J Nanopart Res (2014) 16:2724
DOI 10.1007/s11051-014-2724-4

RESEARCH PAPER

Modeling population exposures to silver nanoparticles present in consumer products

Steven G. Royce · Dwaipayan Mukherjee · Ting Cai · Shu S. Xu · Jocelyn A. Alexander · Zhongyuan Mi · Leonardo Calderon · Gediminas Mainelis · KiBum Lee · Paul J. Lioy · Teresa D. Tetley · Kian Fan Chung · Junfeng Zhang · Panos G. Georgopoulos

Received: 13 July 2014 / Accepted: 29 October 2014 / Published online: 13 November 2014

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 employ 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 published individual-based intake estimates, demonstrating that

S. G. Royce · D. Mukherjee · T. Cai · S. S. Xu · J. A. Alexander · Z. Mi · G. Mainelis · P. J. Lioy · P. G. Georgopoulos
Environmental and Occupational Health Sciences Institute (EOHSI), Rutgers University, Piscataway, NJ, USA

S. G. Royce · D. Mukherjee · T. Cai · S. S. Xu · J. A. Alexander · Z. Mi · P. J. Lioy · P. G. Georgopoulos
Department of Environmental and Occupational Medicine, Rutgers University-Robert Wood Johnson Medical School, Piscataway, NJ, USA

D. Mukherjee · P. G. Georgopoulos
Department of Chemical & Biochemical Engineering, Rutgers University, Piscataway, NJ, USA

T. Cai · L. Calderon · G. Mainelis · P. J. Lioy · P. G. Georgopoulos (✉)
Department of Environmental Sciences, Rutgers University, New Brunswick, NJ, USA
e-mail: panosg@ccl.rutgers.edu

K. Lee
Department of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ, USA

T. D. Tetley · K. F. Chung
National Heart and Lung Institute, Imperial College London, London, UK

J. Zhang
Nicholas School of the Environment and Duke Global Health Institute, Duke University, Durham, NC, USA

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 5 years, as reflected by the rapid increase in the number of consumer products containing MNPs. Data from the US-based Project on 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, which 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)).

Manufactured nanoparticles 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

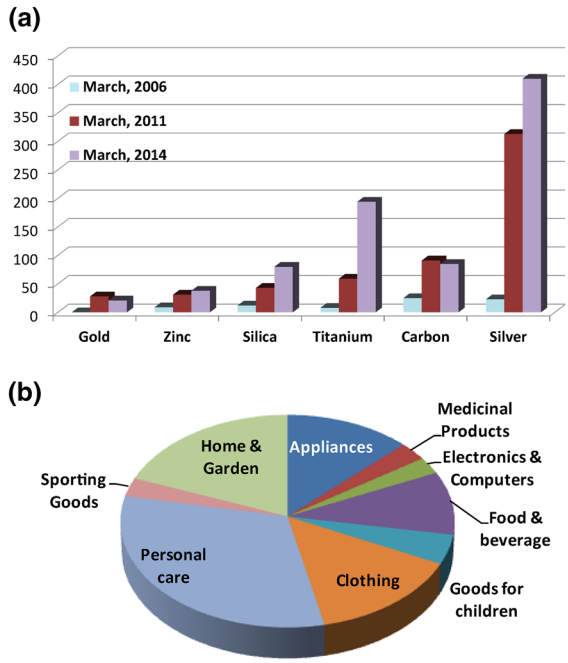


Fig. 1 **a** Number of MNP-containing products in the US as of March, 2014 and **b** distribution of products in the US containing nAg as of March, 2014. Consumer products containing MNPs have shown an almost 5–10-fold increase over the last 5 years with Titanium, Carbon, and Silver being the predominant materials (Source: The Project on Emerging Nanotechnologies (PEN 2014))

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-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, b). 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). Life cycle analysis 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 nanoparticles released 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. (2014) 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 (shown schematically in Fig. 2) has been implemented for nAg from representative consumer products, using new data from laboratory studies employing simulated exposure conditions involving nAg cleaning products, cosmetic, etc., 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

Table 1 Availability of nAg information in databases and reference documents (resources highlighted in bold contain information on nAg, while those in italics 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 worldwide 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/
	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

Table 1 continued

	Resource	nAg data	Website
	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 and 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/

Table 1 continued

	Resource	nAg data	Website
	PEN—Project on Emerging Nanotechnologies Consumer Products Inventory	Inventory of products containing nAg as an ingredient with information on country of origin, product type, potential exposure pathways, coatings, etc	http://www.nanotechproject.org/
	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
Microenvironments 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/

Table 1 continued

Resource	nAg data	Website
NanoEHS Virtual Journal	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	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	Lists of research projects addressing issues of nAg on the environment, human health, and safety, categorized by funding institutions, country, project status, etc.	http://webnet.oecd.org/NANOMATERIALS/Pagelet/Front/Default.aspx?
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

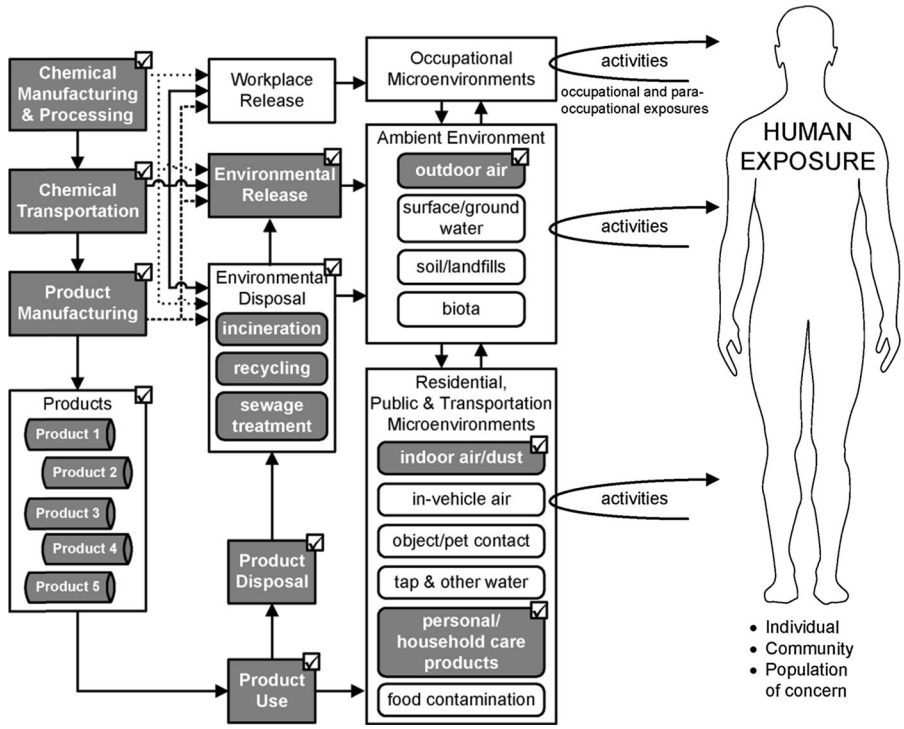


Fig. 2 Overview of the combined life cycle analysis (LCA) and life stage analysis (LSA) PRoTEGE framework for modeling MNP exposure from multiple sources and for multiple exposure routes and pathways

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 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.

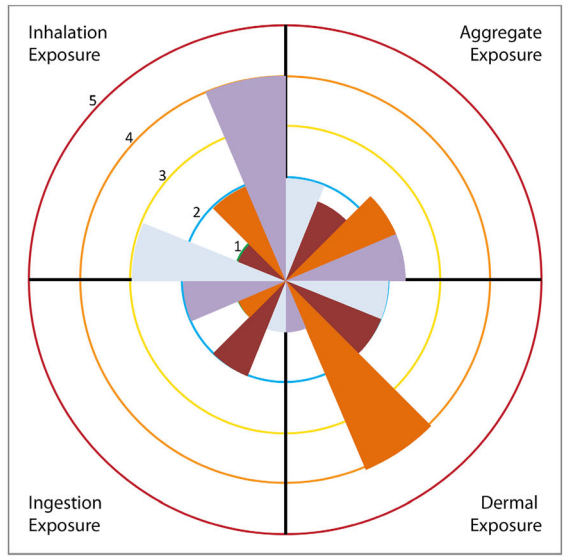
The above four exposure metrics are assigned integer values from 1 to 5, corresponding to very low (1), low (2), moderate (3), high (4), and very high (5) levels of the corresponding metric, based on the information available in the databases accessed and "mined" by PRoTEGE. (A representative subset of these databases is provided in Table 1.) Figure 3 summarizes the PRoTEGE estimates of these metrics, employing data relevant to potential population exposures to nAg in the 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,



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)

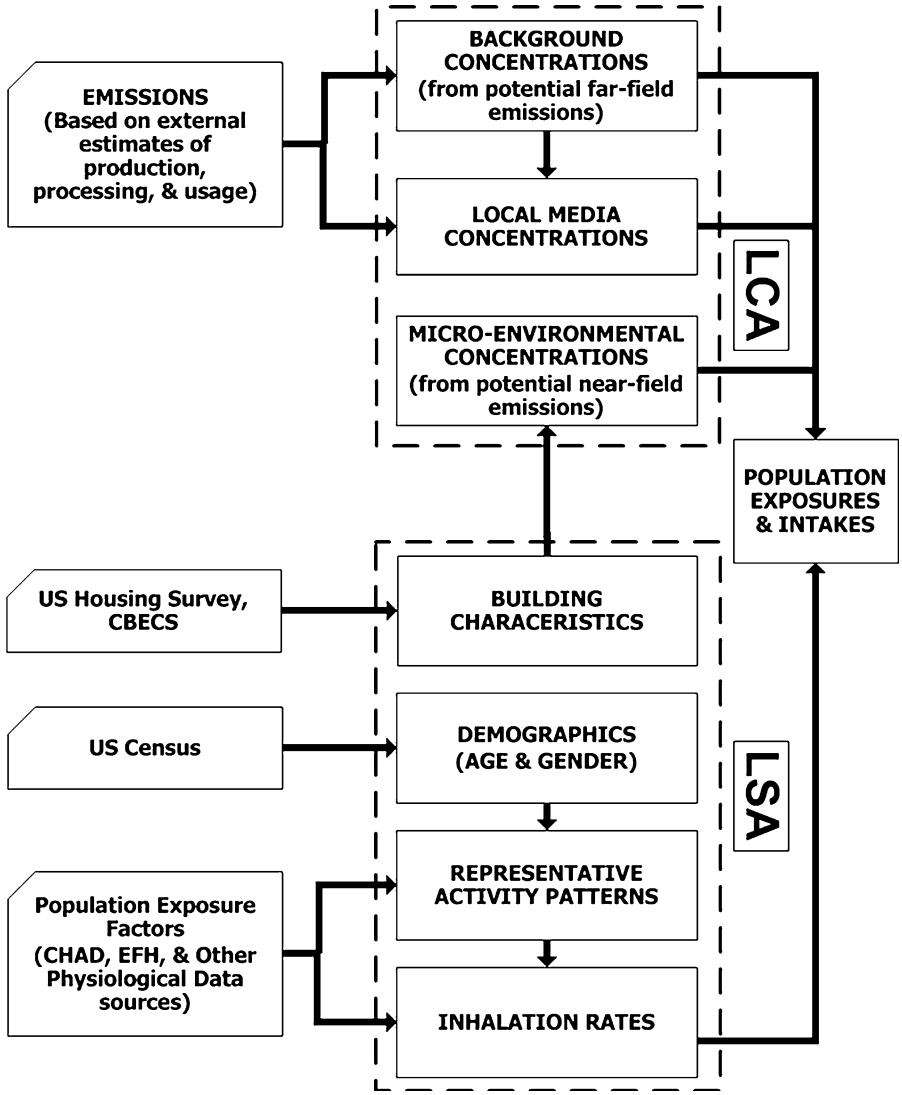


Fig. 4 Schematic of the modeling structure used in "Tier 2" PRoTEGE characterizations of population exposures; here the focus is on inhalation exposures to nAg for the contiguous US (CONUS) population

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 $P(\text{age}, \text{gender})$, and parameterized by age and gender.

$$S \sim P\,(\text{age},\ \text{gender}) \tag{1}$$

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). Exposure Factors Handbook 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 h 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.

$$M_{\text{PMC},t-d} \sim \log \mathcal{N}(\mu, \sigma^2) \tag{2}$$

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 $\mathcal{U}(a, b)$) was constructed, conforming with the lower and upper bounds of the estimated CONUS production volumes:

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

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).

nAg in spray products

Figure 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. 5a 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

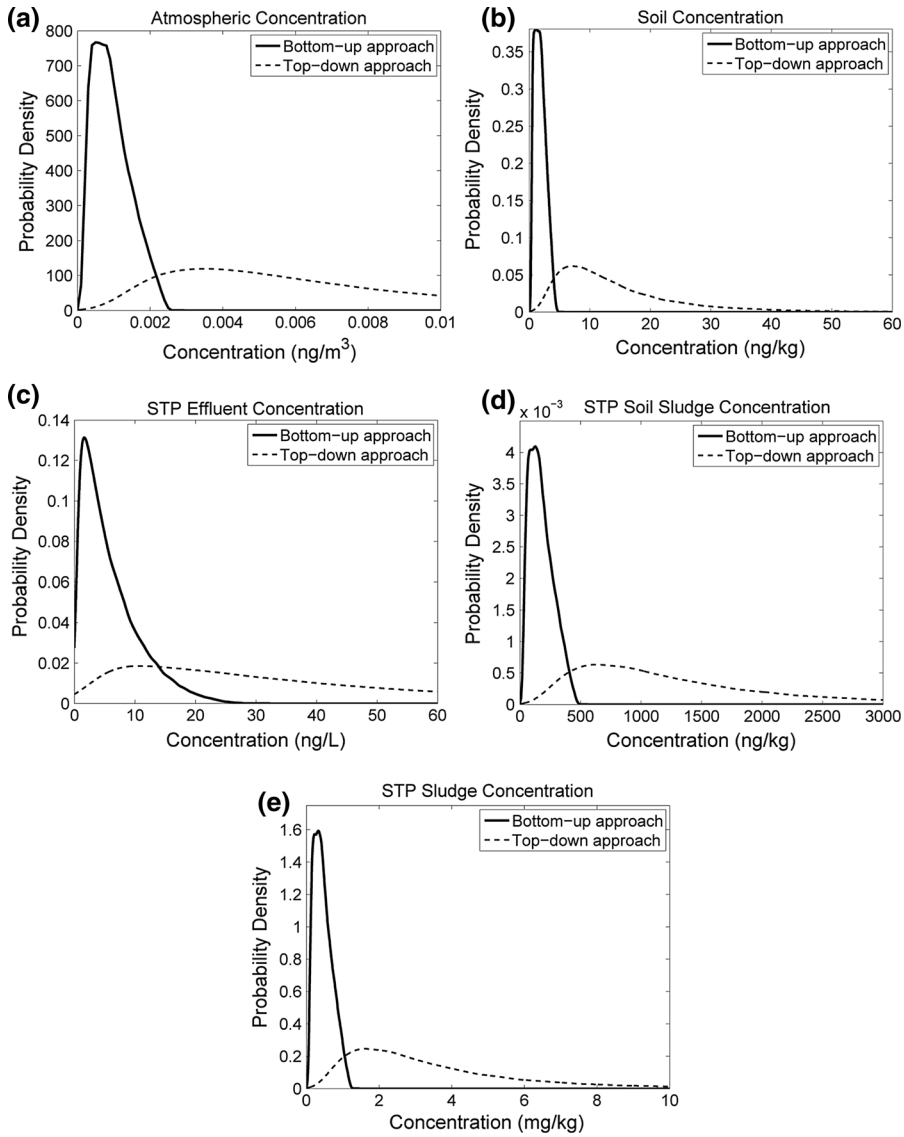


Fig. 5 Modeled probability densities of silver nanoparticle (nAg) concentrations in **a** ambient air, **b** soil, **c** effluent leaving sewage treatment plants, **d** sludge leaving sewage treatment plants, and **e** sludge applied to agricultural soil. These probability densities were calculated with 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*) approach 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)

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:

$$M_{\mathrm{PMC,clean}} \sim M_{\mathrm{PMC}} \cdot \mathcal{U}(0.1, 0.3) \quad (4)$$

$$M_{\mathrm{PMC,cosm}} \sim M_{\mathrm{PMC}} \cdot (0.2) \quad (5)$$

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, $f_{\text{non-res}}$; (ii) all of nAg in cosmetic spray products is assumed to be used in indoor residential settings (i.e. $f_{\text{res}} = 100\%$); and (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, $M_{E,p,r}$, 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

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

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 $\mathbb{I}_{f_{\text{MP}}}(x)$ is an indicator function applied on x, a uniform random variable on [0, 1] as

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

The variability in U_p, the usage of spray products across the CONUS population, was quantified through 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. 6a and b present spending potential index (SPI) data aggregated to

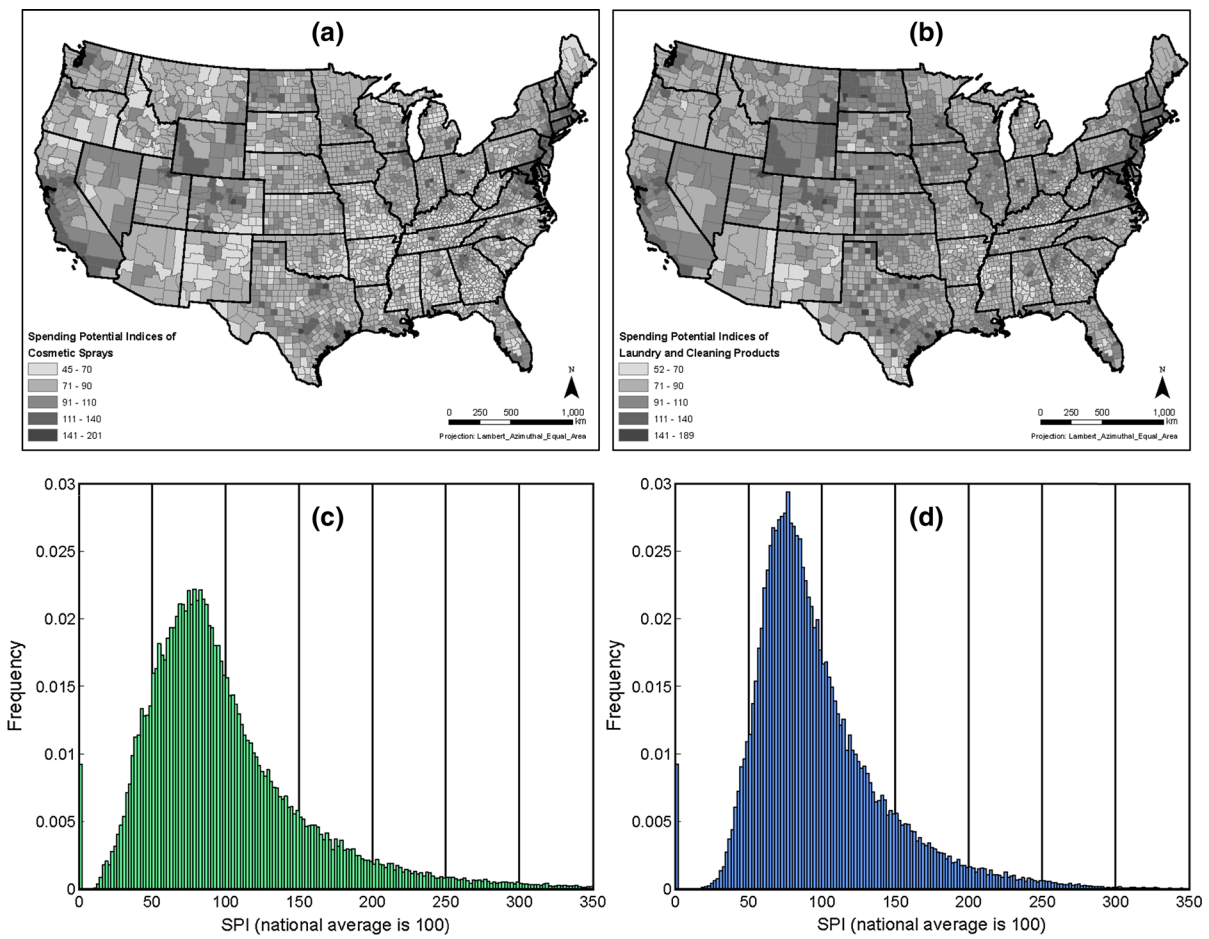


Fig. 6 Spending Potential Index (SPI) data from Bureau of Labor Statistics (2014) on "Laundry and Cleaning Supplies" and "Personal Care Products" used to derive consumer usage and variability of cleaning and cosmetic spray products for the CONUS population: **a** and **b** show SPI data at county level 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"

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, $M_{I,i}$, over emitted amount, $M_{E,i}$:

$$f_{\mathrm{IF},i} = \frac{M_{I,i}}{M_{E,i}}, \tag{8}$$

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, $R_{\mathrm{vent,non-res},i}$, 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

$$\begin{aligned} M_{I,p,i} &= \sum_{\substack{r=\mathrm{res},\\ \mathrm{non-res}}} f_{\mathrm{IF},r,i} \cdot M_{E,p,r,i} \cdot f_{T,r,i} \\ &= \sum_{\substack{r=\mathrm{res},\\ \mathrm{non-res}}} \frac{R_{\mathrm{inh,indoor},i}}{R_{\mathrm{vent},r,i}} \cdot M_{E,p,r,i} \cdot f_{T,r,i}, \end{aligned} \tag{9}$$

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 3,986 (SMPS) and an Aerodynamic Particle Sizer 3,321 (APS) (TSI, Inc., Shoreview, MN, USA) were used to measure airborne particle size distribution and concentration in the combined size range of 14 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 into 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 3 sec to maintain constant aerosol concentration inside the chamber. Each measurement lasted at least 3.5 min, 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. Figure 7 shows

Table 2 Selected spray products from the simulated exposures measurements

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

These spray products are classified into two categories: Household cleaning and personal care products

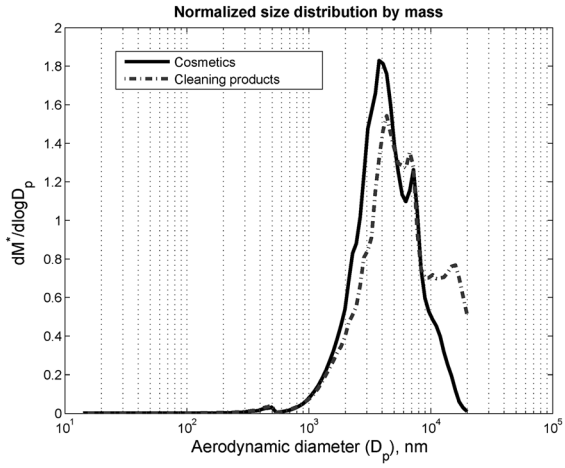


Fig. 7 Size distributions based on mass fraction, M^*, for cosmetics and cleaning products, obtained from the laboratory-based simulated exposure measurements, as described in this study (by G. Mainelis and co-workers)

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

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

Ambient air inhalation exposure

As described earlier, probabilities of ambient air concentrations of nAg are modeled employing an extension of the 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

$$M_I^{\text{out}} = M_E^{\text{out}} \cdot T_{\text{outdoor},i} \cdot R_{\text{inh,outdoor},i}. \tag{11}$$

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, $M_{U,i,k}(d_j)$, for each particle diameter class d_j was estimated as

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

The quantities $M_{U,i,k}(d_j)$ 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: 0–50 nm, 50–100 nm, 100–500 nm, 500–2,500 nm, and 2,500–10,000 nm. $D_{j'}$ 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 microenvironmental 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 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

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:

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

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

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 multizone 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 using MNP concentrations in nAg products for two different

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

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: 0–10, 11–20,

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

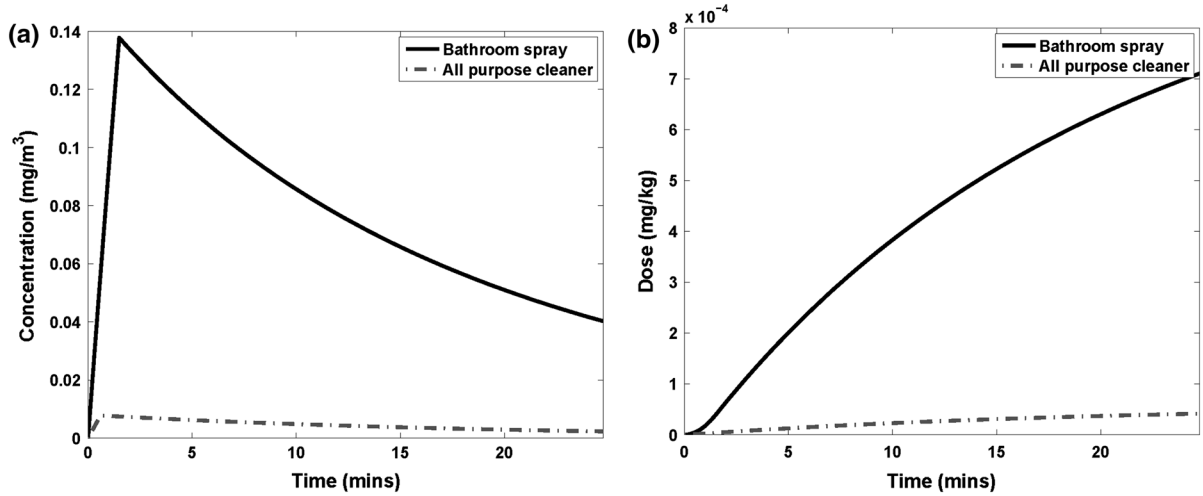


Fig. 8 "Tier 3 individual scenario" PRoTEGE results showing temporal profiles of airborne nAg concentrations indoors immediately following the use of nAg bathroom sprays and all-purpose cleaners in a residential microenvironment (**a**) and the corresponding profile of inhalation dose (mg per kg of body weight) for an individual present in this microenvironment (**b**)

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
$R_{\text{inh,outdoor},i}$ and $R_{\text{inh,indoor},i}$	Value	Outdoor and indoor inhalation rates of subject i
$T_{\text{outdoor},i}$ and $T_{\text{indoor},i}$	Value	Time spent while outdoors and indoors for subject i
M_{PMC}	Distribution	Production-Manufacturing-Consumption (PMC) of nAg. Can be either $M_{\text{nAg},t-d}$ or $M_{\text{nAg},b-u}$
$M_{\text{PMC},t-d}$	Distribution	PMC of nAg for the US, estimated by (Gottschalk et al. 2009) "top-down" approach
$M_{\text{PMC},b-u}$	Distribution	PMC of nAg for the US, estimated by (Hendren et al. 2011) "bottom-up" approach
$M_{\text{Pr,clean}}$	Distribution	US PMC of nAg that are used for making cleaning spray products
$M_{\text{Pr,cosm}}$	Distribution	US PMC of nAg that are used for making cosmetic spray products
f_{res} and $f_{\text{non-res}}$	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
$M_{E,p,r}$	Distribution	Exposure amount with respect to product category p in an indoor environment r
f_{IF}	Value	Intake fraction
$M_{I,p}$	Value	Intake amount with respect to product category p
$R_{\text{vent,r},i}$	Value	Building ventilation rate of subject i for indoor environment r (residential or non-residential)
d_{j}	Value	Represents the diameters from the experiment
$f_{m,p}(d_{\text{j}})$	Distribution	Represents the size distribution of nAg particles for product category p by mass fraction
$M_{I,p}(d_j)$	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 k
k	Index	Lung regions: pharynx, trachea- bronchi, and alveolar are 1, 2, and 3, respectively
$\text{M}_{U,i,k}(d_j)$	Value	Represents the amount of associated nAg deposited in the lung region k
j'	Index	New index to represent one of the 5 diameter classifications of $d_{j'}$
$D_{j'}$	Diameter group	Represents the following diameter classifications: 0–50 nm, 50–100 nm, 100–500 nm, 500–2,500 nm, and 2,500–10,000 nm

21–40, 41–60, and above 61-years old. Figure 9a and b shows the calculated frequency distributions of intakes of nAg from ambient sources, $M_{I,i}^{\text{out}}$, and of nAg from spray products used in the indoor environment, $M_{I,i}$. 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.

Figure 10 shows the predicted nAg intakes by mass in five different size classes, $D_{j'}$, calculated using $f_m(d_j)$ and $M_{I,i}$ for each population age group. These distributions of nAg intakes by mass reflect realistic MNP size characteristics at the point of exposure

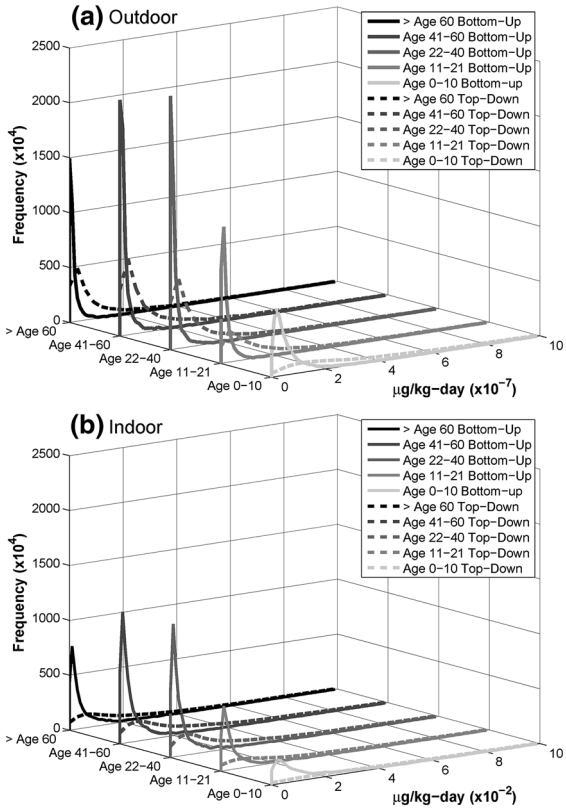


Fig. 9 Population frequency distributions of estimated inhalation intakes (per day, normalized per body mass) of nAg for different age groups across the contiguous US (CONUS), calculated using both a *bottom-up* (Hendren et al. 2011) and a *top-down* (Gottschalk et al. 2010, 2009) inventory approach. **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 Fig. 9a and b

contact and are subsequently used to characterize population-wide nAg depositions in the lung.

"Tier 3" benchmarking

Figure 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 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 Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) 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) are 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

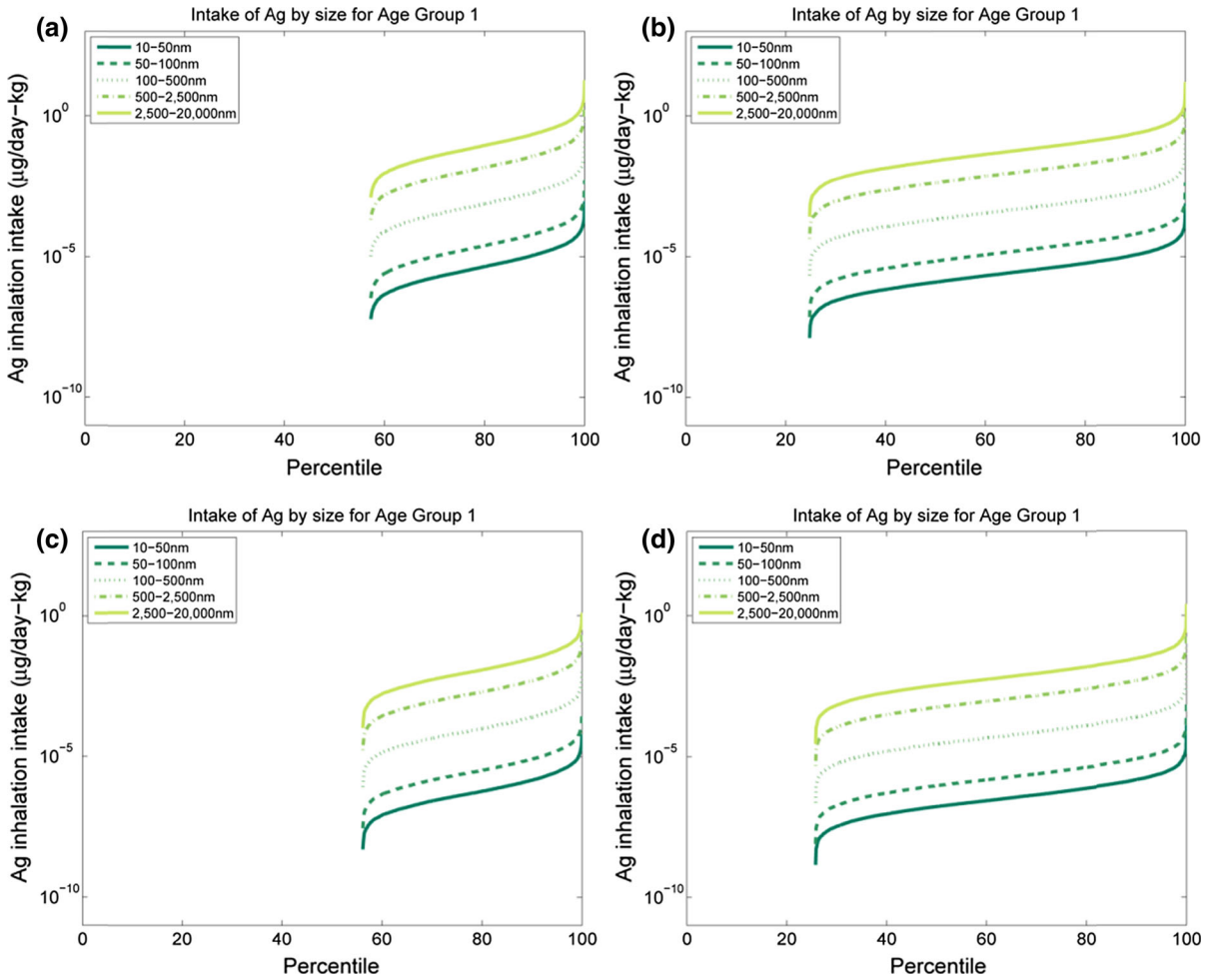


Fig. 10 Estimated intake distributions of inhaled nAg for Age Group 1 (children of ages 0–10 years) in the contiguous US (CONUS) based on modeling calculations that employed a top-down inventory approach with **a** 25 % and **b** 50 % market penetration; and a *bottom-up* inventory approach with **c**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

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. 11a and b vs. Fig. 11c and d) and also with estimates developed for widely different values of market penetration (25 and 50 %) (Fig. 11a and c vs. Fig. 11b 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 being 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

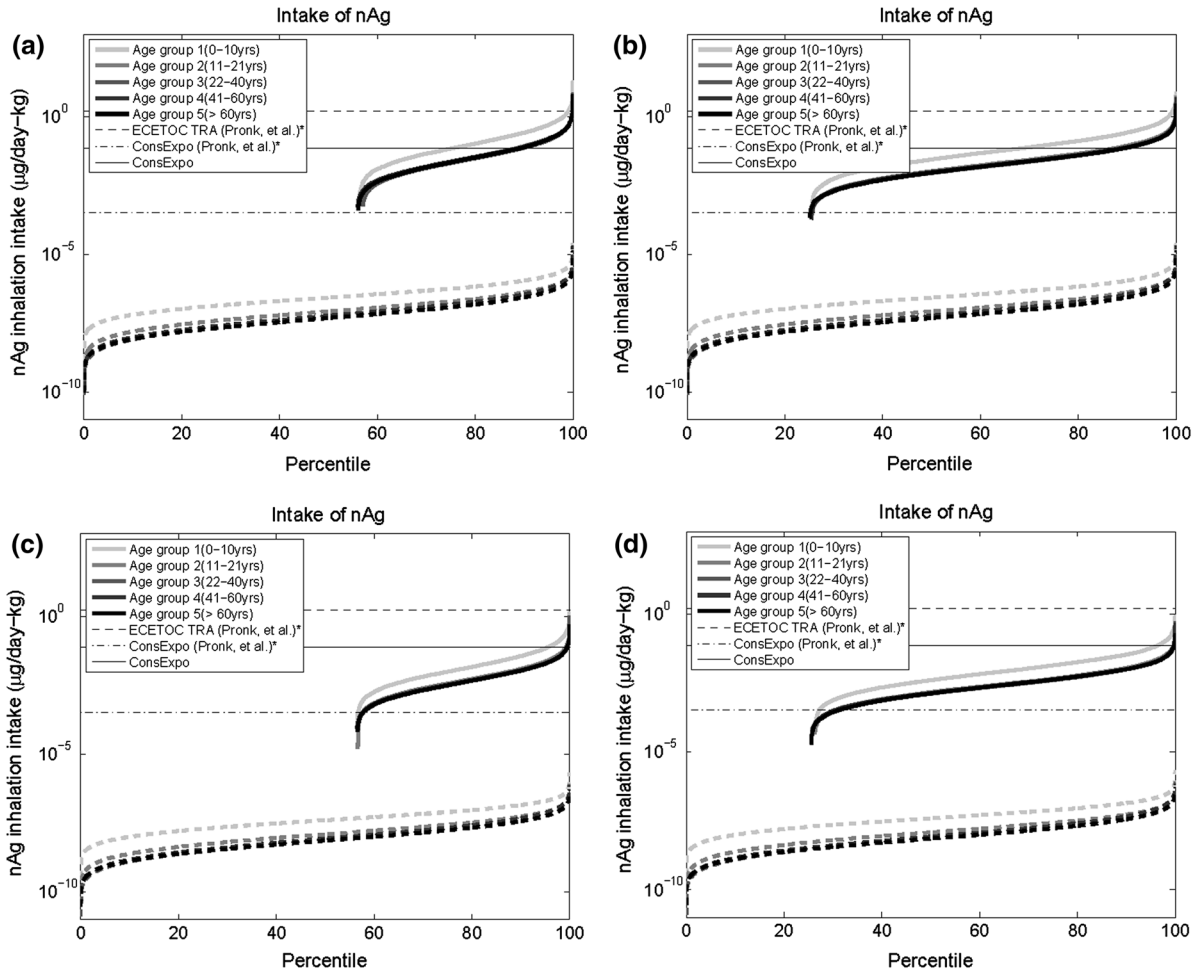


Fig. 11 Estimated distributions of contiguous US (CONUS) population inhalation intakes (normalized per body mass) of nAg from indoor and from ambient air based on calculations employing a *top-down* inventory approach (Gottschalk et al. 2009) with **a** 25 % and **b** 50 % market penetration; and a bottom-up inventory approach (Hendren et al. 2011) with **c** 25 % and **d** 50 % market penetration of cleaning and coating spray products containing nAg

demonstrates that, although a lower-tier framework was used in characterizing population exposures to nAg, estimated intakes are consistent with anticipated and modeled exposures for individual case scenarios.

Population uptakes

Figure 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

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	

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 ENMs 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" are 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 % 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

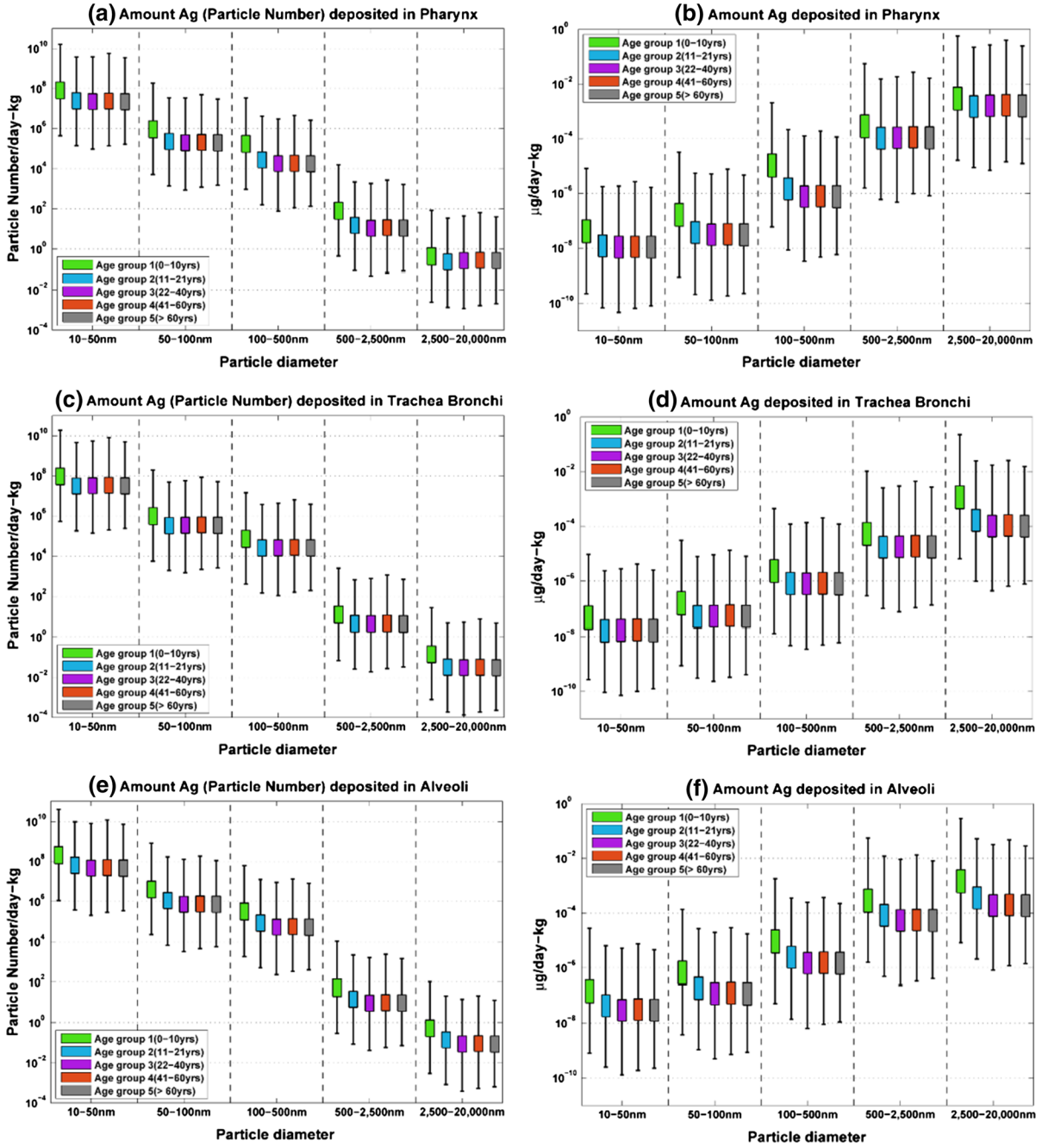


Fig. 12 Estimated distributions of inhalation uptakes for five (5) age groups and five (5) particle diameter ranges in the contiguous US (CONUS) population; results are shown for nAg deposition in pharynx **a** in mass and **b** in particle numbers; in trachea-bronchi **c** in mass and **d** in particle numbers; and in alveoli **e** in mass and **f** in particle numbers

CONUS population and can be updated and improved to reduce the uncertainties in the results 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.

Acknowledgments Support for this work has been primarily provided by the United States Environmental Protection Agency (US EPA) (Grant# 83469302) and United Kingdom Natural Environment Research Council (UK NERC) (Grant# NE/H012893), Risk Assessment for Manufactured Nanoparticles Used in Consumer Products (RAMNUC) project, and by the National Institute of Environmental Health Sciences (NIEHS) funded RESAC Center (Respiratory Effects of Silver and Carbon Nanomaterials—Grant Number U19ES019536-01). Additional support has been provided by the NIEHS sponsored Center for Environmental Exposures and Disease (CEED—Grant Number NIEHS P30E5S005022) at the Environmental and Occupational Health Sciences Institute (EOHSI). This work has not been reviewed by and does not necessarily represent the opinions of the funding agencies. The authors acknowledge assistance from Ms. Linda Everett of EOHSI with editing and proof-reading the manuscript and help in preparing the figures.

References

ARA (2014) Multiple-path particle dosimetry model (MPPD v 2.11). A model for human and rat airway particle dosimetry. Applied research associates. http://www.ara.com/products/mppd.htm. Accessed April 21 2014

Aschberger K, Micheletti C, Sokull-Klüttgen B, Christensen FM (2011) Analysis of currently available data for characterising the risk of engineered nanomaterials to the environment and human health—lessons learned from four case studies. Environ Int 37:1143–1156. doi:10.1016/j.envint.2011.02.005

Bureau of Labor Statistics (2014) Data from 2006 and 2007 consumer expenditure surveys (CEX), accessed using Esri business analyst. http://stats.bls.gov/cex/. Accessed July 1 2014

CBECS (2003) 2003 CBECS survey data. Table B15. Employment size category, number of buildings for non-mall buildings, 2003. US energy information administration. http://www.eia.gov/consumption/commercial/data/2003/pdf/b15.pdf. Accessed April 21 2014

Chen BT et al (2010) Nanoparticles-containing spray can aerosol: characterization, exposure assessment, and generator design. Inhal Toxicol 22:1072–1082. doi:10.3109/08958378.2010.518323

Delmaar JE, Bremmer HJ (2009) The ConsExpo spray model: modelling and experimental validation of the inhalation exposure of consumers to aerosols from spray cans and trigger sprays National Institute for Public Health and the Environment. RIVM, Bilthoven

Delmaar JE, Park MVDZ, van Engelen JGM (2005) ConsExpo 4.0 consumer exposure and uptake models program manual. RIVM, Bilthoven

Esri (2014) ESRI Business Analyst Desktop. http://www.esri.com/software/arcgis/extensions/businessanalyst. Accessed March 28 2014

Gangwal S, Brown J, Wang A, Houck K, Dix D, Kavlock R, Cohen Hubal E (2011) Informing selection of nanomaterial concentrations for ToxCast in vitro testing based on occupational exposure potential. Environ Health Perspect. doi:10.1289/ehp.1103750

Georgopoulos P (2008) A multiscale approach for assessing the interactions of environmental and biological systems in a holistic health risk assessment framework. Water Air Soil Pollut 8:3–21. doi:10.1007/s11267-007-9137-7

Georgopoulos PG, Lioy PJ (2006) From theoretical aspects of human exposure and dose assessment to computational model implementation: the MOdeling ENvironment for TOtal Risk studies (MENTOR). J Toxicol Environ Health 9:457–483

Georgopoulos PG et al (2005) A source-to-dose assessment of population exposures to fine PM and ozone in Philadelphia, PA, during a summer 1999 episode. J Expo Anal Environ Epidemiol 15:439–457. doi:10.1038/sj.jea.7500422

Georgopoulos PG, Wang S-W, Yang Y-C, Xue J, Zartarian VG, McCurdy T, Ozkaynak H (2008) Biologically based modeling of multimedia, multipathway, multiroute population exposures to arsenic. J Eposure Sci Environ Epidemiol 18:462–476

Georgopoulos PG, Sasso AF, Isukapalli SS, Lioy PJ, Vallero DA, Okino M, Reiter L (2009) Reconstructing population exposures to environmental chemicals from biomarkers: challenges and opportunities. J Eposure Sci Environ Epidemiol 19:149–171. doi:10.1038/jes.2008.9

Georgopoulos PG, Brinkerhoff CJ, Isukapalli S, Dellarco M, Landrigan PJ, Lioy PJ (2014) A tiered framework for risk-relevant characterization and ranking of chemical exposures: applications to the National Children's Study (NCS). Risk Anal. doi:10.1111/risa.12165

Goldsmith MR et al (2014) Development of a consumer product ingredient database for chemical exposure screening and prioritization. Food Chem Toxicol 65:269–279. doi:10.1016/j.fct.2013.12.029

Gottschalk F, Sonderer T, Scholz RW, Nowack B (2009) Modeled environmental concentrations of engineered nanomaterials (TiO2, ZnO, Ag, CNT, Fullerenes) for different regions. Environ Sci Technol 43:9216–9222. doi:10.1021/es9015553

Gottschalk F, Scholz RW, Nowack B (2010) Probabilistic material flow modeling for assessing the environmental exposure to compounds: methodology and an application to engineered nano-TiO2 particles. Environ Model Softw 25:320–332. doi:10.1016/j.envsoft.2009.08.011

Hansen SF, Jensen KA, Baun A (2013) NanoRiskCat: a conceptual tool for categorization and communication of exposure potentials and hazards of nanomaterials in

consumer products. J Nanopart Res 16:1–25. doi:10.1007/S11051-013-2195-Z

Hendren CO, Mesnard X, Droge J, Wiesner MR (2011) Estimating production data for five engineered nanomaterials as a basis for exposure assessment. Environ Sci Technol 45:2562–2569. doi:10.1021/es103300g

Hischier R, Walser T (2012) Life cycle assessment of engineered nanomaterials: state of the art and strategies to overcome existing gaps. Sci Total Environ 425:271–282

ISO (2006a) Environmental Management—Life Cycle Assessment—Principles and Framework. International Standardisation Organisation (ISO), Geneva

ISO (2006b) Environmental Management—Life Cycle Assessment—Requirements and Guidelines. International Standardization Organisation (ISO), Geneva

Keil CB, Simmons CE, Anthony TR (2009) Mathematical models for estimating occupational exposure to chemicals, 2nd edn. American Industrial Hygiene Association (AIHA), Fairfax

Money C, Schnoeder F, Noij D, Chang H-Y, Urbanus J (2014) ECETOC TRA version 3: capturing and consolidating the experiences of REACH. Environ Sci 16:970–977. doi:10.1039/C3EM00699A

Mueller NC, Nowack B (2008) Exposure modeling of engineered nanoparticles in the environment. Environ Sci Technol 42:4447–4453

Mukherjee D, Botelho D, Gow AJ, Zhang J, Georgopoulos PG (2013) Computational multiscale toxicodynamic modeling of silver and carbon nanoparticle effects on mouse lung function. PLoS One 8:e80917. doi:10.1371/journal.pone.0080917

Nazarenko Y, Han TW, Lioy PJ, Mainelis G (2011) Potential for exposure to engineered nanoparticles from nanotechnology-based consumer spray products. J Eposure Sci Environ Epidemiol 21:515–528. doi:10.1038/jes.2011.10

Nazaroff WW (2008) Inhalation intake fraction of pollutants from episodic indoor emissions. Build Environ 43:269–277. doi:10.1016/j.buildenv.2006.03.021

NNI (2011) Environmental, health, and safety research strategy environmental, health, and safety research strategy. National Nanotechnology Initiative, Washington DC. http://www.nano.gov/node/681

Oberdorster G (2010) Safety assessment for nanotechnology and nanomedicine: concepts of nanotoxicology. J Intern Med 267:89–105. doi:10.1111/j.1365-2796.2009.02187.x

Panneerselvam S, Choi S (2014) Nanoinformatics: emerging databases and available tools. Int J Mol Sci 15:7158–7182. doi:10.3390/ijms15057158

PEN (2014) The Project on Emerging Nanotechnologies. http://www.nanotechproject.org/. Accessed May 23 2014

Piccinno F, Gottschalk F, Seeger S, Nowack B (2012) Industrial production quantities and uses of ten engineered nanomaterials in Europe and the world. J Nanopart Res 14:1–11. doi:10.1007/s11051-012-1109-9

Pronk MEJ et al (2009) Nanomaterials under REACH: nanosilver as a case study. RIVM, Bilthoven

Quadros ME, Pierson R, Tulve NS, Willis R, Rogers K, Thomas TA, Marr LC (2013) Release of silver from nanotechnology-based consumer products for children. Environ Sci Technol 47:8894–8901. doi:10.1021/es4015844

Reed RB, Faust JJ, Yang Y, Doudrick K, Capco DG, Hristovski K, Westerhoff P (2014) Characterization of nanomaterials in metal colloid-containing dietary supplement drinks and assessment of their potential interactions after ingestion. ACS Sustain Chem Eng 2:1616–1624. doi:10.1021/sc500108m

RIVM (2014) National Institute for Public Health and the Environment. http://www.rivm.nl/English. Accessed July 10 2014

Roberts JR et al (2013) Pulmonary and cardiovascular responses of rats to inhalation of silver nanoparticles. J Toxicol Environ Health A 76:651–668. doi:10.1080/15287394.2013.792024

Schafer B et al (2013) State of the art in human risk assessment of silver compounds in consumer products: a conference report on silver and nanosilver held at the BfR in 2012. Arch Toxicol 87:2249–2262. doi:10.1007/s00204-013-1083-8

Sparks LE (2001) Indoor air quality modeling. In: Spengler JD, Samet JM, McCarthy JF (eds) Indoor Air Quality Handbook. McGraw-Hill, New York

Stallings C, Tippett JA, Glen G, Smith L (2002) CHAD user's guide: extracting human activity information from CHAD on the PC. Prepared for USEPA National Exposure Research Laboratory by ManTech Environmental Technologies, Research Triangle Park, NC

Stark WJ (2011) Nanoparticles in biological systems. Angew Chem Int Ed 50:1242–1258. doi:10.1002/anie.200906684

Sung JH et al (2008) Lung function changes in Sprague-Dawley rats after prolonged inhalation exposure to silver nanoparticles. Inhal Toxicol 20:567–574. doi:10.1080/08958370701874671

Thomas T, Bahadori T, Savage N, Thomas K (2009) Moving toward exposure and risk evaluation of nanomaterials: challenges and future directions. Wiley Interdisc Rev 1:426–433. doi:10.1002/wnan.34

USCB (2012) United States Census 2010. http://www.census.gov/. Accessed March 28 2014

USEPA (2007) Nanotechnology White Paper. USEPA, Office of the Science Advisor, Washington D.C.

USEPA (2011) Exposure factors handbook, 2011th edn. U.S. Environmental Protection Agency, Washington, DC

USEPA (2012) Nanomaterial case study: nanoscale silver in disinfectant spray (Roport number EPA/600/R-10/081F). US Environmental Protection Agency, National Center for Environmental Assessment, Washington

Yang Y, Westerhoff P (2014) Presence in, and release of, nanomaterials from consumer products. Adv Exp Med Biol 811:1–17. doi:10.1007/978-94-017-8739-0_1