1 **Macroscopic to microscopic scales of particle dosimetry: from source to fate in the body**

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16 **Abstract**

17 Additional perspective with regards to particle dosimetry is achieved by exploring dosimetry across a

18 range of scales from macroscopic-to-microscopic in scope. Typically, one thinks of dosimetry as what

19 happens when a particle is inhaled and where it is deposited and how it is cleared from the body.

20 However, this paper shows a much more complicated picture starting with emissions sources, showing

21 how the source-to-intake fraction *(iF)* can be used to estimate changes in the inhaled dose due to

22 changes in emissions and then ending with particle-liquid, particle-cellular and subcellular interactions

23 and movement of ultrafine particles across the lung-blood barrier. These latter issues begin to suggest

24 mechanisms that can lead to adverse health effects the former can provide guidance to policy decisions

25 designed to reduce the health impact of atmospheric particles. The importance of ultrafine particles, their

26 ability to translocate to other parts of the body, and the potential impact of these particles has advanced

27 significantly over the last decade, including studies that show the movement of ultrafine particles along

28 the olfactory nerves in the nose with direct transport to the brain; the neurological effects of which are still

29 unknown. Incremental advancements continue with regards to understanding particle deposition,

30 including regional and local deposition (including hot spots), and clearance and the factors that affect

31 these variables, in part due to the development and implementation of computational fluid dynamics

32 (CFD) models and digital imaging of the lungs. CFD modeling will continue to provide new information for

33 reducing uncertainty in dosimetric calculations. We better understand today how a number of diseases

34 may develop based on the fate of particles after deposition in the lung and how changes in source

35   emissions might impact that dose. However, a number of uncertainties remain some of which can be

36   reduced by addressing the research needs stated in this paper.

37

38   **Introduction**

39   Leonardo da Vinci (1452-1519) warned readers in his Anatomical Atlas that "dust is harmful" (Gehr et al.

40   2010), and Paracelsus (1493—1541) added "The right dose differentiates a poison from a remedy" (Gallo

41   2008). This paper on particle dosimetry integrates and updates these concepts in the interest of reducing

42   the adverse health effects of modern air pollution. This paper also addresses, in part, one of the policy-

43   relevant Science Questions that formed the basis of the 2010 international conference "Air Pollution and

44   Health: Bridging the Gap between Sources and Health Outcomes"[1] (Solomon et al. 2011). Specifically

45   this paper addresses Science Question 4 "*What advances have been made in understanding the*

46   *relationships between exposure, both spatially and temporally, and estimates of dose that tie to health*

47   *outcomes*?"

48   Current research continues to show significant associations of fine particles with adverse health effects

49   (Brook et al. 2010, He et al. 2010, Pope et al. 1995, 2009, Puett et al. 2009). Reducing the adverse

50   health effects from air pollution requires knowledge across the source-to-health effects paradigm: source

51   – atmospheric sciences – exposure – dose – health effect (NRC 1998; Mauderly et al. 2011, this issue;

52   Solomon et al. 2011). Linking sources to adverse health effects is complicated due to the many factors,

53   such as, source variability, the complex and changing nature of pollutants in air (e.g., see Seinfeld and

54   Pandis 1998; Finlayson-Pitts and Pitts 2000) as well as component toxicity, anatomical and physiological

55   factors, susceptibility and vulnerabilities of the target to pollutants, and confounding factors (2009a (Table

56   8-1); Sheppard et al. 2011, this issue; Mauderly et al. 2011, this issue; O'Neil et al. 2011, this issue).

57   Dosimetry research involves a broad understanding of source-to-dose relationships, essentially the first

58   half of the source to health effects continuum. Dosimetric research encompasses a variety of *scales*

59   ranging from the *macroscopic* to the *microscopic*. As well, the dose of the causal agent(s) received and

60   retained are key parameters regarding the impact of an air pollutant that results in an adverse health

61   effect.

62   At the macro-scale, the *intake fraction*, *iF*, is a parameter that provides an estimate of the amount of a

63   pollutant that is inhaled (not deposited nor retained), relative to the amount emitted into the environment

64   from a specified source or source category. The *iF* begins to provide an understanding and quantification

65   of pollutant source-to-intake relationships. The *iF* precedes the deposition in the body of an inhaled air

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[1] American Association for Aerosol Research held in San Diego, CA March 22-26, 2010,
http://aaar.2010specialty.org/ (Solomon et al. 2011).

66   pollutant, which is an important parameter for dosimetry considerations, since the respiratory tract (RT) is
67   the dominant exposure route.

68   Moving from the macro- towards the micro-scale, this paper next considers the fate of a pollutant during
69   and just after inhalation. The inhalability, more specifically the *inhalable fraction* (η_I), describes the
70   sampling efficiency of the nose and/or mouth. The η_I is the ratio of pollutant concentration in the
71   breathing zone (the immediate vicinity of the face) to the concentration that is inspired and enters the
72   *extrathoracic* (ET) airways. The inhalation of particles into the nose or mouth follows the airflow where
73   deposition may occur in any of the major regions of the RT shown schematically in Figure 1a and with
74   micrographs for the gas exchange region of the lungs in Figure 1b. The three main regions include: the
75   ET, *tracheobronchial* (TB), and the *alveolar-interstitial* (AI) regions. The particle deposition efficiencies in
76   each of the major RT regions have been modeled for adults and children breathing at various levels of
77   exertion (e.g. ICRP 1994; EPA 2009a) (e.g., Figure 2).

78   Following deposition within the RT, particles are subject to a variety of fates in the body. They may be
79   retained in the RT for times ranging from minutes (or less) to a lifetime depending on a number of factors
80   described later. Particles not retained in the lungs are removed or cleared by *mechanical processes*
81   (e.g., mucociliary activity, coughing, swallowing), by *phagocytosis* (engulfed by cells and then sometimes
82   digested), and by *translocation*, in which particles or their products move from the RT to other parts of the
83   body. Deposition and clearance phenomena also are individual- and species-dependent (EPA 2009a).

84   At the micro-scale, deposited particles interact with fluids and cells throughout the body. The interactions
85   are varied, and are the subject of ongoing research (Gehr et al. 2010). Interactions with fluids and cells in
86   the body include dissolution, transport within the fluids, uptake by cells and tissue elements, and other
87   physiologic phenomena. These interactions will largely determine the health-related consequences that
88   follow pollutant deposition and again are dependent on a number of factors. Recent research has
89   identified *ultrafine particles* (UF particles; generated by ambient air pollution sources and formed from gas
90   phase precursors in the atmosphere) with dimensions ≤ 0.1 μm, and their intentionally engineered
91   counterparts, *nanoparticles* (NP), as having unique fates in the body and the potential to cause adverse
92   health effects (Wichmann et al. 2000; Renwick et al. 2004; Geiser et al. 2005; Schultz et al. 2005;
93   Oberdörster et al. 2005; de Haar et al. 2006; Donaldson et al. 2006; Kreyling et al. 2002, 2006a, 2006b).
94   Throughout this summary, the term UF particles will be used to refer to both UF particles resulting from air
95   pollution and nanoparticles that are intentionally engineered. UF particles can have access to the entire
96   RT and other organs of the body including the brain (see section, *Particle Translocation*), they likely have
97   the potential for producing greater adverse effects than would be predicted from their mass alone. Thus
98   particle number, composition, or surface area may be more important for dosimetric purposes
99   (Oberdöster 2010).

100   The dose *metric* (or indicator) refers to key pollutant properties that must be measurable, and have a
101   causal relationship to one or more biological responses (Phalen et al. 2010). The metric may have

102   physical and/or temporal properties. Also, the metric need not be causal for every exposed individual
103   (Phalen et al. 2010). Table 1 lists some known or proposed particle-related metrics relevant to the health
104   effects of inhaled air-pollutant particles. In the body, dose metrics differ for soluble versus insoluble
105   particles. For example, common metrics for soluble particles may include particle mass, composition, and
106   aerodynamic diameter (dae). For insoluble particles the metrics also might include surface area, particle
107   count, or other physical properties. Composition is usually a key metric for all air pollutants. All metrics
108   are likely important and should be considered in evaluating pollutants for potential adverse health effects.

109   Relevant biological targets include anatomical (e.g. a cell type, tissue, organ, or organ system) or
110   physiological effects, such as an essential biochemical process (e.g., lung surfactant synthesis) or a
111   system function (e.g., learning or memory).

112   This paper describes the current understanding of selected macro- and micro-scale phenomena related
113   to the adverse health effects of inhaled particles in human subjects, emphasizing current research in
114   dosimetry. *In-vitro* studies have their own set of challenges, and one of the greatest is relating or
115   extrapolating results from *in-vitro* experiments to humans (Gerde 2008), however a detailed discussion of
116   this is outside the scope of this paper. For brevity, details and examples of many other topics discussed
117   can be found in the references, which themselves provide only examples due to the vastness of the
118   applicable literature in this growing field.

119   **Source-to-Intake Relationships: Intake Fraction**

120   Determining source-to-intake relationships for air pollutants allows for an estimate of the relative intake of
121   a pollutant(s) to a population from a particular source category. One advantage is it allows for an
122   estimate of the relative decreases in exposure resulting from decreases in emissions from the subject
123   source category. A source-to-intake relationship takes into consideration the resulting concentrations
124   from a pollutant released into the environment, determines the exposure concentrations, and considering
125   breathing rate, estimates resulting intake to members of the population. A useful measure to estimate
126   source-to-intake relationships is the intake fraction (*iF*) (Bennett et al. 2002a). The *iF* is defined as the
127   integrated incremental intake of a pollutant, summed over all exposed individuals, and occurring over a
128   given exposure time, released from a specified source or source class, per unit of pollutant emitted. The
129   definition is expressed in the equation below:

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131
$$iF = \frac{\sum_{people,\ time} \text{intake of pollutant by an individual} (mass)}{\text{mass released into the environment} (\text{mass})} \qquad \text{eq. 1}$$

132

133   There are two dimensions over which the pollutant intake is summed, population and time. In actuality,
134   when a pollutant is released into the environment there is a distribution of individual exposures within the
135   exposed population. For transient release scenarios, *iF* is made dimensionless by dividing the time-
136   integrated intake by the total quantity released. For steady-state release and exposure conditions, *iF* is

137   the rate of intake divided by the rate of release, both using units expressed as mass per time. If the
138   compound is persistent in the environment, then the exposure that occurs over the duration of the
139   compound being present must be considered.

140   The *iF* allows different pollutant release scenarios to be considered, such as releases into the indoor
141   environment, from outdoor mobile sources, or from industrial facilities (Humbert et al. 2011). Various
142   environments to which the pollutant may be released also can be considered, such that one can
143   differentiate between urban and rural regions or indoor and outdoor. In the case of some chemical
144   pollutants, one may need to sum across multiple exposure pathways (i.e., considering inhalation,
145   ingestion, and dermal pathways) (Bennett et al. 2002b). For air pollutant regulation, *iF* primarily (or
146   exclusively) considers inhalation.

147   There are four attributes of the *iF* that further increases its usefulness. First, *iF* considers both the release
148   scenarios and fates of the pollutant in the environment (Bennett et al. 2002a;)). Second, *iF* can be
149   disaggregated to consider various populations (e.g., susceptible groups) that can then be summed to
150   equal the total *iF* (Tainio et al. 2009; Greco et al. 2007a; Zhou and Levy 2008; Ries et al. 2009; Marshall
151   and Behrentz 2005). Third, *iF* is compatible with dose-response calculations (Levy et al. 2009). Forth, *iF*
152   values can be calculated from models or from measured data (Bennett et al. 2002b, Tainio et al. 2009,
153   Greco et al. 2007a, 2007b, Zhou and Levy 2008, Levy et al. 2009, Hao et al. 2007, Heath et al. 2006,
154   Klepeis and Nazaroff 2006, Li and Hao 2003, Luo et al. 2010, Stevens et al. 2007, Wang et al. 2006; Ries
155   et al. 2009).While the iF value itself is a single, simple value, considerable complexity goes into the
156   calculation. When calculating iF values using a model, the concentration profile in the surrounding area
157   first needs to be determined. Dispersion models with varying levels of complexity have frequently been
158   used in calculations. The concentration profile is then overlaid with the population density to determine
159   the number of individuals exposed to the pollutant. This brings in the population density of the
160   surrounding area. Breathing rates then determine the actual intake, such that a total mass of particulate
161   matter inhaled can be determined.

162   In limited cases there is complete information on the total emissions of the compound into the
163   environment and sufficient measurements of resulting concentrations have been made such that one can
164   calculate an iF value solely from the measured data, without the use of models (Bennett 2002b and Ries
165   2009).

166   The resulting values are therefore subject to uncertainties resulting from model calculations and full
167   quantification of these uncertainties is beyond the scope of this paper. A recent review quantified model
168   uncertainties and found that variability in population density exceeded model uncertainties (Humbert
169   2011). The inclusion of the exposed population in the calculation makes iF values very useful for
170   comparing release scenarios, minimizes the impact of model uncertainties, and points out the need for
171   improved understanding of the exposed population.

172   Research communities can benefit from the numerous applications and models available in which the *iF*

173   can be obtained from and incorporated. Within the modeling community, *iF* can facilitate the evaluation of

174   models, both by comparing *iF* values calculated by models and through measured data (Bennett et al.

175   2002b) and by the comparing results between or among models. Another application is to generate

176   modeling results in one location and use those results in another location after making necessary

177   adjustments, such as for differences in population density (Stevens et al. 2007). This is useful when

178   there are limited available data, or limited resources, such that it would otherwise be difficult to conduct

179   an extensive model evaluation. Although *iF* values cannot be directly used in health assessments, values

180   can be combined with dose-response functions, allowing for comparative risk assessment or evaluation of

181   health-related damages from a release (Levy et al. 2009). The *iF also* is useful with a variety of tools

182   used in decision-making, such as risk management, life cycle assessment, emissions trading, sustainable

183   development, and policy development. Thus, *iF* modeling and the application of *iF* in models can assist in

184   evaluating new sources and for determining the most effective way to reduce sources (Heath et al. 2006;

185   Humbert et al. 2011).

186   When using models to calculate iF values, a wide range of models with varying levels of complexity have

187   been used by various researchers. The resulting values are therefore subject to uncertainties resulting

188   from model calculations and full quantification of these uncertainties is beyond the scope of this paper. A

189   recent review quantified model uncertainties and found that variability in population density exceeded

190   model uncertainties (Humbert 2011). The inclusion of the exposed population in the calculation makes iF

191   values very useful for comparing release scenarios, minimizes the impact of model uncertainties, and

192   points out the need for improved understanding of the exposed population.

193   *Intake fraction values for PM emissions*

194   A series of *iF* values calculated for PM2.5 emissions derived from power plants (Levy et al. 2009; Heath

195   et al. 2006; Wang et al. 2006; Hao et al. 2007; Li and Hao 2003), mobile sources (Greco et al. 2007a;

196   Zhou and Levy 2008; Stevens et al. 2007), area sources (Ries et al. 2009) and indoor sources; Klepeis

197   and Nazaroff 2006) are illustrated in Figure 3. In this figure, *iF* values span over three orders of

198   magnitude among emission sources, ranging from 0.1×10^{-6} to 3×10^{-3}, which is similar to *iF* values

199   calculated for various volatile and semi-volatile organic (VOC and SVOC, respectively) chemicals

200   (Bennett et al. 2002b), also plotted in Figure 3.

201   This extreme range highlights the importance of targeting emission reduction strategies on sources with

202   the highest intake fraction values. When *iF* is taken into account along with the magnitude of the source

203   and any potential differences in the relative toxicity between particle emissions from various sources,

204   regulators could likely develop strategies that could result in health improvements.

205   *iF* values resulting from power plants in Europe, the U.S., and China are shown towards the left side of

206   Figure 3. U.S. values were based on a comprehensive study of PM2.5 emissions from 407 power plants,

207   with exposures estimated using a source-receptor matrix (Levy et al. 2009). *iF* values from power plants

208   in Europe were obtained based on the average *iF* values calculated for different countries within Europe

209   (Tainio et al. 2009). *iF* values for China were calculated from power plants in Beijing (Hao et al. 2007)

210   and the Hunan Province (Li and Hao 2003). Similar *iF* values were observed between the US and Europe

211   but were slightly higher for China due to its higher population density (e.g., 84 per sq mile in the US

212   versus 365 in China; http://www.infoplease.com/ipa/A0934666.html). A value from a hypothetical small

213   distributed energy power plant (DE) in an urban area also is included (Heath et al. 2006).

214   For mobile sources, *iF* values were calculated for urban areas of Boston, MA (Greco et al. 2007a), urban

215   street canyons in New York City, NY (Zhou and Levy 2008), Hong Kong (Luo et al. 2010) and estimated

216   for Mexico City from these previous studies (Stevens et al. 2007). Additional *iF* values from mobile

217   sources are available for each county in the U.S. (Greco et al. 2007b), although these values may be an

218   underestimate due to lack of sufficient detail and modeling of near-road exposures. The variability in

219   values resulting from mobile source emissions among locations largely results from differences in

220   population density (e.g. Hong Kong) and/or high exposure levels (e.g. NY street canyons). An *iF* value for

221   school buses also has been calculated, including exposures to both people inside and outside the bus,

222   thereby resulting in a higher intake fraction value than for other mobile sources (Marshall and Behrentz

223   2005).

224   There are limited examples in the literature of *iF* values for specific area sources. *For example, iF* values

225   for woodsmoke emissions in Vancouver were calculated for a large wildfire (Ries et al. 2009). In this

226   example, levoglucosan, a unique marker for wood smoke was used to determine the portion of the

227   particulate matter that resulted from the wildfire, allowing the authors to determine the relationship

228   between measured concentrations and the source rate.

229   For indoor tobacco smoke, *iF* values were calculated for different scenarios in which individuals were in

230   the same room as the smoker, different room than the smoker, and also by varying the HVAC system

231   (Klepeis and Nazaroff 2006). The resulting *iF* values in the tobacco study were dependent on air

232   exchange rates and the location of people in relation to the source.

233   The *iF* is a simple, transparent, and comprehensive measure of the source-to-intake relationship. As

234   shown in Figure 3, the non-dimensionality of *iF* facilitates comparisons of values calculated from different

235   emission sources and it can be compared among investigators and modeling scenarios. It also is a

236   metric that can be calculated for any scenario and can be reported in addition to plots of concentration.

237   This highlights the utility of *iF* calculations in understanding source-to-intake relationships and in decision-

238   making policies for targeting emission reduction strategies that may have the greatest impact in protecting

239   public health.

240   **The Fate of Inhaled Particles in the Respiratory Tract**

241 Moving from the macroscopic view, and having an estimate of the fraction of air pollutants that can enter
242 the body (*iF*) this section considers the fate of inhaled atmospheric particles inside the body. The fate of
243 inhaled particles involves four general steps: deposition; clearance; translocation; and retention (EPA
244 2009a). *Deposition* occurs when inhaled particles contact the wall of an airway and can occur during
245 inhalation or exhalation. *Clearance* commonly refers to either removal of the particles from the respiratory
246 tract or from the entire body. *Translocation* refers to the extrapulmonary movement of particles from the
247 lungs to other locations in the body. *Retention* is simply what remains in the body at some post exposure
248 time, whether within the lung or elsewhere in the body. Chemical transformation of pollutants also occurs
249 in the body. Each step is dependent on a range of physical, chemical, and biological factors that include:
250 particle properties; exposure location; breathing patterns; and anatomical and physiological
251 characteristics of the exposed subjects such as disease states, body size, age, race, and gender.

252 *Particle Deposition*

253 An inhaled particle can deposit anywhere within the RT upon contacting a surface within the RT; it is
254 assumed that both bounce and re-entrainment are negligible. Within the RT, the AI region of the lungs
255 where gas exchange occurs is of interest due to its large internal surface area of about 150 m^2 and the
256 very thin air-blood tissue barrier of <1 μm in thickness over a large part of the lung's surface, which is
257 primarily located in the AI region (see Figure 1b) (Gehr *et al.* 1978).

258 Particle deposition occurs by several mechanisms in the RT as described below and depends strongly on
259 the size of the inhaled particle, the route of inhalation (nose versus mouth), the tidal volume (V_T), the
260 breathing frequency, RT disease, and the RT morphology (ICRP 1994; EPA 2009a). Physical exertion
261 and reflex-mediated bronchial caliber may be important in some exposure scenarios, for example rescue
262 operations. These factors can influence which deposition mechanisms are dominant within the different
263 regions of the RT (Figure 1). Biological factors depend on the mammalian species, size, status of
264 development and growth and health status, since they will affect lung structure and function, and thus,
265 particle deposition and subsequent fate.

266 Much is known about the deposition of inhaled "ideal" particles, i.e. smooth uncharged solid spheres with
267 unit density (1 gm/cm^3). In the diameter range from 0.01 to 100 μm aerodynamic diameter (d_{ae}), the
268 particle mass, surface area, the number of particles of a given size in 1 μg of ideal particles as well as
269 how far an ideal particle of a given size will travel in a second in still air based on gravitational settling and
270 diffusion are well known Phalen et al. (2010). Such particle characteristics are used for dose calculations.
271 The major mechanisms for the deposition of particles in the RT include inertial impaction, gravitational
272 sedimentation, and Brownian diffusion (ICRP 1994; Brown et al. 2005; EPA 2009a). The first two
273 deposition mechanisms depend on the d_{ae}, which is the physical diameter of a sphere of standard density
274 that has the same gravitational terminal settling velocity as the particle in question. Aerodynamic
275 diameter is most applicable to particles larger that about 0.3 μm (EPA 2009a). Diffusion is

276   thermodynamically controlled, and it dominates the motion of particles less than a few tenths of
277   micrometer in physical diameter, where gravitational and inertial effects are usually negligible.

278   Within the RT, impaction is an efficient deposition mechanism for larger particles, occurring primarily in
279   areas with obstructions or sharp transitions, such as in the nasal turbinates, the larynx, and at airway
280   bifurcations, thus primarily in the ET and upper TB. Sedimentation probability is inversely proportional to
281   the airflow rate and is most important in the lower TB and AI regions, where airflow velocities are low and
282   distances to the walls of airways are small. Both impaction and sedimentation are important for particles
283   in the size range above 1 μm d_{ae} (EPA 2009a). Deposition due to diffusion is proportional to residence
284   times and proximity to airway walls, so it occurs effectively at low velocities and with turbulent flow. Thus
285   particles with diameters under 0.1 μm d_{ae} deposit most efficiently in the lower TB and AI regions.
286   Particles in this size range also tend to deposit due to diffusion in the ET and upper TB regions. Figures
287   2a and 2b illustrate typical deposition curves, including total deposition and deposition in the major RT
288   regions; the curves are for an adult male at rest and at a light exercise. The competing mechanisms of
289   impaction, diffusion, and sedimentation results in the typical U-shaped total RT deposition curves, with a
290   minimum in the range between 0.1 and 1 μm d_{ae}, since particles in this size range are too small to be
291   efficiently impacted or undergo significant gravitational settling, and are too large to be strongly influenced
292   by diffusion. Total deposition approaches 100% for particles larger than about 10 μm d_{ae} and less than
293   0.01 μm in diameter, due to the high efficiency of impaction and sedimentation, and diffusion,
294   respectively. Average curves are shown in Figure 2, but each individual has a unique particle deposition
295   pattern at any given time because of the complexity of the deposition process. Thus, caution must be
296   applied when using average curves for population or individual risk assessment purposes.

297   Respiratory tract disease, from the typical acute infections that adults get 1-3 times per year, to advanced
298   chronic obstructive pulmonary disease (COPD), can significantly influence particle deposition by altering
299   airway structure and ventilatory parameters (see EPA 1996, 2004 for original references). Changes in
300   disease states include differences in regional lung deposition, more heterogeneous deposition patterns,
301   greater deposition in the TB region, and a decrease in the AI deposition due to less particles reaching the
302   AI region. Total RT deposition is generally increased with increasing airway obstruction. Slower
303   clearance in COPD patients was observed by Scheuch et al. (2008), which may be limited to the larger
304   bronchial airways. However, Smaldone et al. (1993) and Brown et al. (2002) found normal clearance in
305   peripheral airways in COPD patients. Relative to healthy adults, individuals with COPD, in which a more
306   limited lung volume receives the total airflow, had a similar resting V_T and an increased breathing
307   frequency; thus a higher than normal tidal peak flow, minute ventilation, and average deposition rate of
308   particles, all suggesting higher doses for individuals with COPD (Bennett et al. 1997; Phalen et al. 2010;
309   EPA 1996, 2004, 2009a). Additional discussion on this topic can be found in Phalen et al. (2010) and
310   EPA (2009a) and references within these publications.

311   The complex morphology of the RT (e.g., bifurcations, bends, and other obstructions to airflow), in
312   conjunction with the several deposition mechanisms results in a strongly non-uniform distribution of
313   deposited particles. Particles greater than about 1 μm d_{ae} and UF particles deposit preferentially at
314   bifurcations, mainly on the carinal ridges, due to impaction and secondary flow patterns. These areas are
315   referred to as *hot spots* that result from high particle deposition in small areas (EPA 2009a; Kleinstreuer
316   and Zhang 2010; Phalen et al. 2006). The size of the hot spot area is referred to as the *patch size* by
317   dosimetry modelers. Hot spots are illustrated in Figure 4. In this figure, computational fluid dynamic
318   (CFD) simulations are used to model the deposition of UF (NP) particles and gases and micrometer sized
319   particles in the ET and upper TB (mouth to large bronchi).

320   Deposition enhancement factors (EFs) are used to quantify hot spot deposition dose enrichments. The
321   EF is defined as the ratio of particles deposited at the hot spot per unit surface area of epithelial cells
322   (e.g., a patch size of 0.1 mm x 0.1 mm) to the average deposition on the surrounding tissue (Kleinstreuer
323   and Zhang 2010; EPA 2009a; Balásházy et al. 1999, 2003). EFs, estimated from CFD modeling, are
324   shown as a function of patch size and particle diameter in Table 2, and as a function of ventilation rate (5
325   and 30 L/min) in Table 3 (Balásházy et al. 1999, 2003). In these examples, EFs range from less than 10
326   to about 400 times that of the surrounding epithelial surface. EFs up to 1,200 have been reported
327   (Farkas and Baláshazy 2008). Hot spots also bring up a unique challenge for cell culture studies with
328   respect to air pollutant dosing of the *in-vitro* system (Phalen et al. 2006). Should an average dose be
329   applied, the enhanced dose applied to the entire culture, or the enhanced dose just applied to a
330   reasonable patch sizes surrounded by cells in the culture with no dose?

331   *Particle clearance*

332   Clearance usually refers to the removal of deposited particles from the RT, whether removed from the
333   body or translocated to other parts of the body (e.g., through the respiratory epithelium) where they may
334   be subsequently removed from the body by other mechanisms. Clearance rate data for inhaled particles
335   from the RT are required in dosimetric calculations. The rates and mechanisms of particle clearance
336   depend on the size of the particle, where it has deposited, whether it is *soluble* or *insoluble*, health status
337   of the individual, particle loading, and other factors (Phalen and Méndez 2009).

338   Although particles are often referred to as insoluble or soluble, it is more appropriate to refer to their
339   dissolution rate in lung fluids, both on RT surfaces and within cells (Phalen et al. 2010). When the
340   dissolution rate is slow compared to the mucus flow or other transport rate, the particles are considered to
341   be *slowly dissolving* or *poorly soluble*. When particles dissolve rapidly, they are considered to be *rapidly
342   dissolving*. For simplicity, soluble and insoluble are used herein.

343   Insoluble particles deposited in the ET are typically cleared by bulk physical processes, such as sneezing,
344   coughing, expectoration, or by mucociliary transport followed by swallowing. The latter mechanism is
345   more important for particles deposited in the posterior portions of the nasal region, with the former

346   mechanisms being more important in the anterior nasal region. UF particles also may clear from the ET
347   via the olfactory nerves with direct transport to the brain (to be described later). Both insoluble and
348   soluble particles deposited in the mouth are removed by swallowing or expectoration.

349   Clearance in the TB region of insoluble particles is primarily by mucociliary movement toward the
350   epiglottis where particles are swallowed (ICRP 1994; EPA 2009a). Mucus movement is faster in larger TB
351   airways than in the smaller ones (EPA 2009a; ICRP 1994). This leads to longer residence times for
352   particles deposited deeper in the TB region. Previously, it was assumed that insoluble particles deposited
353   in the TB region were completely cleared by mucociliary action within 24 hr. Recently, this assumption
354   has been shown to be inaccurate, as a fraction of the deposited particles may be retained for much longer
355   time periods (ICRP 1994; Kreyling et al. 2006a, 2006b; Smith et al. 2008; EPA 2009a; Phalen et al.
356   2010). The mechanisms for such slow bronchial clearance include: mucus stasis, mucus retrograde flow,
357   macrophage/epithelial cell uptake, and particle displacement into the subphase of the mucus (EPA 1996,
358   2004, 2009a; Gehr et al. 1990; Schürch et al. 1990). Results summarized in EPA (2009a and references
359   within), indicate that particle clearance from the TB region also is particle size dependent (therefore,
360   deposition location dependent) with probable slower clearance of UF particles (up to several months for
361   complete clearance) and more rapid clearance of particles in the 6-10 μm diameter range. Bolus
362   inhalation studies used to support slow bronchial clearance in humans have been challenged, since it
363   may have been assumed that particles deposited in AI region were actually deposited in the TB airways
364   (Phalen et al. 2010) and the AI region has slower particle clearance than TB region. This assumption
365   would overestimate the fraction of particles that are cleared slowly. Therefore, TB clearance rates are
366   probably more variable, and uncertain than is usually assumed.

367   The primary mechanisms for insoluble particle clearance from the AI region are believed to include: (1)
368   macrophage phagocytosis with subsequent migration to interstitial spaces, i.e., the lymphatics or terminal
369   bronchioles, where the engulfed particles are cleared by mucociliary action; (2) transport in alveolar
370   surface fluids to ciliated airway; or (3) uptake by non-mobile alveolar cells. Macrophage uptake is more
371   efficient for particles larger than 1 μm (Oberdörster 1988), allowing insoluble UF particles to have longer
372   residence times in the AI region, and thus, more time to be taken up by epithelial cells and/or translocate
373   intact across the alveolar epithelium. Translocation, discussed below, is a forth mechanism for particle
374   clearance from the AI region, and noted separately here since the particles remain intact the body.

375   Respiratory tract disease (e.g., acute respiratory infections or COPD) can slow the clearance of insoluble
376   particles from the TB region of the lungs, although there is conflicting information in the literature on this
377   issue as summarized in EPA (2009a), Phalen et al. (2010), Scheuch et al. (2008) and Brown et al. (2002).
378   No difference related to disease was observed in the AI region (EPA 2009a) possibly because RT
379   disease influences where particles deposit, and when there are narrowed RT airways (AI region),
380   particles tend to have more proximal deposition in the lungs. Also, RT infections can slow TB clearance
381   rates, and hence stimulate life-saving coughing fits.

382   Soluble particles dissolve in the lung fluid into their constituents that are cleared by mechanisms that
383   depend on the site of deposition, particle surface area, chemical composition of the particle, particle
384   surface coatings, and molecular weights of the dissolved constituents (EPA 2009a). Soluble particles and
385   constituents may be absorbed by, or diffuse through, the epithelial layers of the TB and AI regions. The
386   rate of this mechanism would be inversely proportional to molecular weight. In the TB region, Lay et al.
387   (2003) observed that mucociliary transport may be slower for soluble than insoluble particles. Water
388   soluble metals may transport through the lung via transepithelial absorption more rapidly than low water
389   or low acid soluble metals and may lead to translocation to other organs within 24 hours (Wallenborn et
390   al. 2007). This is likely important for redox active metals (e.g., often Ni and V as well as Zn, Al, Cd, Fe(II),
391   Pb) (Chen and Lippmann 2009), since they can generate reactive oxygen species (ROS), which can lead
392   to adverse health outcomes.

393   *Particle translocation*

394   The process of extrapulmonary translocation primarily refers to the migration of particles across the lung
395   fluid and tissue lining to the circulatory systems (Kreyling et al. 2002; Geiser et al. 2005). The
396   mechanisms of translocation are varied including blood and lymph systems, and particle movement
397   through membranes. Once in the circulatory system, particles can translocate to other organs in the body
398   with the potential to cause adverse health effects in the impacted organs (Ferin et al. 1992; Geiser et al.
399   2005; Semmler et al. 2004; EPA 2009a; Nemmar et al. 2002; Mühlfeld et al. 2007; Brown et al. 2002;
400   Oberdörster et al. 2004; Renwick et al. 2004). Under normal physiological conditions, the translocation
401   rate of insoluble particles with diameters larger than about 200 nm is assumed to be negligible (Geiser
402   and Kreyling 2010). After deposition in the AI region, UF particles, which have a longer residence time in
403   the AI region than larger particles, can enter circulation through the air-blood tissue barrier in the alveoli
404   (Geiser et al. 2005). Results indicate that small but detectable amounts of circulating UF particles can
405   accumulate in secondary target organs such as the liver, spleen, heart, kidney, and brain (Kreyling et al.
406   2002; Semmler et al. 2004). The most studied UF particle types included particles composed of carbon,
407   TiO_2, Au, and Ir. For human lungs, however, only one study exists that describes a rapid and significant
408   translocation of inhaled and deposited carbonaceous UF particles to systemic circulation and, thus, to
409   secondary organs (Nemmar et al. 2002). In most other studies translocation for iridium (Kreyling et al.
410   2002) or carbonaceous UF particles was minimal (Mills et al. 2006, Wiebert et al. 2006). It is accepted
411   nowadays that the degree to which inhaled UF particles translocate into the circulatory system is rather
412   small but it is significant (Mühlfeld et al. 2007; Figure 5). However, information on cumulative effects of
413   this translocation process is lacking.

414   Another pathway of UF particle translocation, that does not involve systemic circulation, is transport via
415   the olfactory nerve in the nose to the brain (EPA 2009a; Oberdörster 2010; Phalen et al. 2010 and
416   references within). This latter mechanism was reported in 1934 (Brodie and Elvidge 1934) and recently
417   brought to attention by Oberdörster et al. (2004), and Elder et al. (2006). Translocation of UF particles to

418   the brain from the nose has been observed in several species including humans (EPA 2009a;
419   Oberdörster 2010; Phalen et al. 2010 and references within) and likely occurs in less than an hour.
420   Comparison between rodents and humans may be difficult since rats and mice have much larger olfactory
421   regions of epithelial mucosa (about 50% of the nasal epithelium) than people (about 5%), since humans
422   are more visual than olfactory (Aschner et al. 2005).   However the potential health impact of this
423   mechanism is still not understood for air-pollutant particles (Doty 2008, 2009; EPA 2009a; Phalen et al.
424   2010; Oberdörster 2010).

425   *Subject characteristics*

426   Human characteristics that influence particle dose include body size, gender, race, age, and RT disease
427   (the later noted above). Phalen et al. (2010) and EPA (2009a) summarized the effects these parameters
428   have on RT deposition of particles. Dosimetric calculations are often normalized to body weight (or body
429   mass) since airway size, lung volume, and minute ventilation vary with body size. Deposition in average
430   men and average women vary, in part because average women have smaller ET and TB airways, which
431   can shift deposition proximally. This effect can cause greater total deposition in the ET and TB regions;
432   more rapid clearance; and reduced deposition in the AI region. Biological variables, primarily in the ET
433   region influence deposition across race (Phalen et al. 2010, EPA 2009a). In healthy adults, age per-se
434   does not seem to alter deposition; although differences may occur between young children and adults
435   due to body size differences and differences in RT anatomy and ventilation parameters (Bennett and
436   Zeman 2004; Ginsberg et al. 2005; Foos et al. 2008; EPA 2009a).

437   Young children are generally assumed to represent a susceptible population in comparison to adults
438   (O'Neil et al. 2011, this issue). Evidence is limited, but potential effects in children also may include
439   adverse birth outcomes, infant mortality, respiratory effects, such as cough, bronchitis, and asthma
440   attacks, and possibly incomplete lung development. However, such effects are not yet firmly established.

441   Multiple factors affecting particle deposition in children include breathing pattern (healthy young children
442   presumably breathe more through the nose than the mouth), possibly lower efficiency of particle
443   deposition in the nose for children, smaller V_T, faster breathing rate, and differences in airway dimensions
444   and shapes. Modeled and experimental deposition data for children were reviewed and compared by
445   Isaacs and Martonen (2005). Results indicated that the deposited dose per unit surface area of the RT is
446   greater in small children than adults at given similar levels of exertion. Bennett and Zeman (1998)
447   performed clinical studies that indicated that the deposition rate of fine particles normalized to lung
448   surface area might be greater in children than adults. They also noted a correlation of an increased
449   deposition rate in children with higher body mass index, with heavier children having higher V_T and minute
450   ventilation, both which led to a higher deposition rate.

451   Interspecies differences in the clearance of insoluble particles from the TB and AI regions have been
452   noted (Snipes, et al. 1989; Phalen and Méndez 2009; EPA 2009a and references within). Mice and rats,

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453 commonly used laboratory subjects, have faster clearance of insoluble particles than people. In the AI
454 and TB region this may be due to shorter distances for removal (e.g., from the AI region, as particles
455 captured by macrophages are transported to the TB region). Also, the lack of respiratory bronchioles in
456 rodents, results in easier access to TB mucus, and thus, may lead to faster clearance.

457 **The Fate of Deposited Particles in the Lung**

458 After having described the fraction which enters into the RT and the mechanisms for deposition and
459 clearance within the RT, the fate of the deposited particles and their effects at the microscopic scale are
460 presented. Specifically, the interactions of UF particles with the internal surface of the airways and the
461 subsequent interaction with cells and cellular sub-structures are described.

462 The focus on UF particles is because research indicates that respiratory and cardiovascular diseases
463 related to inhaled UF particles are frequent and increasing (Schultz *et al.* 2005). UF particles that enter
464 cells are of particular risk because they can cause oxidative stress through the generation of ROS
465 (MacNee 2001). Oxidative stress can cause a reduction in cell metabolic competence via a reduction in
466 mitochondrial respiration as well as an increase in pro-inflammatory cytokine production and other cellular
467 inflammatory reactions and toxicity that can lead to apoptosis, pulmonary and cardiovascular disease, or
468 cancer (Donaldson et al. 2003, 2006; Poland et al. 2008). The generation of oxidants is likely due to the
469 high organic content and pro-oxidative potential of UF particles (Oberdörster et al. 2005). UF particles
470 deposited in the AI region have longer residence times, and thus, more time to interact with cells or
471 translocate through lung tissue and into capillary blood vessels as noted earlier. Epidemiological studies
472 also have convincingly shown the association between UF particles and adverse health effects (Pope et
473 al. 1995; Peters et al. 1997, 2001; Wichmann et al. 2000; Künzli et al. 2005).

474 Understanding particle interactions at the tissue and cellular level allows for the development of
475 hypotheses regarding possible adverse health effects, appropriate particle metrics, and causal
476 relationships. An important goal of the microscale research is to define the properties of air pollutants
477 and mechanisms of interaction that produce adverse health effects.

478 *Particle interactions with pulmonary fluids*

479 The fate of inhaled and deposited particles depends on their physicochemical characteristics, deposition
480 location, on the exposed cell types, and on other properties of their microenvironment. Upon deposition,
481 particles contact the internal surface of the RT which is assumed to consist of a continuous extracellular
482 fluid lining from the larynx to the most distal alveoli, including the surfactant (Gehr et al. 1990, Schürch et
483 al. 1990). In the ET and TB airways the fluid layer is thought to consist of two phases, a *sol* phase, in
484 which the cilia beat, and a viscous *gel* phase, the mucus layer (Kilburn 1968). Particle removal is by
485 mechanisms discussed earlier. Throughout the RT, the surfactant system represents a first line of
486 defense (Gehr et al. 1996). The composition and structure of the surfactant is complex and varies

487 between airways and alveoli as well as in the AI region during the breathing cycle. In general, it consists
488 of a continuous phospholipid layer containing four different surfactant proteins (Gehr et al. 1990, Schürch
489 et al. 1990) that reduce the surface tension at the air-lung tissue interface to help maintain a particle free
490 surface. This is important in the AI region for gas exchange.

491 Inhaled particles deposited in the RT are displaced into the aqueous subphase below the surfactant film,
492 by surface tensions and possibly other forces exerted on them by the surfactant film (Gehr et al. 1990,
493 Schürch et al. 1990). Particles may be modified by surfactant components or coated with surfactant or
494 surfactant components during the displacement process (Gil and Weiber 1971; Gehr et al. 1990, 1996;
495 Schürch et al. 1990). As a result of the displacement, particles come first into contact with surfactant
496 components in the aqueous subphase and then with the RT epithelium where they may interact with
497 pulmonary cells, such as alveolar or airway epithelial cells and cells of the immune system (e.g.,
498 macrophages and dendritic cells) and be effectively removed from causing potential harm (Geiser et al.
499 2005; Holt and Stumbles 2000; Peters et al. 2004; Vermaelen and Pauwels 2005). In the AI region, UF
500 particles may also translocate into the capillary blood and be transported to elsewhere in the body, as
501 noted earlier. If particles are not removed by these processes, then they can cause pulmonary
502 inflammation by the interaction with cells leading to a range of adverse health effects (de Haar et al.
503 2006).

504 *Particle-cell interactions*

505 After displacement into the hypophase, inhaled and deposited particles come into close contact with cell
506 membranes, such as those associated with epithelial cells and cells that are part of the immune system
507 and can enter these cells by a range of processes (Brandenberger et al. 2010).

508 All mammalian cells have a common membrane structure that allows or limits what can enter a cell, under
509 most conditions. Cell membranes consist of a very thin film of lipid and numerous protein molecules,
510 mainly held in place by noncovalent interactions (Singer and Nicolson 1972; Kendall 2007). The lipid
511 molecules are arranged as a continuous double layer about 5 nm thick in cell membranes. This lipid
512 bilayer serves as a relatively impermeable barrier to the passage of most water-soluble molecules. The
513 protein molecules are interspersed within, and pass through the lipid bilayer and are referred to as
514 transmembrane proteins. These proteins mediate specific functions, such as transporting molecules
515 across the bilayer or catalyzing membrane-associated reactions. Some proteins serve as structural links
516 that connect the cytoskeleton through the lipid bilayer to the extracellular matrix or an adjacent cell by
517 integrins and cadherins, while others serve as receptors to detect and transduce chemical signals into the
518 cells' environment (Eisenberg et al. 1984).

519 Small molecules can traverse the cellular plasma membrane through the action of protein pumps or
520 channels, while macromolecules must be carried into cells in membrane-bound vesicles derived from the
521 invagination and pinching-off of pieces of the plasma membrane to form endocytic vesicles. Micron-sized

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522   particles, which cannot directly penetrate the cellular plasma membrane, enter cells via phagocytosis
523   largely mediated by macrophages, granulocytes and dendritic cells. UF particles can enter the cells via a
524   variety of endocytic pathways or by another, yet to be defined mechanism (Rothen-Rutishauser et al.
525   2007a). Apart from these mechanisms, it has been proposed that UF particles can passively pass
526   through the cellular membrane with subsequent access to subcellular organelles such as the
527   mitochondria and the nucleus (Gehr et al. 2010).

528   Depending on the entry mechanism, particles may be found in vesicles or free in the cellular cytoplasm
529   (Rothen-Rutishauser et al. 2007b; Geiser et al. 2005) (Figure 6). While micron-sized particles are usually
530   found in membrane-bound vesicles, in-vitro studies have shown membrane-free UF particles present in
531   the cytoplasm where they can have direct access to cytoplasmic proteins, and important biochemical
532   molecules in organelles (e.g., the respiratory chain in the mitochondria and the DNA in the nucleus),
533   which may greatly enhance their toxic potential.

534   Once inside the cells, particles transported via endocytic pathways are thought to be distributed non-
535   randomly due to intracellular trafficking pathways. However this might not be the case for UF particles,
536   which can be found free in the cytoplasm. The intracellular trafficking and distribution of particles within
537   the cell is of great interest since it can help identify the relationship among cellular responses and specific
538   intracellular targets. Intracellular trafficking as well as the intracellular location of the particles will have an
539   influence on their effects. However, many knowledge gaps remain in this area due to the technical
540   difficulties of quantifying the intracellular distribution of UF particles, their allocation to specific subcellular
541   structures, and their trafficking.

542   **Dosimetry Modeling of Inhaled Particles**

543   Deposition in the RT is often estimated mathematically based on: (1) semi-empirical models; (2)
544   traditional mechanistic models; or (3) newer sophisticated CFD modeling (Rostami 2009). Studies
545   consider the total (entire RT) and/or regional (ET, TB, AI) deposition, or even more specific subsections
546   within regions. The Association for Inhalation Toxicologists (Alexander et al. 2008) reviewed a number of
547   studies and determined that the total inhaled delivered dose (DD, mg/Kg) can be estimated as follows:

548       $DD = (C \times RMV \times D \times \eta_I)/BW$ (Eq. 2)

549   Where C is the pollutant concentration in air (mg/L); RVM is respiratory minute volume (L/min); D is the
550   exposure duration (min); η_I is the inhalable fraction; and BW is body weight (kg). This is the dose to
551   which the RT is *exposed*, but not the *deposited* dose. Including a RT deposition term, the deposition
552   fraction, allows for an estimate of the initial total dose delivered and deposited (Alexander et al. 2008;
553   Ginsberg et al. 2005; Méndez et al. 2010). Finlay and Martin (2008) estimated total and regional
554   deposition fractions empirically, based on a review of a number of studies. They proposed separate
555   equations for impaction, sedimentation, and diffusion deposition mechanisms. Separate equations were

556   given for total RT deposition during mouth breathing and nasal breathing, and regional deposition
557   efficiencies.

558   Equation 2 and several semi-empirical models partially based on laboratory data, typically fit the existing
559   clinical data well, but have limited predictive value for situations that were not tested. More complex
560   traditional mechanistic mathematical models apply simplifying assumptions regarding airway structure to
561   predict deposition in major regions of the RT based on particle deposition mechanisms (e.g. ICRP 1994,
562   1995). Traditional models include the ICRP (International Commission on Radiation Protection) and the
563   multiple path particle dosimetry (MPPD, http://www.ara.com/products/mppd_capabilities.htm) models.
564   These models have been used to compare inhalation deposition in rats and humans Brown et al. (2005)
565   and for adults versus children (3-mo old) by RT region Ginsberg et al. (2005). A comparison of these
566   models is given in Figure 2 for both nose and mouth breathing, for rest (Figure 2a) and light exercise
567   (Figure 2b), and for total and major RT regions (ET, TB, and AI) (EPA (2009a; ICRP 1995).

568   CFD models are even more sophisticated, being based on fundamental equations of airflow structure
569   using iterative numerical techniques (Rostami 2009). In CFD models, particles are introduced into the
570   predicated flow fields and deposit where they cross an airway-wall boundary. Many assumptions are
571   used in CFD modeling, such as isothermal airflow, rigid airways, and spherical non-interacting particles.
572   Challenges in validating CFD models are discussed in Oldham (2006). More recently, lung structure is
573   being obtained by medical imaging techniques, such as magnetic resonance imaging, positron emission
574   tomography, computed tomography, and ultrasound. Digitized data obtained from these methods
575   potentially allow for more detailed and reliable CFD simulations of particle deposition using more realistic
576   lung morphology. Results are dependent on numerous selectable inputs that still require validation. Also,
577   due to the complexity of the pulmonary region, CFD models currently model only limited airway regions,
578   e.g., from the nose and mouth to the 15th airway generation (Kleinstreuer and Zhang 2010). An example
579   of CFD modeling is given in Figure 4 for UF (NP) particles and micrometer sized particles. From this
580   figure, it is easy to see hot spots that develop for both UF particles and micrometer sized particles as well
581   as the more uniform deposition for UF particles throughout the upper RT, as noted earlier.

582   **Areas of Future Research**

583   Significant advancements have occurred over the last 5-7 years with regards to particle dosimetry as
584   touched upon in this paper. However, as understanding has improved, many new questions have arisen
585   that once addressed should further reduce uncertainty in estimating particle dose that will provide
586   important information for health researchers examining mechanisms and the adverse health effects of PM
587   pollution. Listed here is a subset of suggested research that should further reduce uncertainties across
588   the source-to-dose-to-health effects continuum.

589   *Source to Intake:*

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590   • *iF* values should be obtained for scenarios in more developing countries, where urban population
591   densities greatly exceed those in the developed world, where there are significantly more people
592   on the streets receiving high levels of exposure, and where buildings likely allow for greater
593   infiltration of particles.

594   • Further work should be done differentiating the *iF* resulting from exposures to low socio-economic
595   status individuals and those of higher socio-economic status, as those with lower socio-economic
596   status may be more vulnerable to exposures to PM as a result of living and working close to
597   pollution sources.

598   • Continued communication with policy makers is needed to determine how to provide *iF* values
599   with the needed attributes to best incorporate this tool into policy decisions, enabling them to
600   determine the most efficient way for reducing PM exposures to improve health.

601   • Chemical processes in the atmosphere, including the formation of secondary pollutants and
602   movement of pollutants between the gas and solid/liquid phases should be more clearly
603   elucidated for incorporation into *iF* calculations.

604   *Fate in the Respiratory Tract*

605   • Identification of the appropriate dose metrics for PM, given the great variability of particles,
606   exposed populations, and potential health effects, represents a major important challenge.
607   Specifically, each adverse health-effect scenario may require an evaluation of the proper metric,
608   or metrics.

609   • Understanding differences in the delivered dose among species, within strains, and animal
610   models that are created by pretreatment to produce diseases will improve our understanding of
611   the impact of these diseases in humans.

612   • Quantifying differences in deposition patterns, clearance phenomena, and air-pollutant effects in
613   human subpopulations due to differences in anatomy and physiology, (e.g., for children, the
614   elderly and the diseased) is needed to reduce uncertainty in dosimetric calculations, and the
615   impact of changes in lung morphology due to differences among humans.

616   • Translating results between animal studies to *in–vitro* studies and from animal studies and from
617   *in-vitro* studies to humans, particularly as far as dose is concerned is critical since many needed
618   studies cannot be directly performed using human subjects, due to practical and ethical
619   constraints.

620   • Computational fluid dynamic (CFD) models of PM deposition hold great promise for calculating
621   local and regional deposition doses. Improvements are needed in computational capabilities to
622   allow for a greater extent of the lung to be modeled and models should be more thoroughly
623   evaluated, In additional, advances in medical imaging approaches should allow for more detailed
624   airway morphometric data assisting computational studies to model beyond the 16th TB branch.

625 • Most traditional mechanistic and CFD dosimetric models are validated for ideal particles (e.g.
626 smooth, uncharged, spheres). Realistic environmental particles are, as yet, to be modeled leaving
627 significant uncertainty with regards to actual dose for ambient PM..

628 • Measuring and modeling particle deposition hot spots, quantifying enhancement factors
629 associated with hot spots, and verifying modeling results are needed to understand the
630 toxicological significance of hot spots.

631 • The influence of particle size and other properties on the mechanisms driving slow-bronchial
632 clearance still need to be elaborated since this process may drive the fraction of particles and
633 components retained in the lungs and allows UF particles to translocate across the air-blood
634 tissue barrier to other parts of the body   .

635 *Tissue, Cellular, and Sub-cellular Interactions*

636 • UF particles, their translocation, micro dosimetry, and health effects, are still in an early phase of
637 understanding, although significant progess has occurred over the last decade. Engineered NPs
638 represent a vast area of research that is just beginning to be explored as these particles become
639 widely used in commercial applications.

640 • A major research frontier involves elucidating the interactions of PM, in its great variability, with
641 the varied cells of the body. The complexities of particle fates in cells and the resulting potential
642 toxicities (e.g. cytotoxicity, genotoxicity, immunotoxicity) and cascades of biological responses
643 are still at the beginning of being understood.

644 • The coating of airborne particles (outside the body) with potentially toxic substances and the
645 coating of the particles upon interaction with body fluids, tissues, and cells is just beginning to be
646 investigated and is poorly understood. Coating with fluids of any kind, i.e., coating most likely with
647 proteins, may be the key to better understand toxicity and health effects.

648 • The mechanism of entry into cells and specifically, interactions of UF particles with subcellular
649 structures and possible enhancements in particle toxicity due to these interactions is recent area
650 of research that should be pursued to better understand the mechanisms that drive PM health
651 effects.

652 **Summary**

653 This paper provides a brief summary of the current science associated with air pollution dosimetry and
654 begins to address the forth policy-relevant Science Question addressed in part at 2010 International Air
655 Pollution and Health conference[2]. The paper begins at the macroscale describing the definition and

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[2] Air Pollution and Health, 2010 (Solomon et al. 2011) SQ4: "What advances have been made in understanding the relationships between exposure, both spatially and temporally, and estimates of dose that tie to health outcomes?"

656   attributes of the intake fraction (*iF*), a parameter that provides an estimate of the amount of pollutant

657   inhaled (not deposited or retained) relative to the mass emitted into the environment and allows for a

658   better understanding and quantification of source-to-intake (inhaled) relationships. Inhalation of air

659   pollution is the first step in dosimetry since the respiratory tract (RT) is the primary route for air pollutants

660   to enter the body. The dimensionless parameter, *iF*, also allows for evaluation of how the amount inhaled

661   of a pollutant might vary as a function of emissions control strategies or other interventions (van Erp et al.

662   2011, this issue) that reduce pollutant concentrations from a source(s). The next section describes what

663   happens once a pollutant is inhaled and provides updates on recent advances in dosimetry and factors

664   that relate to quantifying dose. A description of the processes and mechanisms of how pollutants,

665   specifically particles, are deposited and cleared from the RT is given. Translocation, the movement of

666   particles from the lungs to other parts of the body, also is discussed.

667   Looking at the microscale, the next section examines how UF particles interact at the cellular and sub-

668   cellular levels. UF particles constitute a unique size range that recently has been identified as a key

669   pollutant of interest, since they can penetrate deep into the lungs and have the ability to cross the air-

670   blood barrier of the lung and translocate to other systems and organs. UF particles also have been

671   shown to translocate to the brain directly from inside the nose.

672   Considerable uncertainty remains with regards to UF particle interactions within the RT, in part because

673   most of the experimental data, except for the epidemiological data, have been obtained from animal and

674   in vitro experiments. Data received from these experiments are providing a significant basic idea of how

675   adverse health effects develop, but the extrapolation to humans is still not well defined and additional

676   research is needed to better understand the adverse health effects of ultrafine particles in people.

677   The last section describes dosimetric modeling from semi-empirical to CFD modeling. Continued

678   advances in application of medical imaging techniques to provide digital data bases for CFD models will

679   allow CFD models to simulate the lower TB and AI regions of the lung.

680   A series of research needs also is presented

681   **Acknowledgements**

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958

Table 1.   Some particle-related that may apply to the effects of inhaled air-pollutant particles. Note that these properties are not mutually exclusive.

Mass related to aerodynamic size intervals (e.g. PM_{10}, $PM_{2.5}$, and coarse particles)

Size distribution properties (e.g. geometric standard deviation)

Number per unit volume of air

Surface area (e.g. BET surface), or projected area

Surface reactivity in the body

Chemical composition (e.g., metals (e.g., V, Ni), acids, OC, EC (or BC), organic species etc.)

Oxidative properties (e.g., reactive oxygen potential)

Mobility within the body

Fractal properties

Electrical properties (e.g. net change and/or zeta potential)

Dissolution rates in biological fluids and other media

Volatility of particle components

Shape (e.g. aspect ratio of fibers)

Infectivity, irritancy, allergenicity, and odor (odor may be important for dogs and rodents)

Biochemical interactions and metabolic products

Presence of gaseous co-pollutants

Changes in exposure level (e.g. spikes in air-pollutant concentrations)

History of exposure (e.g. producing sensitization and/or adaptation)

959

960

961

962 Table 2. Computed particle deposition enhancement factors (DEFs) vs. square patch dimension and
963 particle diameter for unit specific gravity spheres.

964

	DEF		
	Patch size (mm)		
Particle Diam. (µm)	0.1	1.0	3.0
0.01	52	18	6.7
0.1	58	18	7.1
1.0	81	20	6.9
10.0	113	42	22

965 Data from Balásházy et al. (1999).

966
967
968
969 Table 3. Computational fluid dynamics modeled hot spot deposition enhancement factors (DEF) for an
970 adult male at resting (5 L/min) and exercising (30 L/ min) ventilation states. Source: Phalen
971 et al. (2010).

Particle aerodynamic diameter (µm)	Ventilation (l/min)	DEF
1	5	107
2	5	110
5	5	115
1	30	80
2	30	190
5	30	380

972 Data from Balashazy et al. (2003).

973

974 Figure Captions.

975 Figure 1a. Diagrammatic representation of respiratory tract regions in humans. Structures are anterior
976 nasal passages, ET1; oral airway and posterior nasal passages, ET2; bronchial airways, BB;
977 bronchioles, bb; and alveolar interstitial, AI. Reproduced from EPA (2009)

978 Figure 1b. Human lung structure, tissue barrier structure. (a) Low magnification of human lung tissue,
979 showing gas exchange parenchyma (GP), blood vessels (BV), and airways (AW); magnification
980 x15. Courtesy of the Institute for Anatomy, University of Bern, Bern, Switzerland. (b) Low
981 magnification scanning electron micrograph of gas exchange parenchyma, clearly showing alveoli
982 (A); magnification x60. (c) Higher magnification scanning electron micrograph of alveolar duct
983 (AD) with concentrically arranged alveoli (A) around it; magnification x180. Modified from Gehr et
984 al. (1978). (d) Scanning electron micrograph of boken up interalveolar septum showing
985 erythrocytes (EC) in a capillary and the air–blood tissue barrier (AT); A, alveoli; magnification
986 x550. Modified from Gehr et al. (1978). (e) Low magnification transmission electron micrograph of
987 interalveolar septa, with capillaries containing erythrocytes (black) meandering around a
988 connective tissue frame; A, alveolar air; magnification x500. Modified from Gehr et al. (1978). (f)
989 Higher magnification transmission electron micrograph of a capillary (C) with erythrocytes (black)
990 in an interalveolar septum; the three layers of the air–blood tissue barrier (AT) can be recognized;
991 A, alveolar air; magnification x4500. Picture sequence a-f from Chang et al. (2010), original
992 source, Zhang et al. (2005). Reprinted from Journal of Aerosol Science, 36(2), Zhang et al. 2005,
993 Copyright (2005), with permission from Elsevier.

994 Figure 2a. Comparison of total and regional deposition results from the ICRP and MPPD models for a
995 resting breathing pattern (VT = 625 mL, f = 12 min-1) and corrected for particle inhalability.
996 Regions are extrathoracic, ET; tracheobronchial, TB; and alveolar, A. Panels a-b are for nose
997 breathing; panels c-d are for mouth breathing. (Reproduced from EPA 2009a, Chapter 4)

998 Figure 2b. Comparison of total and regional deposition results from the ICRP and MPPD models for a
999 light exercise breathing pattern (VT = 1250 mL, f = 20 min-1) and corrected for particle
1000 inhalability. Regions are extrathoracic, ET; tracheobronchial, TB; and alveolar, A. Panels a-b are
1001 for nose breathing; panels c-d are for mouth breathing. (Reproduced from EPA 2009a, Chapter 4)

1002 Figure 3. Intake Fraction ranges for various release scenarios. Ranges for PM2.5 from power plants and
1003 industrial sources for various regions and countries are listed, with median values indicated, as
1004 well as from a hypothetical distributed energy power plant (DE) (Tainio et al. 2009; Levy et al.
1005 2009; Hao et al. 2007; Heath et al. 2006; Li and Hao 2003; Wang et al. 2006). Ranges for mobile
1006 source emissions of PM2.5 in the US and Mexico are included, as well as point values for NY
1007 street canyons and Hong Kong (Greco et al. 2007a; Zhou and Levy 2008; Greco et al. 2007b;
1008 Luo et al. 2010; Stevens et al. 2007). A range of indoor iF values for PM2.5 from smoking

1009   sources is included (Klepeis and Nazaroff 2006). Values resulting from school buses and wood

1010   smoke are also included (Marshall and Behrentz 2005; Ries et al. 2009), as well as for a range of

1011   VOCs and SVOCs from outdoor emissions (Bennett et al. 2002b).

1012   Figure 4. Comparisons of micron- and nanoparticle deposition in an idealized upper airway model

1013   (Kleinstreuer and Zhang 2010). DEF, deposition enhancement factor. Reprinted from Annual

1014   Review Of Fluid Mechanics, 42, Kleinstreuer and Zhang 2010), Copyright (2010), with permission

1015   from Annual Reviews.

1016   Figure 5. Quantitative analyses of translocation of deposited UF particles from the air into the capillary

1017   blood in alveoli. (a) Illustration of the observed (white columns) and the expected (black columns)

1018   UF particles within the four tissue compartments which were analyzed at 1 h after exposure, (b)

1019   24 hours after exposure. The total chi-squared showed that the distributions of observed and

1020   expected particles differed significantly. There is only one compartment with an RDI > 1 and a

1021   substantial contribution to the total chi squared: the connective tissue is the only compartment

1022   that is preferentially targeted by the UF particles at 1 h after exposure and the capillary lumen is

1023   the only compartment that is preferentially targeted at 24 h after exposure respectively. Figures

1024   reproduced from Mühlfeld et al. (2007). Reproduced with permission from Particle and Fibre

1025   Toxicology 2007 per open access license.

1026   Figure 6. A 549 epithelial cells (cell line) with gold UF particles (A, plain gold) and (B, PEG-coated gold).

1027   In (A), the particles (arrows) are localized within vesicles of different sizes, in (B) within a

1028   lysosome (arrows I) and in the cytosol (arrow II); n: nucleus, m: mitochondria; scale bars: 500 nm.

1029   Pictures from Brandenberger et al. (2010). Reprinted from Small, 6(15), Brandenberger et al.

1030   (2010), John Wiley and Sons, Copyright © 2010 Wiley-VCH Verlag GmbH & Co.

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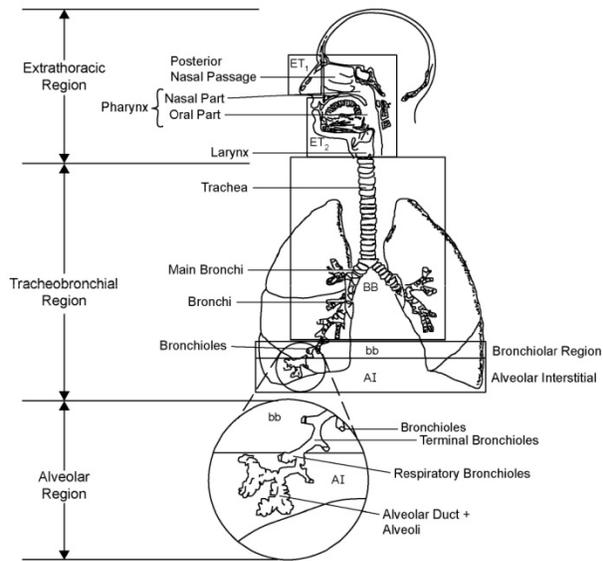
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1034   Figure 1a.
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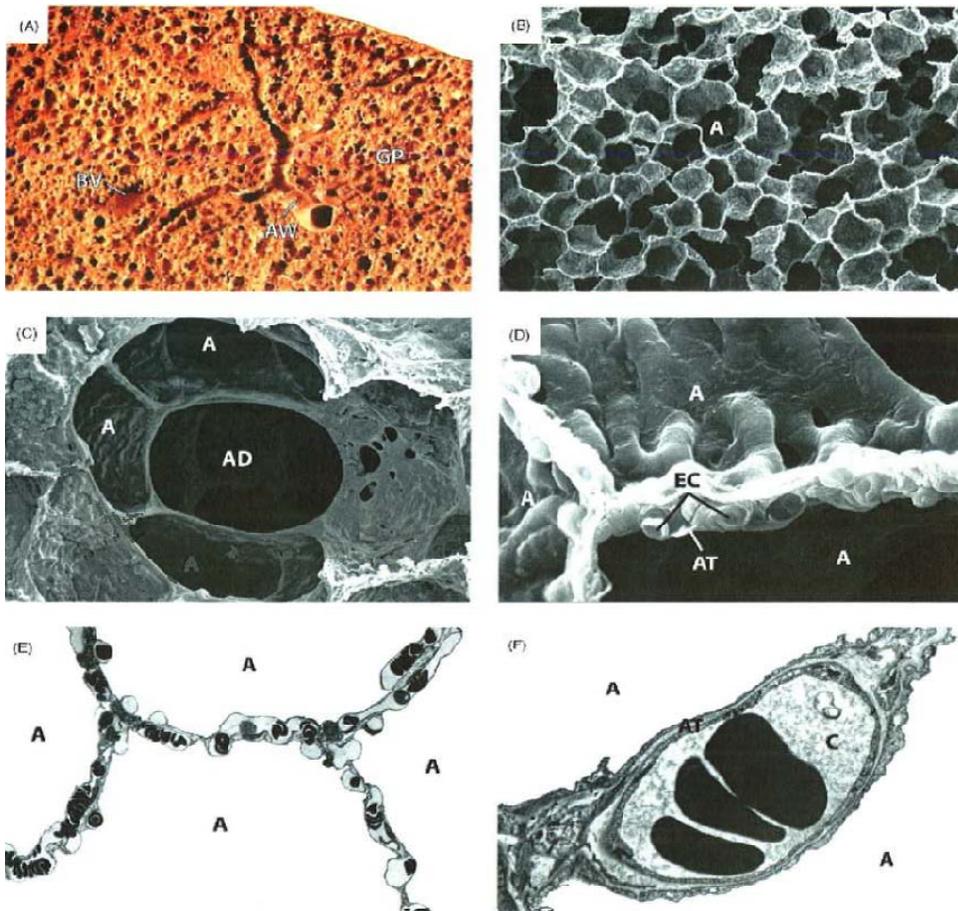
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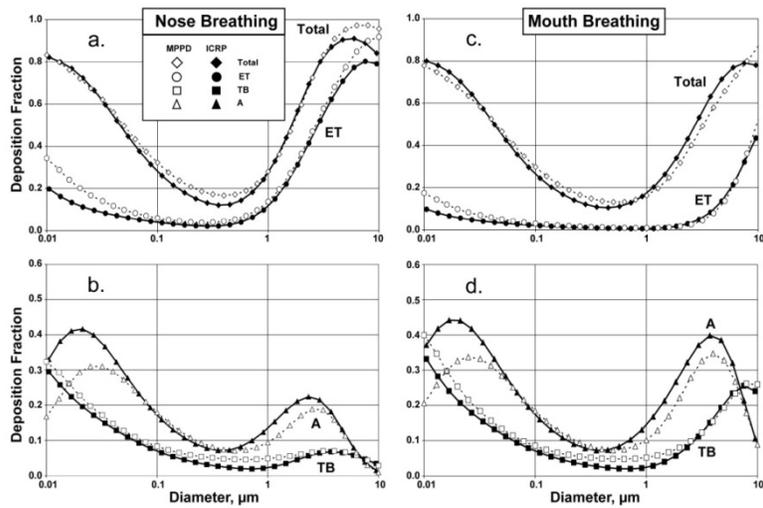
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1042   Figure 2a.
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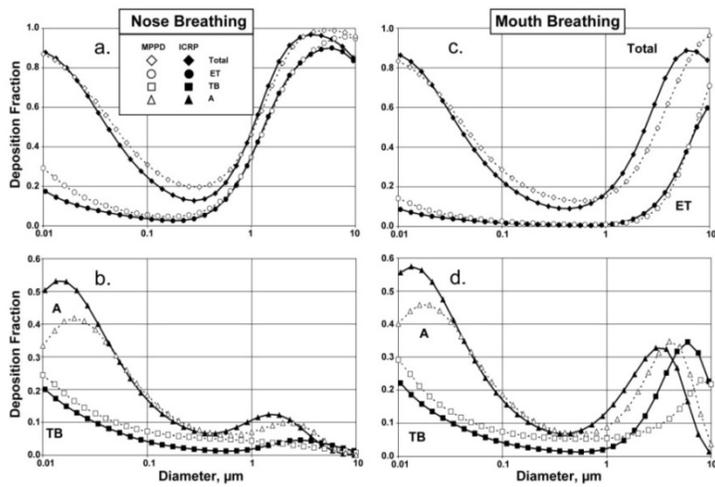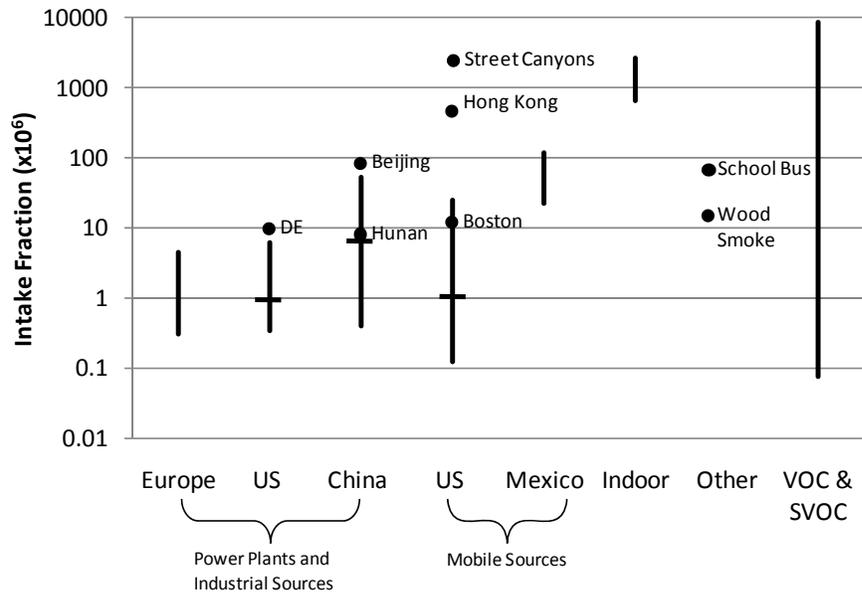
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1046   Figure 2b
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1051   Figure 3.
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1056   Figure 4.
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Comparison between observed and expected particles at 1h after exposure

RDI: 0.92
X^2: 2.42

Total X^2: 34.02
P<0.01

RDI: 1.14
X^2: 0.52

RDI: 2.64
X^2: 28.64

RDI: 1.26
X^2: 2.44

1062
1063
1064   Figure 5a.
1065
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Comparison between observed and expected particles at 24h after exposure

RDI: 0.96
X^2: 0.59

Total X^2: 15.01
P<0.01

RDI: 0.73
X^2: 1.63

RDI: 1.15
X^2: 0.22

RDI: 1.65
X^2: 12.56
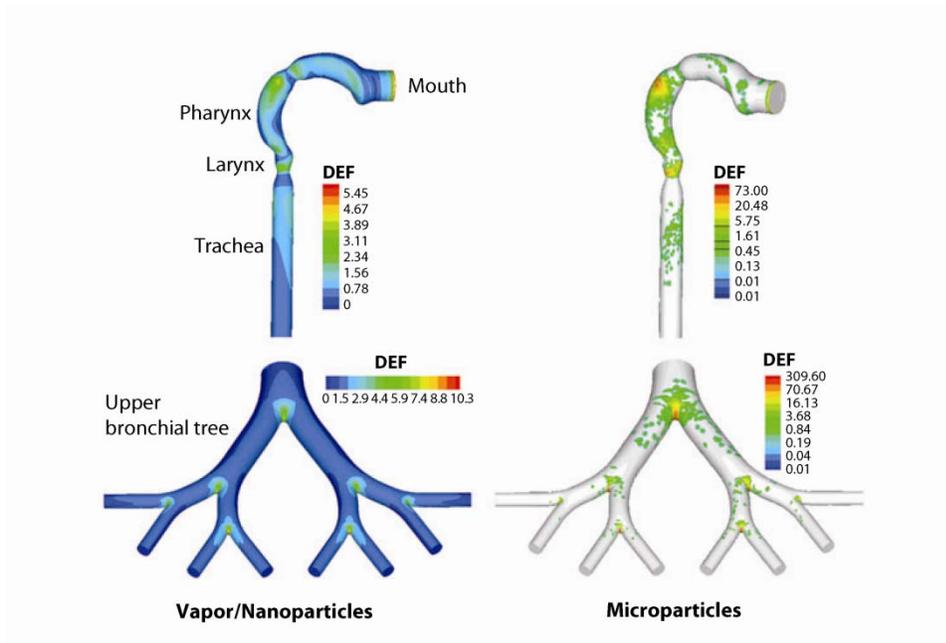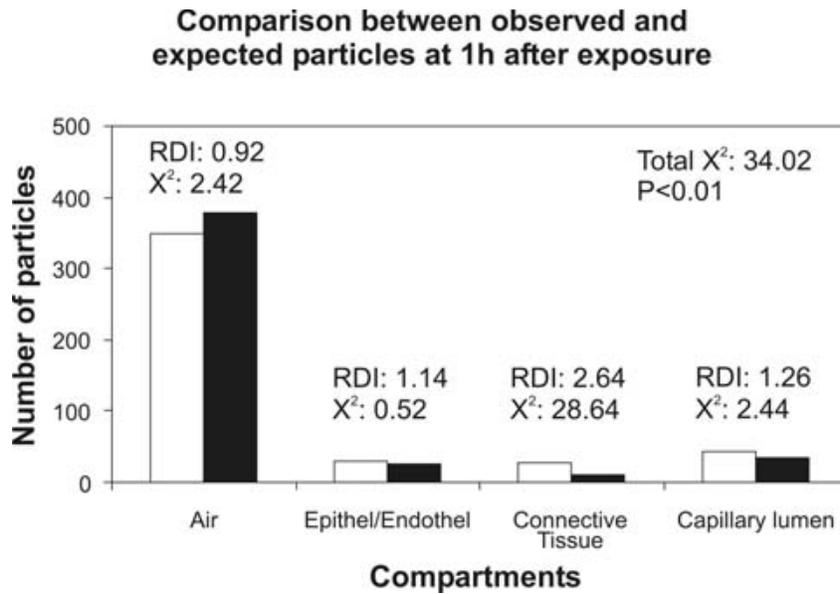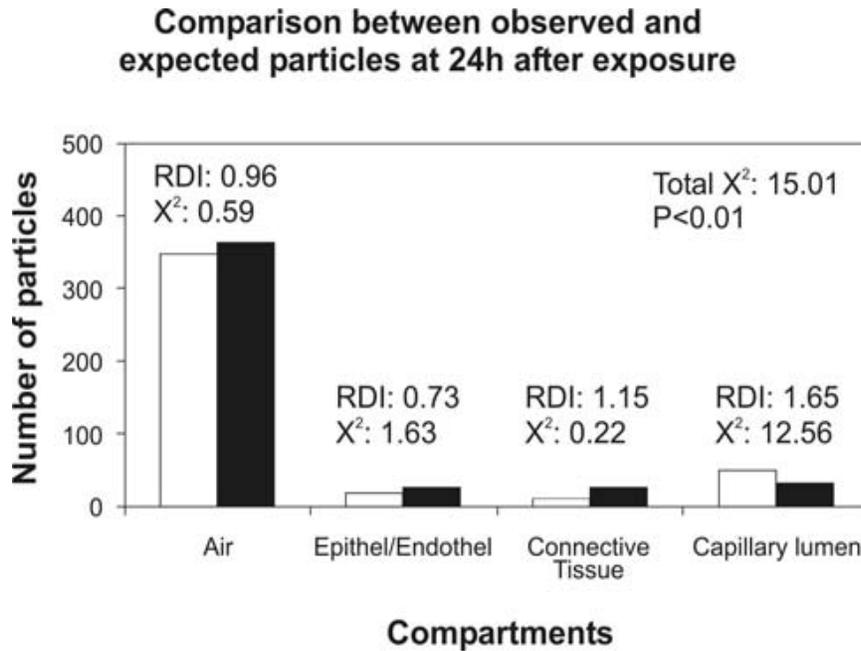
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1068
1069   Figure 5b.

1072   Figure 6.