suitable tool for calculating MNP depositions, as per Gangwal et al. (2011), who employed it to inform selection of nAg concentrations relevant to *in vitro* testing. The calculation of deposition fractions is dependent on a person's age: the age-specific 5-lobe model setting was selected for children and young adults, and the Yeh-Schum 5-lobe model for adults. The deposition fraction for MPPD lung region k , for particle diameter d_j, and the ith individual's age, a_i, is represented as $F_k(d_j, a_i)$, where k takes values 1, 2 and 3, corresponding to the pharynx, trachea-bronchi and alveolar regions, respectively. The aerosolized particle density was assumed to be 1 g/cm^3 as per Nazarenko et al. (2011) and the aerosol particles were assumed to be monodispersed for each diameter and spherical in shape. The parameters (lung morphology, breathing frequency, etc.) in MPPD for different age groups were selected according to the respective exposure and population attributes for the ith individual. Thus the inhalation uptake, $M_{\mathrm{U},i,k}(d_j)$, for each particle diameter class $d_j$was estimated as:

$$M_{\mathrm{U},i,k}(d_j) = F_k(d_j, a_i) \cdot M_{\mathrm{I},i}(d_j) \quad (12)$$

The quantities $M_{\mathrm{U},i,k}(d_j)$ represent the amounts of particulate matter deposited in lung region k for individual i , for particles with diameter d_j, and are grouped together according to the following five diameter classifications: 0-50nm, 50-100nm, 100-500nm, 500-2,500nm, and 2,500-10,000nm. $D_{j'}$, denotes these diameter classifications, where j' is an index representing a specific diameter range.

"Tier 3" PRoTEGE modules of indoor concentrations and exposures

Tier 3 applications of the PRoTEGE framework allow for more detailed micro-environmental exposure assessment, considering factors such as air flow patterns, size and geometry of rooms, locations and sizes of windows and doors, etc. Detailed material balances are performed for each relevant, indoor and outdoor, compartment. A simple "mixed room option" treats indoor personal spaces as homogenous, completely mixed

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control volumes, with the mass balance for the control volume described by the following equation (Sparks 2001):

$$V_m \frac{dC_m}{dt} = \sum_{m-1}^{N} Q_{nm} C_n - \sum_{n=1}^{N} Q_{mn} C_m + S_m + \sum_{n=1}^{N} K_{mn} a_{mn} \left(C_{mn}^* - C_m\right) + R_m \quad (13)$$

where V_m is the volume of compartment; (m^3); C_m is the airborne concentration of the "chemical of concern" in compartment m (mol/m^3); K_{mn} is the mass transfer coefficient from compartment m to n (m/hr); a_{mn} is the interfacial air exchange area between compartments (m^2); C_{mn}^* is the concentration in compartment m in equilibrium with concentration in compartment n (mol/m^3); Q_{nm} is the volumetric flow rate from compartment m to n (m^3/hr); and R_m is the rate of formation of species in compartment m (gmol/hr).

and

$$S_i \begin{cases} S_{i,\text{emis}} - S_{i,\text{depos}} - S_{i,\text{condens}} & ;\text{for} \quad \text{gases} \\ S_{i,\text{emis}} - S_{i,\text{depos}} + S_{i,\text{resusp}} + S_{i,\text{condens}} + S_{i,\text{nucl}} + S_{i,\text{coag}} & ;\text{for} \quad \text{PM} \end{cases} \quad (14)$$

For more detailed analyses, multizone models can be used instead of the "mixed room" option; the simplest case of a multizone model is the basic two-zone (bizone) model (Keil et al. 2009), which "divides" the control volume of concern into two zones: a "source field" (in the immediate vicinity of a contaminant source), and "receptor field" (vicinity of a potentially exposed receptor). This description leads to the following coupled mass balance equations:

$$\text{Source} \quad \text{Field:} \qquad V_N \cdot dC_N = S \cdot dt + q \cdot C_F \cdot dt - q \cdot C_N \cdot dt \quad (15)$$

$$\text{Receptor} \quad \text{field:} \qquad V_F \cdot dC_F = q \cdot C_N \cdot dt - [q + Q] \cdot C_F \cdot dt \quad (16)$$

where the parameters and variables involved are as follows: V_N and V_F are the source-field and receptor-field volumes, respectively (m^3); C_N and C_F are the source-field and receptor-field concentrations, respectively (mg/m^3); S is the mass emission rate (mg/min); q is the "inter-zone" airflow rate (m^3/min) between the source and receptor fields; Q is the room supply air rate (m^3/min); and dt is an infinitesimal time interval (min). Multizone models should in principle be more accurate in capturing spatial variability in exposure intensity due to usage of nAg spray products.

PRoTEGE provides options for either using customized single-zone and multi-zone models (coded in Matlab) for indoor concentrations, or using the ConsExpo 4.1 model developed by RIVM (Delmaar et al. 2005) for "individual scenario" simulations. As an example scenario of Tier 3 application, individual consumer exposures to nAg via inhalation of nAg in consumer products were estimated using ConsExpo 4.1 and were compared with related point values from the distributional population exposure assessment conducted in a Tier 2 application of the PRoTEGE framework. Estimates of individual intake were calculated

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using MNP concentrations in nAg products for two different spray product categories ("bathroom cleaning sprays" and "all-purpose cleaners"). In this example, the mass fractions of the nAg in bathroom cleaning and all-purpose cleaning products were both assumed to be 0.001 g/g, consistent with values reported in PEN (2014). Updated default parameter values (summarized in Table 3) in ConsExpo (Delmaar and Bremmer 2009) were used for this calculation. The resulting temporal variation in nAg exposure concentration and dose is represented in Fig. 8. The estimated average exposure concentrations are 0.077 and 0.00251 mg/m^3 for bathroom cleaning sprays and for all-purpose cleaners, respectively. Table 4 summarizes all the variables and parameters used in the equations described in the Methods Section.

RESULTS

Population intakes

Predicted population intakes were grouped by age according to the following classification: 0 to 10, 11 to 20, 21 to 40, 41 to 60, and above 61 years old. Fig. 9(a) and Fig. 9(b) show the calculated frequency distributions of intakes of nAg from ambient sources, $M_{\mathrm{I},i}^{out}$, and of nAg from spray products used in the indoor environment, $M_{\mathrm{I},i}$. As these figures illustrate, the predicted population intakes from indoor sources, even though only two product categories were considered, are orders of magnitude higher than those associated with all ambient sources. The uncertainties and data-gaps concerning information on MNP production and usage are also incorporated in the calculations and are reflected in the estimated distributions. It should be noted that while a certain level of variability is expected for any population-based intake characterization, the predicted distributions are impacted by high uncertainties associated with MNP production, manufacture and usage data. For calculations performed with the bottom-up production inventory, the estimated indoor population intakes span five (5) orders of magnitude. For the even more uncertain top-down production inventory, the intake estimates span six (6) orders of magnitude. The PMC values alone in the top-down estimate contribute more than two (2) orders of magnitude to the variability of the predicted population-wide intakes.

Fig. 10 shows the predicted nAg intakes by mass in five different size classes, D_j, calculated using $f_m(d_j)$ and $M_{\mathrm{I},i}$ for each population age group. These distributions of nAg intakes by mass reflect realistic MNP size characteristics at the point of exposure contact and are subsequently used to characterize population-wide nAg depositions in the lung.

"Tier 3" benchmarking

Fig. 11 presents a comparison between the predicted population intake distributions and individual intakes estimated by three independent implementations of existing consumer exposure models (shown as three horizontal lines), in order to "benchmark" the PRoTEGE estimates developed in this work against other established models in the absence of available real world measurements. The first two estimates are from Pronk et al. (2009), who developed them using the two "standard" EU models, ConsExpo (Delmaar et al. 2005) and ECETOC TRA (Money et al. 2014), to calculate individual consumer exposures to bathroom cleaning products containing nAg for specified usage scenarios. The first two

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columns of Table 3 summarize the relevant parameters for these two model implementations; the intake values that Pronk et al. (2009) estimated for different exposure routes are summarized in Table 5. ECETOC TRA is a first-tier model used to evaluate "exposures arising from the manufacture and use of chemicals" and has been extensively "applied to assess worker, consumers and the environmental risks" for the REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) process in the EU (Money et al. 2014; Pronk et al. 2009). The model considers different exposure scenarios and uses conservative assumptions in providing worst-case estimates of exposures for workers and consumers (Pronk et al. 2009). The top horizontal line in Fig. 11 represents the estimate of intake for a single individual obtained via ECETOC TRA with default model parameters (summarized in Table 3). This line represents a worst-case estimate corresponding to the use of a cleaning product, and only a small percentage of the modeled CONUS population in the present study is predicted to experience this or higher levels of intakes. It can therefore be stated that the highest percentile population estimates calculated in the present work are consistent with EU worst-case estimates. Pronk et al. (2009) also used ConsExpo as a higher-tier model for performing a more detailed assessment. The model considers "more specific descriptions of exposure" and removal processes to provide more realistic time-dependent estimates of exposures "arising from the use of consumer products (Pronk et al. 2009)." The ConsExpo estimates obtained with default model parameters (summarized in Table 3) is also shown as the bottom dotted horizontal line in Fig. 11. As the figure illustrates, the estimate of intake by ConsExpo intersects the predicted distributions of intakes for the population that is exposed to indoor emissions from nAg sprays at the "lower end" of these distributions, demonstrating that only a low percentage of the potentially exposed population in each age group is exposed at that or at a lower level. This indicates that the predicted population intakes are conservative compared to the more realistic estimates of intake by ConsExpo, which is a reasonable outcome, given that the modeled intakes in this work, calculated according to the lower-tier population-based modeling framework of the PRoTEGE system, are being compared with a higher-tier prediction for an average individual from ConsExpo. This result is consistent with intake estimates developed with both the "top-down" and the "bottom-up" inventories [Fig. 11 (a) and (b) vs Fig. 11 (c) and (d)] and also with estimates developed for widely different values of market penetration (25% and 50%) [Fig. 11 (a) and (c) vs Fig. 11 (b) and (d)].

Additionally, estimates of individual intake in microenvironmental settings were calculated for the present study using ConsExpo and realistic MNP concentrations in nanosilver products (PEN 2014) for two different product categories, as discussed in the Methods Section. The corresponding chronic inhalation dose combined for both product categories is 1.58×10^{-4} μg/kg/day, and this individual-based dose estimate is represented as the solid horizontal line in Fig. 11, which compares well with the population estimates produced under the Tier 2 framework of PRoTEGE. Despite the differences in the level of exposure information utilized and the substantial uncertainties associated with each step of the calculations, the predicted population intakes in this study were consistent with the corresponding individual estimates obtained using alternative (both lower and higher tier) established models. This demonstrates that, although a lower-tier framework was used in

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characterizing population exposures to nAg, estimated intakes are consistent with anticipated and modeled exposures for individual case scenarios.

Population uptakes

Fig. 12 presents the calculated distributions of population uptakes in terms of both mass and particle numbers for three (3) different regions of the lung, $M_{U,i,j',1}$, $M_{U,i,j',2}$ and $M_{U,i,j',3}$, calculated with deposition fractions obtained from the MPPD v2.11 model. In estimating these population uptakes, age dependent factors affecting deposition fractions (e.g., lung morphology, breathing rate, etc.) were selected so as to be consistent with the age distribution of the virtual population used in this study. In addition, the MPPD calculations were conducted using particle size distributions obtained from the measurements described in the Methods Section, and the measured mass fractions were used to weight the retrieved deposition fractions for calculating the uptakes. Therefore, the estimated uptakes should be relevant to exposure conditions that the general population could actually encounter.

DISCUSSION

The modeling framework described here is the first comprehensive attempt at population-wide exposure characterization of human exposures to nAg, accounting for both indoor (near-field) emissions from consumer products and total ambient (far-field) emissions, across different age groups, while explicitly considering differences in activity patterns and physiological parameters. The approach of the present study incorporated measured size distributions of MNPs from spray products and calculated both intakes and uptakes for realistic inhalation exposure scenarios.

Age-dependent distributions of nAg intakes were further used to calculate biologically-relevant uptakes and respiratory tract depositions through application of dosimetric modeling, accounting for variation of activity levels and of their effects on respiratory parameters. Despite large uncertainties and variabilities in MNP production, usage, and disposal, population-wide exposure characterizations of MNPs can provide useful starting information to support future risk estimates. Risk assessment for MNPs is very different from that of conventional toxic environmental chemicals due to the absence of clear-cut toxicity metrics such as NOAEL, LD50, etc. Toxicity based risk characterization can be based on observed changes in target organ systems due to nanomaterial exposure, as shown for respiratory system responses by Mukherjee et al. (2013) (for mice) and Sung et al. (2008) (for rats). Aschberger et al. (2011) have used ENM levels from Sung et al. (2008) for lung function changes to compute “estimated human indicative no-effect level (INELs) for workers of different ENM for chronic inhalation exposure”. For nAg, the INEL values for workers were estimated by Aschberger et al. (2011) to be 0.33 μg/m3, corresponding to levels associated with reduced lung function observed in rats by Sung et al. (2008). The equivalent daily dose considering an inhalation rate of 24.1 L/min and body weight of 65 kg for an average human (ConsExpo v4.1) was estimated to be 0.15 μg/kg-day for an 8-hour work day. Based on this estimate of inhalation intake, 7% of the “virtual CONUS population” is predicted to exceed this level under the top-down inventory scenario and 0.3% of the population under the bottom-up inventory scenario (both calculated at 50%

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market penetration). This demonstrates that a small percentage of the modeled virtual population would be exposed to a daily dose exceeding the INEL level calculated for humans by Aschberger et al. (2011) for observed changes in lung function. This preliminary risk estimate, calculated for a combination of only two nAg consumer product categories, shows that further work is needed to bring other products containing MNPs under the purview of such exposure modeling, which would help in assessing cumulative risk levels due to consumer exposures to MNPs. The modeling framework presented here also computes MNP deposition in different parts of the respiratory airways to assess tissue dosimetry of MNPs, and this can inform assessment of toxicity pathways and adverse outcomes due to MNP exposures. The alveolar region of the respiratory system represents one of the most critical locations in the body with respect to inhalation exposure, as it is a major gateway for inhaled environmental chemicals to reach the systemic circulation. Thus alveolar deposition of inhaled MNPs can provide critical information required to assess downstream toxicodynamic effects in the respiratory system, involving multiple alveolar cells, surfactant components and cytokines. The predicted population-wide alveolar uptakes (shown in Fig. 12) can be used in a mechanistic toxicodynamic framework to predict potential adverse outcomes across the entire population.

Considering the uncertainties and data gaps present in information regarding MNP production and use, the present study demonstrated the feasibility of a framework that provides population-wide estimates of nAg exposures from consumer products, based on state-of-the-art information available across databases and literature. The framework considers essential exposure, demographic, and behavioral patterns within the CONUS population and can be updated and improved to reduce the uncertainties in the results by using more refined data regarding production, manufacturing and consumption of MNPs, as these data become available. The modeling framework described here can be applied to other MNPs (e.g. carbon nanotubes and zinc MNPs), as well as to other products containing nAg. The model can provide benchmark values and ranges for population exposures, to be used for designing field studies focusing on specific subpopulations or geographical areas. The model also calculates MNP dosimetry for specific locations of the respiratory system, thus helping quantify systemic uptake, distribution, and clearance of such particles using whole body physiologically-based toxicokinetic (PBTK) models for MNPs, to estimate biologically effective doses for various tissues in the body across time. This would help formulate a comprehensive source-to-dose-to-effect framework for characterizing MNP-related risks to human populations.

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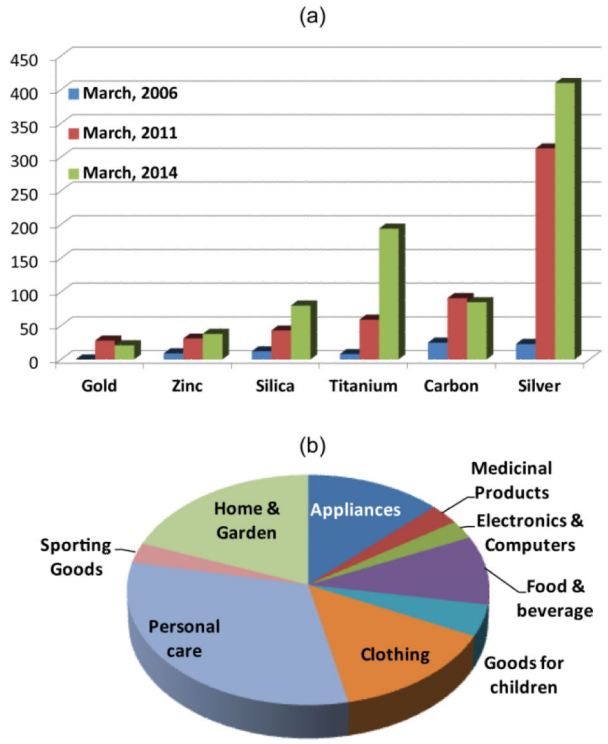

Fig. 1.

(a) Number of MNP-containing products in the US as of March, 2014 and (b) distribution of products in the US containing nAg as of March, 2014. Consumer products containing MNPs have shown an almost 5-10 fold increase over the last 5 years with Titanium, Carbon, and Silver being the predominant materials (Source: The Project on Emerging Nanotechnologies (PEN 2014))

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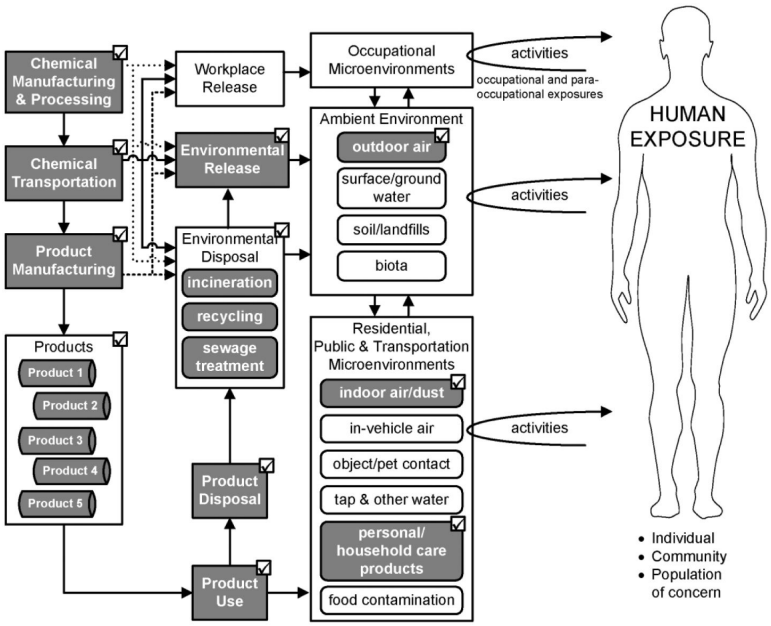

Fig. 2.

Overview of the combined LCA (Life Cycle Analysis) and LAS (Life Stage Analysis) PRoTEGE framework for modeling MNP exposure from multiple sources and for multiple exposure routes and pathways

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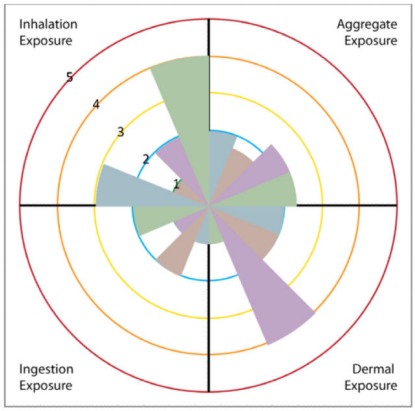

Semi-Quantitative Exposure Ranking				
	Pervasiveness	Persistence	Severity	Efficacy
Inhalation	3	1	2	4
Ingestion	1	2	1	2
Dermal	2	2	4	1
Aggregate	2	1.66	2.33	2.33

Fig. 3.

"Tier 1" PRoTEGE population exposure characterization and ranking for nAg (see Methods Section for definitions of the exposure metrics)

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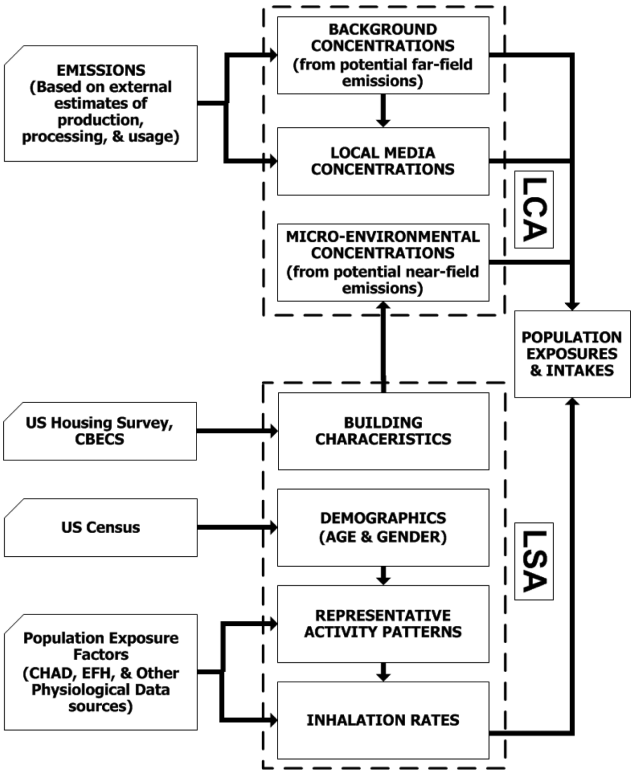

Fig. 4.

Schematic of the modeling structure used in "Tier 2" PRoTEGE characterizations of population exposures; here the focus is on inhalation exposures to nAg for the contiguous US (CONUS) population

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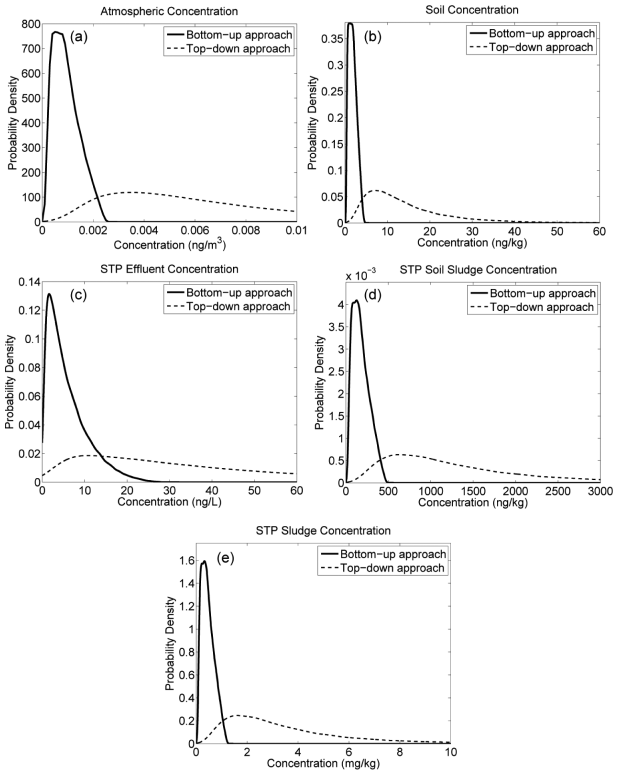

Fig. 5.

Modeled probability densities of silver nanoparticle (nAg) concentrations in (a) ambient air, (b) soil, (c) effluent leaving sewage treatment plants, (d) sludge leaving sewage treatment plants, and (e) sludge applied to agricultural soil. These probability densities were calculated with PRoTEGE employing a probabilistic material flow analysis approach for the contiguous US (CONUS) with two alternative nAg "inventories" developed through a bottom-up (solid line) and a top-down (dotted line) approach. The methodology and the results shown for the top-down approach approximates the analysis of Gottschalk et al. (2010; 2009).

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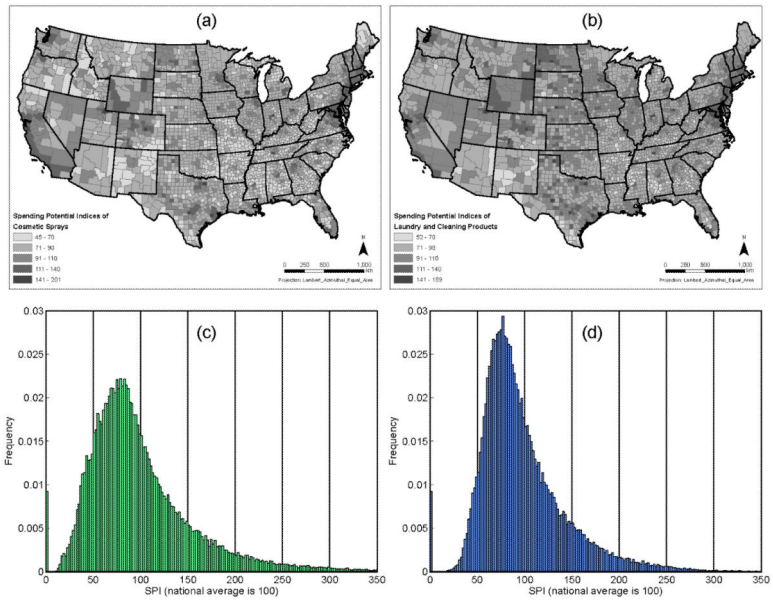

Fig. 6.

SPI (Spending Potential Index) data from (Bureau of Labor Statistics 2014) on “Laundry and Cleaning Supplies” and “Personal Care Products” used to derive consumer usage and variability of cleaning and cosmetic spray products for the CONUS population: (a) and (b) show SPI data at county level and (c) and (d) show SPI data at census tract level. The SPI is “household-based, and represents the amount spent for a product or service relative to a national average of 100.”

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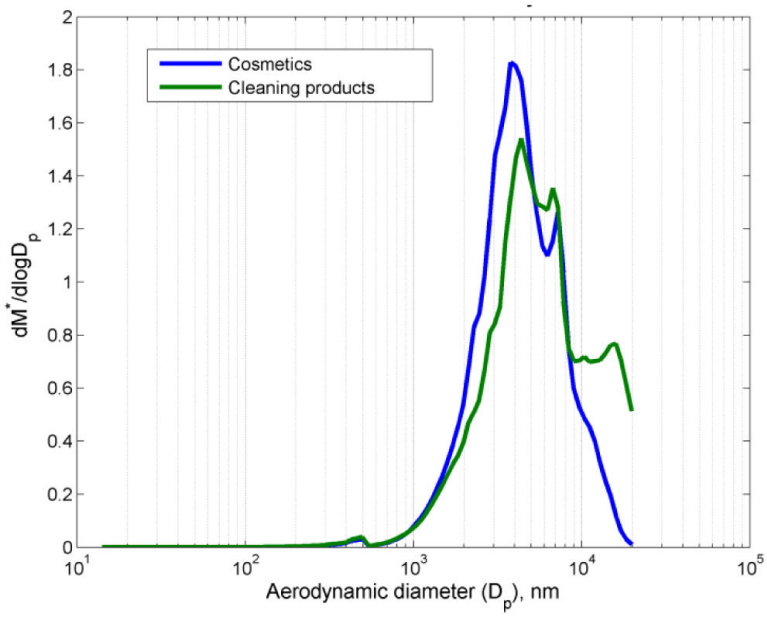

Fig. 7.

Size distributions based on mass fraction, M^*, for cosmetics and cleaning products, obtained from the laboratory-based simulated exposure measurements, as described in this study (by G. Mainelis and co-workers).

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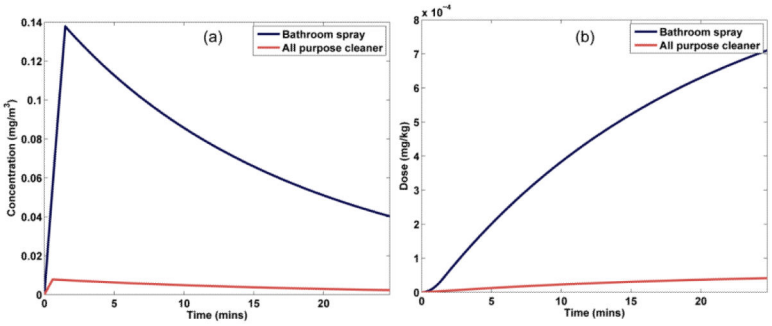

Fig. 8.

"Tier 3 individual scenario" PRoTEGE results showing temporal profiles of airborne nAg concentrations indoors immediately following use of nAg bathroom sprays and all-purpose cleaners in a residential microenvironment (a), and the corresponding profile of inhalation dose (mg per kg of body weight) for an individual present in this microenvironment (b).

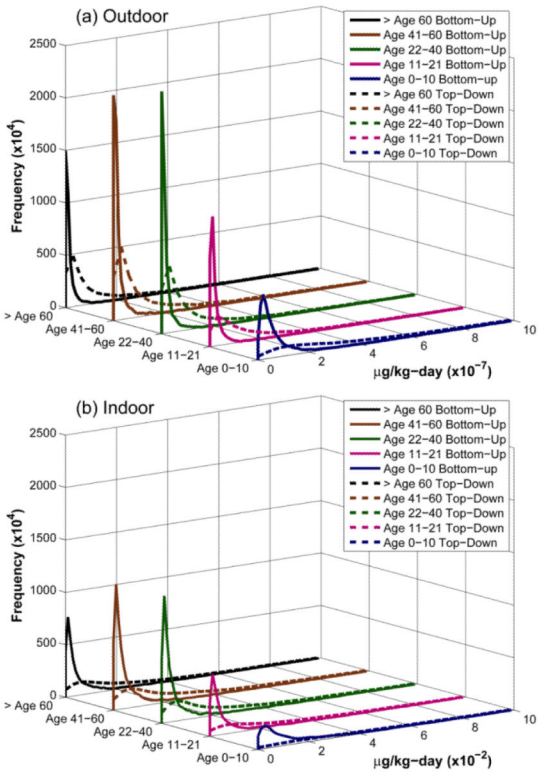

Fig. 9.

Population frequency distributions of estimated inhalation intakes (per day, normalized per body mass) of nAg for different age groups across the contiguous US (CONUS), calculated using both a bottom-up (Hendren et al. 2011) and a top-down Gottschalk et al. (2010; 2009) inventory approach. (a) presents population intakes of nAg from ambient air; (b) presents population intakes of nAg from spray products for the exposed individuals in the population. A market penetration of 50% was assumed for the indoor exposure and intake calculations (b). Sampling for the frequency distributions employed the CONUS population of 306,675,006 (USCB 2012) and the age groups 1 through 5 represent 14.5, 15.3, 25.4, 27.4 and 17.4% of the population, respectively. Note that the orders of magnitude of intake values are different for Figures 9(a) and 9(b).

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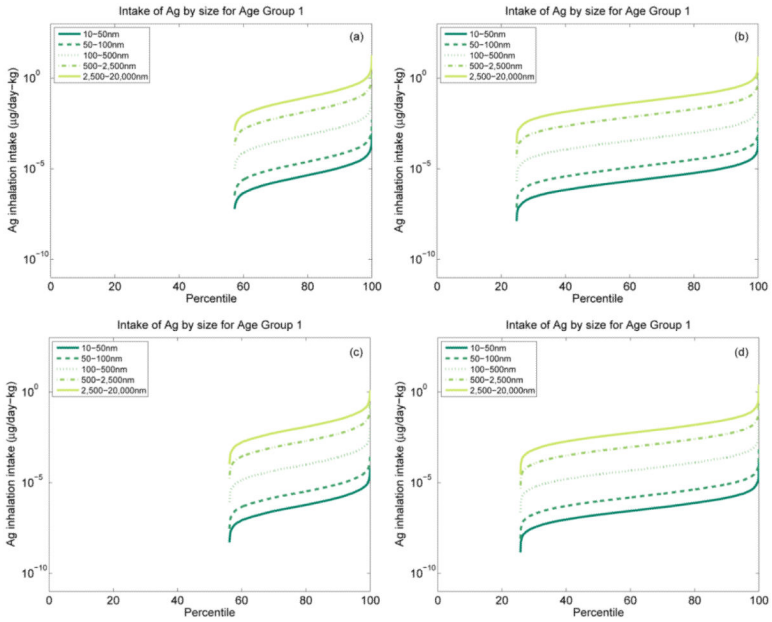

Fig. 10.

Estimated intake distributions of inhaled nAg for Age Group 1 (children of ages 0 to 10 years) in the contiguous US (CONUS) based on modeling calculations that employed a top-down inventory approach with (a) 25% and (b) 50% market penetration; and a bottom-up inventory approach with (c) 25% and (d) 50% market penetration of cleaning and coating spray products containing nAg for children (0 - 10 years)

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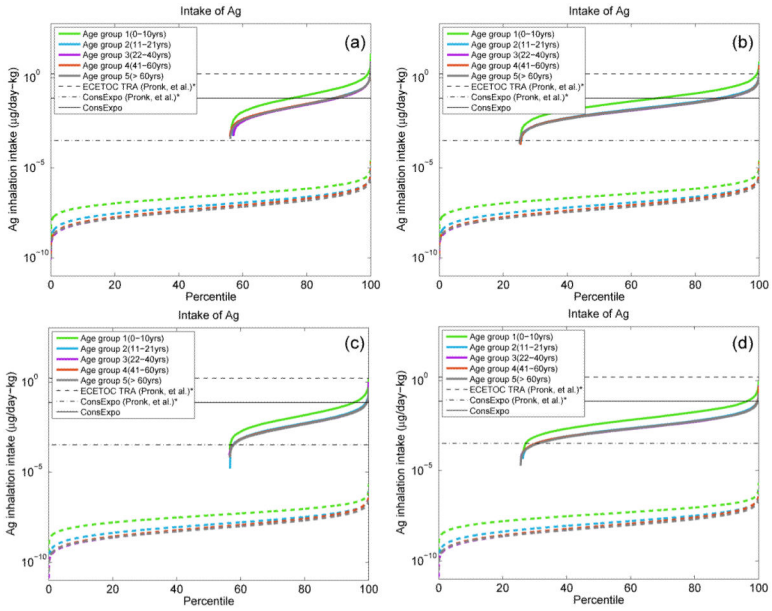

Fig. 11.

Estimated distributions of contiguous US (CONUS) population inhalation intakes (normalized per body mass) of nAg from indoor and from ambient air based on calculations employing a top-down inventory approach (Gottschalk et al. 2009) with (a) 25% and (b) 50% market penetration; and a bottom-up inventory approach (Hendren et al. 2011) with (c) 25% and (d) 50% market penetration of cleaning and coating spray products containing nAg.

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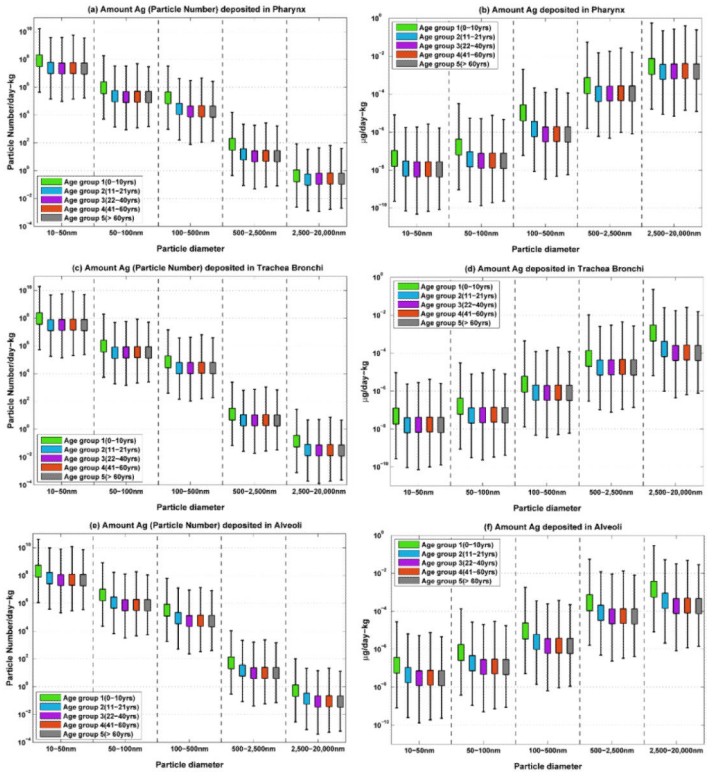

Fig. 12.

Estimated distributions of inhalation uptakes for five (5) age groups and five (5) particle diameter ranges in the contiguous US (CONUS) population; results are shown for nAg deposition in pharynx (a) in mass and (b) in particle numbers; in trachea-bronchi (c) in mass and (d) in particle numbers; in alveoli (e) in mass and (f) in particle numbers.

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Table 1

Availability of nAg information in databases and reference documents (resources highlighted in green contain information on nAg while those in orange do not)

	Resource	nAg data	Website
Physicochemical and/or Toxicological Properties	HSDB - Hazardous Substance Databank	Inventory of data from peer reviewed literature on nAg toxicity effects based on animal, in-vitro and ex-vivo studies; probable routes of human exposures; ecotoxicity on aquatic species and plants; and pharmacokinetics and environmental modeling	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
	Nanomaterial – Biological Interactions Knowledgebase	Inventory of data concerning adverse effects of nAg on embryonic zebrafish represented as a single metric; values provided for different particle sizes and coating of nAg.	http://nbi.oregonstate.edu/ https://wiki.nci.nih.gov/download/attachments/138281854/Harper-EZ_Metric_for_nanoSARs.pdf?version=1&modificationDate=1378874234000
	Nanowerk Nanomaterial Database	List of world-wide nAg suppliers; information on particle sizes, phases, and purity	http://www.nanowerk.com/phpscripts/n_dbsearch.php
	Nanomaterial Registry	Curated data on nAg, categorized by particle size, aggregation state, purity, surface area and charge, availability of biological and environmental interaction data, etc.	http://www.nanomaterialregistry.org/
	RIVM - National Institute for Public Health and the Environment Reports	Lists of nAg reports, documents and publications including RIVM reports on consumer exposure assessment, review of available data and knowledge gaps, etc.	http://www.rivm.nl/en/RIVM
	TOXLINE – Toxicology Literature Online	Lists of peer-reviewed literature on studies concerning nAg toxicity	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE
	TOXNET – Toxicology Data Network	Inventory of databases on toxicology, hazardous chemicals, environmental health, and toxic releases; for nAg - information from TOXLINE, DART (developmental and reproductive toxicity) , HSDB and HPD (household product database)	http://toxnet.nlm.nih.gov/

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	Resource	nAg data	Website
	CEBS - Chemical Effects in Biological Systems	--	http://www.niehs.nih.gov/research/resources/databases/cebs/
	DSSTox - Distributed Structure-Searchable Toxicity	--	http://www.epa.gov/ncct/dsstox/
	GESTIS - Information system on hazardous substances of the German Social Accident Insurance	--	http://www.dguv.de/ifa/Gefahrstoffdatenbanken/GESTIS-Stoffdatenbank/index-2.jsp
	HPVIS - High Production Volume Information System	--	http://www.epa.gov/hpvis/
	IARC - International Agency for Research on Cancer	--	http://www.iarc.fr/
	ICSC - International Chemical Safety Cards	--	http://www.ilo.org/dyn/icsc/showcard.home
	IRIS - Integrated Risk Information System	--	http://www.epa.gov/IRIS/
	ITER - International Toxicity Estimates for Risk	--	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?iter
	JRC Nanomaterials Repository	--	http://ihcp.jrc.ec.europa.eu/our_activities/nanotechnology/nanomaterials-repository
	MSDS - Material Safety Data Sheets	--	http://www.msdsonline.com/msds-search/
	NIOSH - National Institute for Occupational Safety and Health	--	http://www.cdc.gov/niosh/
	NTP - National Toxicology Program	--	http://ntp.niehs.nih.gov/
	PAC - Protective Action Criteria	--	http://orise.orau.gov/emi/scapa/chem-pacs-teels/
	PSAP- Priority Substances Assessment Program	--	http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/eval-prior/index-eng.php
	REACH - Registration, Evaluation. Authorisation and Restriction of Chemicals	--	http://ec.europa.eu/enterprise/sectors/chemicals/reach/index_en.htm
	SCP - Scorecard Chemical Profiles	--	http://scorecard.goodguide.com/chemical-profiles/
	TMI - The Merck Index	--	http://www.rsc.org/merck-index
	ToxCast Phase I & II - EPA Toxicity Forecaster I & II	--	http://www.epa.gov/ncct/toxcast/
	ToxProfs - Toxicological Profiles	--	http://www.atsdr.cdc.gov/toxprofiles/
	ToxRefDB - Toxicity Reference Database	--	http://www.epa.gov/ncct/toxrefdb/
Production and Use	Factual - Global Products with Ingredients and Nutrition	Inventory of products containing nAg as an ingredient with information on brand, manufacturer, and product type	http://www.factual.com/data/t/products-cpg-nutrition
	InterNano	Lists of articles and government reports concerning manufacturing of nAg	http://www.internano.org/
	Nanodatabase	Inventory of products containing nAg as an ingredient with information on manufacturer, product type and NanoRiskCat (ranking of exposures to professionals, consumers and environment and of effects to human and environment)	http://nanodb.dk/
	PEN - Project on Emerging Nanotechnologies Consumer Products Inventory	Inventory of products containing nAg as an ingredient with information on country of	http://www.nanotechproject.org/

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	Resource	nAg data	Website
		origin, product type, potential exposure pathways, coatings, etc.	
	CPCat - Chemical and Product Categories	--	http://actor.epa.gov/actor/faces/CPCatLaunch.jsp
	ECD - Existing Chemicals Database	--	http://webnet.oecd.org/hpv/ui/Search.aspx
	EHPV - Extended High Production Volume	--	http://www.americanchemistry.com/Policy/Chemical-Safety/High-Production-Volume
	HPD - Household Products Database	--	http://householdproducts.nlm.nih.gov/
	IUR - Inventory Update Reporting	--	http://cfpub.epa.gov/iursearch/
	Nanowerk Nanotechnology Products and Applications	--	http://www.nanowerk.com/products/products.php
	SIDS - Screening Information Data Set	--	http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html
	SRD - Source Ranking Database	--	http://www.epa.gov/oppt/exposure/pubs/srd.htm
Releases	NEI - National Emission Inventory	--	http://www.epa.gov/ttnchie1/trends/
	TRI - Toxics Release Inventory	--	http://www2.epa.gov/toxics-release-inventory-tri-program
Environmental Quality	AQS - Air Quality System	--	http://www.epa.gov/ttn/airs/airsaqs/detaildata/downloadaqsdata.htm
	CERCLIS - Comprehensive Environmental Response, Compensation and Liability Information System	--	http://www.epa.gov/enviro/facts/cerclis/
	NATA - National-Scale Air Toxics Assessment	--	http://www.epa.gov/nata/
	NAWQA - National Water-Quality Assessment Program	--	http://water.usgs.gov/nawqa/
	NGA - National Geochemical Atlas	--	http://minerals.cr.usgs.gov/projects/nat_geochem_db_II/task5.html
Micro-environments and Biomarkers-Human and Ecological	caNanoLab - Cancer Nanotechnology Laboratory	Lists of peer-reviewed literature on studies involving nAg in biomedicine and information on in-vivo and in-vitro characterizations of nAg	http://cananolab.nci.nih.gov/caNanoLab/
	ChEBI - Chemical Entities of Biological Interest	Provides ChEBI ontological classification of nAg, "whereby the relationships between molecular entities or classes of entities and their parents and/or children are specified"	http://www.ebi.ac.uk/chebi/
	NanoEHS Virtual Journal (peer-reviewed literature on studies involving nAg in medicine)	Lists of peer-reviewed literature on studies of nAg concerning the environment, health, and safety	http://icon.rice.edu/virtualjournal.cfm
	NIL – Nanoparticle Information Library (potential health effects; For nAg, Health and Safety Info are listed as "not known")	Information involving nAg and occupational health such as method of production, physical and chemical characteristics, associated publications, etc.	http://nanoparticlelibrary.net/
	OECD Database on Research into the Safety of Manufactured Nanomaterials (details of research projects involving nAg:	Lists of research projects addressing issues of nAg on the environment,	http://webnet.oecd.org/NANOMATERIALS/Pagelet/Front/Default.aspx?

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	Resource	nAg data	Website
	Investigators; institutions; project status; relevance; sponsorship; project summary; funding amount; outcomes; etc.)	human health and safety, categorized by funding institutions, country, project status, etc.	
	NHANES - National Health and Nutrition Examination Survey 2003-04, 2005-06, 2007-08, 2009-10	--	http://www.cdc.gov/nchs/nhanes.htm
	NHEXAS - National Human Exposure Assessment Survey	--	http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=22424
	SDWIS - Safe Drinking Water Information System	--	http://www.epa.gov/enviro/facts/sdwis/search.html
	TDS - Total Diet Study	--	http://www.fda.gov/Food/FoodScienceResearch/TotalDietStudy/default.htm

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Table 2

Selected spray products from the simulated exposures measurements. These spray products are classified into two categories: Household cleaning and personal care products.

Product	Description
Household cleaning	
A	Used to clean surfaces
B	Used to prevent unpleasant odors in shoes
C	Used to prevent unpleasant odors in shoes
Personal care	
D	Used as cosmetic spray, dermatologic application
E	Used for skin enhancement
F	Used to clean skin
G	Dermal application as antifungal spray
H	Used as cosmetic for skin protection

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Table 3

Summary of parameter values used for ConsExpo and ECETOC TRA modeling implementations for estimating indoor personal exposures.

	ECETOC TRA (Pronk et al. 2009)	**ConsExpo (Pronk et al. 2009)**	**ConsExpo - Bathroom Cleaning**	**ConsExpo - All-Purpose Cleaner**	**Units**
Frequency of use	7	1	1	7	per week
Amount used per application	0.035	0.035	0.072	0.02	kg
Duration of use per application	4	0.42	0.42	1	h
Inhalation rate	1.37	1.37	1.37	1.37	m^3/hr
Room size	20	10	10	15	m^3
Ventilation rate	NA	2	2	2.5	1/hr
Body weight	60	60	65	65	kg
Weight fraction compound	0.01	0.01	0.001	0.001	-
Airborne fractions	NA	0.2	0.02	0.006	-
Weight fraction non-volatile	NA	0.1	0.1	0.05	-
Density non-volatile	NA	1.8	1.8	1.8	g/cm^3

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Table 4

List of parameters used in the modeling framework

Symbol	Type	Description
P(age, gender)	Distribution	Virtual US population from census demographics data.
i	Index	Index used for identifying an arbitrary individual in the virtual population
S **or** s_i	Distribution	Virtual population sampled from ***P(age, gender)***, each individual is represented as s_i
$R_{inh,\ outdoor,i}$ **&** $R_{inh,\ indoor,\ i}$	Value	Outdoor and indoor inhalation rates of subject i
$\boldsymbol{T_{outdoor,\ i}}$ **&** $\boldsymbol{T_{indoor,\ i}}$	Value	Time spent while outdoors and indoors for subject i
M_{PMC}	Distribution	Production-Manufacturing-Consumption (PMC) of nAg. Can either be $M_{nAg,t\text{-}d}$ or $M_{nAg,b\text{-}u}$.
$M_{PMC,\ t\text{-}d}$	Distribution	PMC of nAg for the US, estimated by (Gottschalk et al. 2009) "top-down" approach
$M_{PMC,b\text{-}u}$	Distribution	PMC of nAg for the US, estimated by (Hendren et al. 2011) "bottom-up" approach
$\boldsymbol{M_{Pr,clean}}$	Distribution	US PMC of nAg that are used for making cleaning spray products
$\boldsymbol{M_{Pr,cosm}}$	Distribution	US PMC of nAg that are used for making cosmetic spray products
$\boldsymbol{f_{res}}$ **and** $\boldsymbol{f_{non\text{-}res}}$	Value	Fraction of time spent in residential and non-residential settings while indoors
f_{MP}	Value	Market penetration (either 25 or 50%)
N	Value	Size of US population
U_p	Distribution	Usage of spray product p across the CONUS population retrieved from ESRI Business Analyst
$\boldsymbol{M_{E,p,r}}$	Distribution	Exposure amount with respect to product category p in an indoor environment r
$\boldsymbol{f_{IF}}$	Value	Intake fraction
$\boldsymbol{M_{I,P}}$	Value	Intake amount with respect to product category p
$\boldsymbol{R_{vent,r,i}}$	Value	Building ventilation rate of subject i for indoor environment r (residential or nonresidential)
d_j	Value	Represents the diameters from the experiment
$f_{m,p}(d_j)$	Distribution	Represents the size distribution of nAg particles for product category p by mass fraction
$\boldsymbol{M_{I,p}(d_j)}$	Distribution	Represents the size distribution of associated nAg inhaled from product category p by mass
$F_k(d_j, a_i)$	Value	Represents the deposition fraction retrieved from MPPD for age a_i, diameter size d_j and lung region $\boldsymbol{k}$
k	Index	Lung regions: pharynx, trachea- bronchi and alveolar are 1, 2 and 3 respectively
$M_{U,i,k}(d_j)$	Value	Represents the amount of associated nAg deposited in the lung region k
$\boldsymbol{j'}$	Index	New index to represent one of the 5 diameter classifications of d_j,
$D_{j'}$	Diameter group	Represents the following diameter classifications: 0-50nm, 50-100nm, 100-500nm, 500-2,500nm and 2,500-10,000nm.

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Table 5

Consumer exposure estimates per event from ConsExpo and ECETOC TRA models presented in Pronk et al. (2009) (from cleaning products)

Dermal exposure	1.43 mg/kg-bw	Using ECETOC TRA model (Pronk et al. 2009)
Inhalation exposure	1.75×10^{-2} mg/m^3	
Total exposure	1.43 mg/kg-bw	
Dermal exposure	1.06×10^{-2} mg/kg-bw	Using ConsExpo model (Pronk et al. 2009)
Inhalation exposure	3.3×10^{-6} mg/kg-bw	
Ingestion exposure	3.17×10^{-4} mg/kg-bw	
Total exposure	1.1×10^{-2}mg/kg-bw	