CRITICAL REVIEW DISCUSSION

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Nanoparticles and the Environment

Judith C. Chow and John G. Watson
Desert Research Institute, Reno, NV

Nora Savage
U.S. Environmental Protection Agency, Research Triangle Park, NC

C. Jack Solomon
Praxair, Inc., Danbury, CT

Yung-Sung Cheng
Lovelace Respiratory Research Institute, Albuquerque, NM

Peter H. McMurry
University of Minnesota, Minneapolis, MN

Lisa M. Corey, Gretchen M. Bruce, and Richard C. Pleus
Intertox, Seattle, WA

Richard C. Pleus
University of Nebraska Medical Center, Omaha, NE

Pratim Biswas
Washington University, St. Louis, MO

Chang-Yu Wu
University of Florida, Gainsville, FL

INTRODUCTION

This paper is a discussion of the 2005 A&WMA Critical Review[1,2] on nanoparticles and the environment. In the review, Drs. Pratim Biswas and Chang-Yu Wu described how nanoparticles and ultrafine particles (nominally those with diameters <100 nm) are created, interact among themselves, interact with gas molecules and larger particles, and where they end up in the environment. The authors observed that nanoparticles are created inadvertently as a portion of combustion emissions, but they are also created intentionally for commercial uses. Manufactured nanoparticles are playing an increasing role in water, soil, and air treatments; efficient energy production and storage; and medicine. The authors called for greater efforts to understand the potential environmental consequences of nanoparticles. Having observed the unintended consequences of many new technologies, they believe that a thorough understanding of the potential hazards and benefits of nanoparticles in the environment can mitigate against future problems that might arise from their manufacture and use.

The discussions presented here agree and disagree with points made in the review and add information relevant to the topic. Each discussion is self-contained. Joint authorship of this article does not imply that a discussant subscribes to the opinions expressed by others. This discussion was compiled from written submissions and presentation transcripts, which were revised for conciseness and to minimize redundancy. Substantial deviations from the intent of a discussant are unintentional and can be addressed in a follow-up letter to the *Journal*. Invited discussants are described below.

- Dr. Nora Savage, an environmental engineer with U.S. Environmental Protection Agency (EPA) Office of Research and Development, National

Center for Environmental Research, Environmental Engineering Research Division, is one of the coordinators of the EPA nanotechnology programs in partnership with other government agencies involved in the National Nanotechnology Initiative.[3]

- Dr. Jack Solomon, Director of Technology Assessment and External Relations of Praxair, Inc., represents Chemical Industry Vision 2020[4] and the Council for Chemical Research. Vision 2020 is a collaboration of several chemical companies working to create and encourage coordinated research. Council for Chemical Research is a combination of chemical companies, research university chemical and chemical engineering departments, and the National Laboratories. These organizations, in collaboration with the National Nanotechnology Initiative, have created a roadmap for Nanomaterials by Design.[5]
- Dr. Yung-Sung Cheng, Director of the Inhalation Drug Delivery Center at Lovelace Respiratory Research Institute, has performed basic and applied research on aerosol drug delivery; particle deposition in the respiratory tract; air quality in ambient, occupational, and indoor environments; and inhalation toxicology. Dr. Cheng has been heavily involved in the design and operation of high-quality systems for animal inhalation exposure studies.
- Dr. Peter McMurry, department head and professor for the University of Minnesota Mechanical Engineering Department, has invented, utilized, and characterized many different methods for nanoparticle measurement, generation, modeling, and characterization.
- Additional comments are contributed by Lisa M. Corey, staff toxicologist, Gretchen M. Bruce, senior scientist, and Dr. Richard C. Pleus, director and toxicologist at Intertox, Inc., and adjunct associate professor in the department of Pharmaceutical and Experimental Neuroscience at the University of Nebraska Medical Center. Intertox is an independent multidisciplinary public health research firm that assesses the impact of chemicals and biological agents on human health.

INVITED COMMENTS BY DR. NORA SAVAGE

The emergence of engineered or manufactured nanomaterials into commerce, incorporated into a variety of consumer products from sunscreens and cosmetics to electronics and clothing, will significantly affect various federal regulatory agencies. In addition, several nongovernmental organizations, consumer advocate groups, the media, and public-citizen consortia are increasingly interested in the manufacture, use, and disposal of these materials. Each of these groups will play a role in shaping how nanotechnology-derived products are handled, valued, and regulated.

Nanotechnologies encompass broad interdisciplinary areas of research, development, and industrial activity that have been growing rapidly for the past decade. Disciplines include areas of physics, chemistry, biology, engineering, and electronics. The definitive characteristics of nanotechnologies are as follows: (1) size (1–100 nm); (2) unique properties; and (3) the ability to be manipulated at the molecular level. Careful control of the nanoscale morphology allows for control of the end product. Nanoparticles result from a wide variety of physical, chemical, and biological processes, some of which are novel and others that are commonplace. Particle size, morphology, and composition can be manipulated to produce materials of similar molecular compositions but with different properties. These manufactured substances have distinct properties when compared with their constituent, or bulk, materials. Properties of specific nanomaterials are derived from structural changes and are not correlated with those properties of the corresponding bulk material. This discussion focuses on processes for the deliberate development and manufacture of nanoparticle products, that is, the particles resulting from nanotechnology processes. Nanoparticle products include but are not limited to nanotubes, nanowires, and quantum dots.

Because living organisms are composed of cells ~10 μm in diameter (cell parts are much smaller; i.e., submicron and nanometer), enhancing our knowledge of biological processes on the nanoscale level is a strong driving force in nanotechnology. The composite material industry is another force, given that colloidal dispersions are critical to a variety of industrial technologies. Colloids are also used in plastics processing, electronic materials, and other applications. Paints, deposited materials, and coatings are made from particle suspensions, which require appropriate colloidal stability for optimal performance. However, ever-present, long-range attractive forces cause particles to coagulate and leave the suspensions too viscous for some applications. New research indicates that small amounts of highly charged nanoparticles can achieve the much-needed stability. Nanoparticles can improve materials in other ways, as well; they can increase the strength and hardness of metals and ceramics, and they can make protective coatings transparent.

Medical diagnostics and therapeutics are providing another stimulus for developing nanotechnologies. The apparent ability of some nanoparticles to get into the brain is cause for concern, so there is a need to ensure the safe and responsible development of this technology. Yet, this ability has tremendous potential benefits. Nanoparticles can be used as vectors for gene therapy, as methods to enhance imaging, or as drug delivery devices.

The increased development and use of nanoparticles for various industries could lead to increased exposure, affecting human health and the environment. Consequently, research into the characterization, exposure, engineering controls, potential toxicity, fate and transport, and life cycle assessment of these engineered particles is needed. This type of research is currently being sponsored through grants, and contracts to some degree, by several federal agencies participating in the National Nanotechnology Initiative. In addition, collaborative activities between agencies and between U.S. researchers and researchers in other countries are increasing. These efforts will help avoid unnecessary duplication, verify research results and data, foster a spirit of collaboration, and increase both the quality and quantity of research results. The review[1,2] provides an important step in understanding what we know, what we have learned from other technologies and processes that may serve to inform this burgeoning area, and what is needed for the future responsible development of nanotechnologies.

INVITED COMMENTS BY DR. JACK SOLOMON

The review[1,2] was thorough in its treatment of environmental safety and health (ESH) issues associated with nanoparticles. Vision 2020[4] is compiling a comprehensive database of ESH information that will soon be publicly available.

Nanocatalysts can increase efficiency in the chemical industry by reducing feedstocks and energy consumption and, in the petroleum refining industry, by reducing process temperatures and increasing gasoline production. Nanocatalysts by design may eliminate the need for precious metal catalysts in the chemical, petroleum, and automotive industries. Nanocoatings by design can increase hardness, thereby increasing the life spans of tools and dies for manufacturing industries. Nanocoatings could reduce ship fouling without the use of toxic materials. Table 1 summarizes the values estimated for several of these applications in different industrial sectors.[6]

An integrated plan to form the foundation of ESH efforts on nanomaterials is needed. The key work required is to establish the methods and procedures in the following three areas from which additional work can be done: (1) toxicological hazard assessment; (2) measurement and detection; and (3) worker protection and industrial hygiene. Chemical and semiconductor industry nanotechnology ESH experts are now preparing a plan with detailed recommendations for research and development with the expectation that these recommendations will be funded within the next few years.

Table 1. Estimates of cost and energy savings for nanoparticle applications in different U.S. industrial sectors.[6]

Sector	Cost Savings $ billion/yr	Energy Savings Trillion BTU/yr	Nanomaterial Application
Chemical	2.5–4	200–400	Catalysts
Petroleum	1–1.7	80–200	Catalysts
Automobile	0.3–1	N/A	Catalysts
Shipping	1.7–2.7	80	Coatings
Manufacturing	1.7–3.5	N/A	Coatings
Natural Gas	1–2.7	N/A	Membranes

Note: BTU = British thermal units; N/A = information not available.

INVITED COMMENTS BY DR. YUNG-SUNG CHENG

The review[1,2] provides a comprehensive analysis of the health impact of nanoparticles in terms of respiratory deposition, translocation, and toxicity, as well as pharmaceutical applications. Regarding potential exposure to nanoparticles, the review addresses many studies of nanoparticle exposure from industrial and mobile combustion sources. The following comments add perspectives on the health effects of nanoparticles.

As production facilities for nanotechnology particles multiply, there is a need to assess occupational exposures. Maynard et al.[7] report on laboratory studies that evaluate aerosol release during the handling of unrefined single-walled carbon nanotube material. They found that the raw material was difficult to suspend in the laboratory using a fluidized-bed aerosol generator. Aerosol was released when different shakers were used in conjunction with the aerosol generator. The released aerosol had a bimodal size distribution with a mode in the 5–7 nm and a large mode ~500–700 nm. They also measured the aerosol and dermal exposures of handling the bulk material. No appreciable increase of aerosol was measured by pouring and transporting the bulk material; however, when a vacuum cleaner was used to clean up nanotube material, the aerosol concentration increased to 53 $\mu g/m^3$.

In terms of respiratory deposition, nanoparticles deposit in all regions of the respiratory tract by diffusion. Deposition efficiency increases with decreasing particle size. Several deposition studies were performed using physical replicas of human airways. These studies demonstrated high deposition in the nasal airways, which have been verified by limited deposition studies using human volunteers.[8,9] In terms of deposition in the tracheobronchial region, detailed deposition measurements[10,11] showed higher deposition values than theoretical prediction of diffusion deposition in a straight tube assuming a fully developed flow profile,[12] which was used in most lung dosimetry models. By adopting the enhanced deposition in the tracheobronchial region, the National Council of Radiation Protection lung dosimetry model[13] showed a higher tracheobronchial deposition and lower pulmonary deposition values than those calculated with the International Commission on Radiological Protection model.[14] The National Council of Radiation Protection and International Commission on Radiological Protection models estimated a similar total deposition, which has been verified by human volunteer studies.[15]

Because of high deposition in the nasal airways, there is a potential pathway of nanoparticle translocation from the olfactory region of the nasal airways to the brain.[16] Oberdörster[17] conducted an aqueous exposure of large-mouth bass to fullerenes (large carbon-cage molecules). After a 48-hr exposure, significant lipid oxidation was found in the brains exposed to 0.5 ppm of these nanoparticles.

Calderon-Garciduenas et al.[18] found nickel and vanadium in a gradient from olfactory to olfactory bulb to frontal cortex in healthy dogs naturally exposed to heavy urban pollution in Mexico City as compared with healthy dogs living in smaller cities with cleaner environments. Nickel and vanadium are associated with nanoparticles from oil combustion sources. There was an acceleration of Alzheimer's-type pathology in dogs chronically exposed to air pollutants, suggesting that the brain is adversely affected by pollutants. They also investigated whether residency in cities with high levels of air pollution was associated with human brain inflammation.[19] Autopsy brain samples from long-time residents in Mexico City were compared with similar human samples in less-polluted cities. Residents of cities with severe air pollution have significantly higher cyclooxygenase (COX)-2 expression in the frontal cortex and hippocampus and greater accumulation of Aβ42 compared with residents in lower air pollution cities. These findings suggest that exposure to severe air pollution is associated with brain inflammation and Aβ42 accumulation. These symptoms often precede the appearance of neuronal plaques resulting in a neurofibrillary tangle, a hallmark of Alzheimer's disease.

INVITED COMMENTS BY DR. PETER MCMURRY

The review[1,2] broadly discusses the role of nanoparticles in the environment, including discussions of sources, emission control, measurement, effects, and new technological applications that use nanoparticles. The recommendation that potential societal impacts and concerns be addressed now, rather than after problems are discovered, is wise and timely.

This is a rapidly moving area, and several related reviews have recently appeared that provide additional information on nanoparticles. The Royal Society and the Royal Academy of Engineering[20] discuss nanomanufacturing and possible adverse health and environmental impacts. Social and ethical issues are addressed, and the need to engage the public in discussions before a backlash against this new technology occurs is emphasized. Although the discussion extends beyond nanoparticles, they are included. Brown et al.[21] present an edited collection of papers on this topic, which is not intended as a coherent review. McMurry[22] discusses instrumental techniques for measuring physical and chemical properties of aerosols, including ultrafine particles. The North American Research Strategy for Tropospheric Ozone (NARSTO) particulate matter (PM) assessment[23] includes a discussion of atmospheric particulate matter and is intended to provide guidance for policy-makers charged with responsibility for meeting ambient air quality standards. Some discussion of nanoparticles is included, but the assessment does not focus primarily on nanoparticles. Especially germane are the extensive discussions of measurement methods in chapter 5[23] and appendix B.[23] Literature pertinent to the formation and growth of new particles in the atmosphere by nucleation is reviewed by Kulmala et al.[24] and includes a macroanalysis of data reported in >100 studies from many different environments.

In the area of nanoparticle science and technology, standard terminologies have not yet been accepted, and contradictory usage is common. I summarize here my recollections about how terminology has evolved over the past several decades and compare this with how it was used in the review. I also provide my personal preferences for how terminology should evolve.

During a workshop of aerosol scientists from around the world in the late 1970s, it was decided that "ultrafine" should refer to particles smaller than ~20 nm. As a result, Stolzenburg and McMurry[25] named the condensation particle counter (CPC), developed during the 1980s to efficiently detect particles as small as 3 nm—the "ultrafine CPC." This instrument was the prototype for the TSI 3025 CPC, which, for the past 15 years, has been widely used for detecting nanoparticles. Health effects researchers, unaware of this convention, defined particles as "ultrafine" if they were <100 nm. The term "nanoparticle" was then introduced to distinguish them from larger "ultrafine" particles. Pui and Chen[26] suggested that "nanoparticles consist of particles smaller than 50 nm." Friedlander and Pui,[27] however, define nanoparticles as "smaller than 100 nm." The review[1,2] defines nanoparticles <100 nm, and the authors use the terms "ultrafine particles" and "nanoparticles" interchangeably.

In my view, "nanoparticle" and "ultrafine" particle should not be used synonymously. I would prefer that "nanoparticle" refer to particles <10–20 nm. Because of quantum size effects, particles in this size range can have properties that are different from their bulk material counterparts. They also tend to be different morphologically and chemically from “ultrafine” particles in the 10–100 nm range, and they are likely to have originated from different sources. In particular, most particles of <10 nm are formed by nucleation, whereas a variety of processes can contribute to the formation and ultimate composition of larger particles. If it is impractical at this stage to identify sub-10 nm particles as “nanoparticles,” then another term needs to be coined, such as “superfine particles.”

Another related terminology issue, as illustrated in Figure 1, has to do with modes in the aerosol distribution and how the terminology appears to be gaining acceptance among atmospheric scientists. It is instructive to compare terminology illustrated in Figure 1 with that shown in Figure 3 of the review,[1,2] which defines the “nuclei” mode as somewhere around 10–20 nm. The review’s Figure 3 is based on Kittelson’s[28] review of particulate emissions from engines, and it reflects the terminology used most frequently by the engine emissions community.

Another important definition is that of particle “size.” Reported sizes are defined by the measurement methodology. For example, the aerodynamic diameter of a chain agglomerate soot particle can be a factor of two to three smaller than its mobility diameter.[29] A particle that might be reported as “fine” by one instrument could be reported as “ultrafine” when measured with a different technique. It is important to always identify the measurement principle used when reporting size-sensitive data.

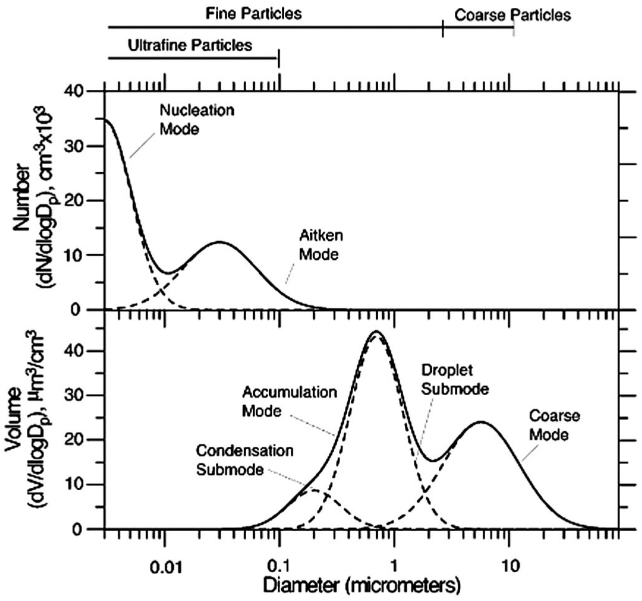

Figure 1. Terminology used to describe the modes of atmospheric aerosols (McMurry et al.[23]).

It is conventional to use different terminology to refer to particles in decades of size. For example, fine particles range from 0.1 to 2.5 µm (or perhaps include all particles <2.5 µm), and coarse particles range from ~2.5 to ~25 µm (or perhaps include all particles >2.5 µm). A standard terminology needs to emerge for particles smaller than this. As referenced before, it would be my preference to define “ultrafine” particles as those in the 10–100 nm range and “nanoparticles” as <10 nm.

Nanoparticle science and engineering is truly an intellectual frontier. Our ability to measure the physical and chemical properties of nanoparticles is progressing rapidly, and we now know that both manmade and natural nanoparticles are ubiquitous in the environment. New technological applications of engineered nanoparticles are being explored, but their potential impacts on human health or the ecosystem are poorly understood. The review[1,2] has done a terrific job of summarizing our current state of knowledge in this rapidly emerging area.

CONTRIBUTED COMMENTS BY LISA M. COREY, GRETCHEN M. BRUCE, AND DR. RICHARD C. PLEUS

These comments are intended to add focus to the discussion of the potential health and environmental risk from nanoparticle exposures presented in the review.[1,2] As practitioners of human health risk assessment and toxicology, we are familiar with the challenges that have confronted ESH managers with regard to assessing the health and environmental risk from chemical exposures, and foresee how similar challenges could affect developments in nanotechnology.

The successful evaluation of chemical risks depends on the knowledge of possible rates of exposure, as well as the dose-response of the chemical (how toxicological effects change in relation to dose). For nanoparticles, physical as well as chemical properties will affect the response; particles of the same chemistry but a different range of shapes or types of appendages could produce different physiological responses. This represents a particular challenge, because dose-response data generated for a specific mix of particles may have limited applicability, because exposure to other mixtures of the same composition in different settings might not occur.

Health risk assessment frameworks are fairly well-developed for the evaluation of chemicals, allowing ESH managers to rely, with a reasonable degree of comfort, on comparisons between monitoring data and regulatory levels. Similar types of data will be needed for nanoparticles. Some of the challenges in this process can be highlighted by examining the typical risk assessment steps:

Hazard Identification

Understanding potential hazards will require the ability to determine not only the chemical nature of the nanoparticles but also their size, shape, and number. A standard dose metric for nanoparticles, whether surface area or particle number, would facilitate cross-comparisons between toxicity studies and exposure measurements.

Exposure Assessment

Because the behavioral and toxicokinetic properties of nanoparticles are dominated by the physical characteristics, different assumptions about their potential absorption and distribution of nanoparticles will be required. For example, their small size may allow for transport to areas where larger particles cannot pass, such as across the blood–brain barrier or into cellular organelles.

Dose Response

Although growing, the database of toxicological information for nanoparticles is limited. Attention to the possible effect of species differences will be important, because it is well known that chemicals can have different effects in animals than in humans. The additive effect, or potential synergism, of exposure to different nanoparticles will also warrant consideration. As noted in the review,[1,2] several types of nanoparticles have proven to induce oxidative stress, suggesting that particles of different types could initiate and aggravate inflammation and tissue damage leading to neurodegenerative and cardiovascular disease, carcinoma, and other disorders.[30]

Risk Characterization

Risk characterization will require a combination of accurate exposure data and toxicological information specific to the measured agents. Typical risk characterization methods involve the application of factors to account for uncertainties in how the toxicological data could apply to specific exposure situations or subpopulations. For nanoparticle risk assessment, additional types of uncertainty factors may need to be determined through collaboration of the regulators and the regulated to establish adequate, yet appropriate, levels of protection for exposed individuals.

Managing possible risks may be most effective during the design-and-engineering phase of nanomaterial production, rather than after development. For example, nanoparticles could be designed with low-biological reactivity in the event of inadvertent human exposures. Similarly, nanomaterials could be developed with high affinity for specific coagulants to allow immediate and effective consolidation of materials in the event of a leak or spill. Studies might also consider the fate or “death” of a nanoparticle to understand what happens to aged nanomaterials after consumer products are disposed.

A methodology for grouping and ranking nanoparticles based on their intrinsic behavior in biological systems could be used to assign priorities in testing schedules. Such a physiological behavior classification system could describe the characteristics of the particle in terms of size, shape, solubility, polarity, chemistry, and accessibility to certain cells and tissues. Registries of nanoparticle sizes and chemical compositions could be tied to mechanistic models. The same could be achieved for nanoparticles in an ecologically based system.

As the quickly growing field of nanotechnology moves forward, it is important for companies that manufacture and use nanomaterials to openly discuss the emerging issues in human and ESH, particularly because questions will be posed by scientists, communities, and policy-makers charged with protecting community and environmental health and welfare. The challenges confronting ESH managers will be less daunting once a risk assessment framework specific to nanomaterials is established and used.

RESPONSE FROM DRS. PRATIM BISWAS AND CHANG-YU WU, CRITICAL REVIEW AUTHORS

We thank the critical review discussants for their insightful comments and for highlighting other areas of importance. Although our review focused on the emerging field of nanoparticle aerosol science and technology as it relates to the environment, the subject matter is much broader as highlighted by the discussant comments. Of special note are the additional review documents and papers that were pointed out, such as Vision 2020, the NARSTO PM assessment, the Environmental Safety and Health Database, recent studies on comparison between models and human volunteer studies, and guidelines for evaluating nanoparticle risks.

Extensive comments and a lengthy discussion ensued after the oral presentation at the annual meeting. One particular area that was mentioned was the need for educational modules, ranging from basic to advanced topics. This was not addressed in the review. Several books (e.g., Goldman and Coussens,[31] Theodore and Kunz,[32] and Ratner and Ratner[33]) cover other aspects of this important field. Our own efforts have focused on developing online instructional modules[34,35] that include software applicable to the analysis of nanoparticle data and interactive illustrations of respiratory deposition and measurement systems. Several universities are now introducing coursework in this exciting field, and the hope is that the impacts on society and the environment are an integral part of the topics that are taught.

In summary, the field of nanoparticle technology is at an exciting stage of development. Timely understanding of the impacts with ongoing studies is essential before widespread adoption of nanotechnology. The benefits of nanotechnology are immense, and with effective scientific studies, it can be ensured that the technology has minimal deleterious impacts on the environment.

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About the Authors

Judith C. Chow and John G. Watson are from Desert Research Institute. Nora Savage is from U.S. Environmental Protection Agency. C. Jack Solomon is from Praxair, Inc. Yung-Sung Cheng is from the Lovelace Respiratory Research Institute. Peter H. McMurry is from the University of Minnesota. Lisa M. Corey, Gretchen M. Bruce, and Richard C. Pleus are from Intertox. Richard C. Pleus is also affiliated with University of Nebraska Medical Center. Pratim Biswas is from Washington University. Chang-Yu Wu is from the University of Florida. Address correspondence to: Judith C. Chow, Desert Research Institute, 2215 Raggio Parkway, Reno, NV 89512; phone: +1-775-7050; e-mail: judy.chow@dri.edu.