



Inhaled nanoparticles

Robert Sturm

Determining the health effects of inhaled nanoparticles is an important research program in occupational hygiene. Vital to that effort is a physical understanding of how those particles are transported in the lungs.

Nanoparticles are just one type of the many particulate substances in the atmosphere, but they have commanded increasing attention in the past few decades. Some enter our environment through such anthropogenic chemical and mechanical processes as burning and grinding. Others, such as viruses or cell fragments, are of biogenic origin. Still more are created by attrition of larger particles, or when substances released by plants react with other atmospheric chemicals. Nanoparticles are taken up by the human body mainly via the respiratory and gastrointestinal systems. The inhalation route is the more important because the lung's ample surface area enables particles to quickly accumulate to large concentrations in the lung and lung-associated tissues.

Medical and other biological scientists are working hard to address open questions concerning the possible health effects of inhaled nanomaterials; in fact, the topic has prompted intense, collegial debates all over the world. Industrial workers can be exposed to soot, the health effects of which remain uncertain due to a lack of experimental and epidemiological data. Meanwhile, various nanoparticles have been identified as potent allergens or as triggers of inflammation, and may even lead to cancer formation. (Diesel particles and others produced by incomplete combustion are examples of potential carcinogens.) Some nanoparticles are able to modify blood consistency; others congeal into aggregates that can plug capillaries and cause necrosis of the tissues normally supplied by those blood vessels.

Small spheres and tiny tubes

Nanoparticles range in size from 1 nm to 100 nm. Such a definition poses no problem in discussions of spherical particles; size just means diameter. For nonspherical particles, defining a precise size can be complicated, but if at least one of the particle's dimensions is less than 100 nm, it's fair to call it a nanoparticle. In particular, cylindrically shaped carbon nanotubes (CNTs), which have applications to electronics, optics, and more, are considered nanoparticles even though they can have lengths of up to 10 μm —much greater than their 5–100 nm diameters. To give a better feel for the nanoscale, figure 1 illustrates examples of objects with comparable and larger sizes.

The exceptional physical and chemical properties of CNTs have increasingly attracted the interest of materials scientists worldwide. The CNTs have a strength that exceeds steel's by several orders of magnitude, extraordinary electrical conduc-

tivity, and remarkable hardness, and they are insoluble in water. Modern nanotechnology would be almost unthinkable without them.

In the lung

Nanoparticles exist both as single objects and as larger agglomerates that most likely form due to electrostatic attraction, chemical affinity, or diffusion. Once they enter the respiratory tract, they are subject to various forces and torques that influence their probability to be deposited on the airway walls or in the alveoli where oxygen and carbon dioxide exchange takes place. The net forces and torques experienced in the air stream by single, small nanoparticles differ from those experienced by the larger, clumpier agglomerates, so the two classes of nanoparticles behave differently when inhaled.

Modeling the aerodynamic behavior of nanoparticles carried along in lung and other respiratory structures represents a rather complicated challenge for experimental and computational physics; nevertheless, some of the basics can be readily summarized. One important fundamental is that inhaled nanoparticles interact in what is called the free-molecular regime. That means the distance inhaled particles travel in the

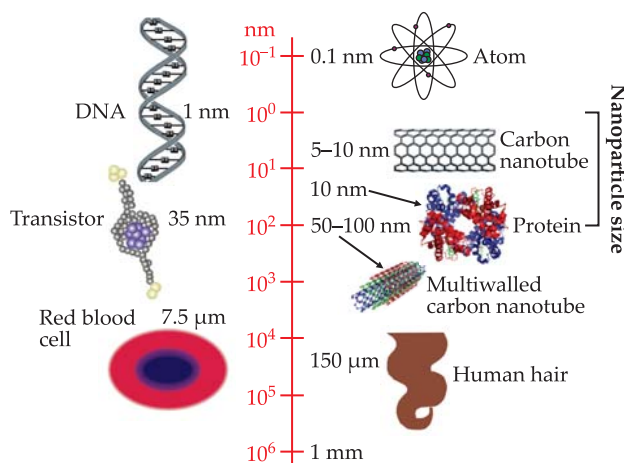


FIGURE 1. THE MICROCOSM. The nanoscale includes proteins but excludes simple atoms, which are too small, and cells, which are too large. Among the technologically most important nanoparticles are carbon nanotubes, which consist of one or more graphite sheets rolled up into cylinders. The diameters of CNTs (and the illustrated DNA fragment) fall within the nanoscale, though the length of those nanoparticles is well beyond the nanoscale.

lungs between encounters with the oxygen and nitrogen molecules of air is greater than the size of the nanoparticles themselves. Thus, the collisional events determine nanoparticle movement. The free-molecular regime is distinguished from the continuum regime, which assumes the inhaled gas phase to be a continuous fluid; that approximation is appropriate for describing the transport of micron-sized particles.

The way in which nanoparticles move in an air stream depends on several factors, especially surface area and shape. For example, torque has no significant effect on spherical particles, but it induces consequential rotation in fibers, platelets, aggregates, and other nonspherical particles. Modelers distinguish two types of torque. The first, Brownian torque, comes from the steady collisions between a nanoparticle and air molecules. The second, fluid-dynamic torque, arises because the velocity throughout an inspired air stream is not constant; the speed decreases as airways branch and get smaller and, within a given airway, from the center of the tube to the airway wall. A particle moving in such a varying velocity field will experience different pushes in different places—and hence a net torque.

The main mechanisms by which nanoparticles deposit onto airway walls include Brownian motion (diffusion), interception, and so-called phoretic phenomena; all those are illustrated in figure 2. Brownian motion, the random translational motion caused by nanoparticle–air collisions, can eventually propel a nanoparticle into an airway wall. Interception is a deposition mechanism that primarily applies to CNTs and other extremely elongated particles. Such a particle can contact the airway wall even as its center of mass follows a streamline, especially if the particle is rotating. Phoretic mechanisms chiefly include electrophoresis and thermophoresis. Electrophoresis refers to the motion of charged particles in an electric field; thermophoresis, also called the Ludwig–Soret effect, describes the response of a particle to forces resulting from a temperature gradient.

Breathe in, breathe out

Among the issues that I and other modelers have explored are the likelihood that inhaled nanoparticles actually remain in the lungs or other parts of the respiratory system and whether nanoparticles of a given size preferentially deposit on specific targets. As part of our modeling, we need to define the breathing conditions under which particle uptake takes place; in most theoretical studies we assume subjects are engaged in light exercise such as walking and that they breathe through the nose. In that case, models find, only 5–40% of inhaled nanoparticles are exhaled; the rest are deposited.

Particles with a size of several nanometers are predominantly lodged in the nasal, nasopharyngeal (upper part of the throat, behind the nose), and upper bronchial airways, but are typically cleared from the respiratory system within several

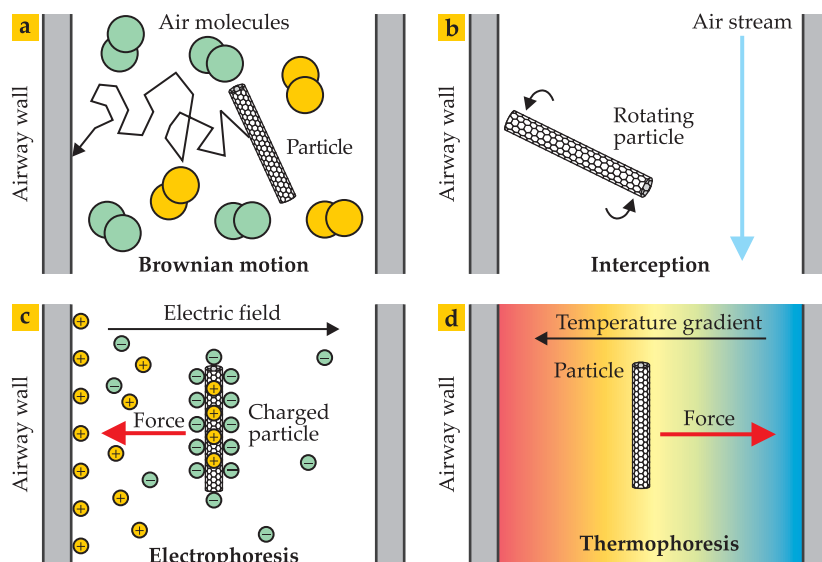


FIGURE 2. FOUR PARTICLE-DEPOSITION MECHANISMS. Illustrated here are four important mechanisms by which nanoparticles can be deposited on the walls of a pulmonary or other airway passage. **(a)** Brownian motion results from the extensive collisions between a particle and air molecules. **(b)** Interception refers to a particle, especially a rotating one, contacting an airway wall as it courses along an air stream. **(c, d)** So-called phoretic forces arising from charge distributions or thermal gradients can also lead to deposition.

hours to days. Larger particles varying between 10 nm and 100 nm in size tend to deposit in small airways and can also enter the alveoli. Their clearance may require several months, even years; the necessary time depends primarily on the solubility and shape of the deposited particle, with highly elongated molecules being especially persistent. Details of deposition and clearance may also be a function of age, since the sizes of respiratory-system components change as one grows. The topic is not of merely academic interest; several months ago CNTs were observed for the first time in the lungs of children.

Additional resources

- A. D. Maynard, “Nanotechnology: The next big thing or much ado about nothing?” *Ann. Occup. Hyg.* **51**, 1 (2007).
- A. D. Maynard, “Safe handling of nanotechnology,” *Nature* **444**, 267 (2006).
- K. Donaldson et al., “Carbon nanotubes: A review of their properties in relation to pulmonary toxicology and workplace safety,” *Toxicol. Sci.* **92**, 5 (2006).
- R. Sturm, “Theoretical models of carcinogenic particle deposition and clearance in children’s lungs,” *J. Thorac. Dis.* **4**, 368 (2012).
- R. Sturm, W. Hofmann, “A theoretical approach to the deposition and clearance of fibers with variable size in the human respiratory tract,” *J. Hazard. Mater.* **170**, 210 (2009).
- R. Sturm, “Theoretical and experimental approaches to the deposition and clearance of ultrafine carcinogens in the human respiratory tract,” *Thorac. Cancer* **2**, 61 (2011).
- R. Sturm, “A stochastic model of carbon nanotube deposition in the airways and alveoli of the human respiratory tract,” *Inhal. Toxicol.* **28**, 49 (2016).
- *New Scientist*, “Carbon nanotubes found in children’s lungs for the first time,” <https://www.newscientist.com/article/dn28370-carbon-nanotubes-found-in-childrens-lungs-for-the-first-time>.

PT