Workshop Summary: Epidemiologic Design Strategies for Studies of Nanomaterial Workers

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Objective: The potential health consequences of exposure to nanomaterials have yet to be elucidated though increasing evidence points to the potential for nanomaterials to cause adverse human health effects. This workshop addressed the feasibility of developing studies to measure health risks among nanomaterial workers. **Methods:** Breakout groups discussed different epidemiologic designs and methods to encourage companies to collect and retain exposure and health data. **Results:** Major challenges include defining and recruitment of appropriate study populations and obtaining adequate exposure data. Both prospective cohort studies and small cross-sectional panel studies utilizing biomarkers of exposure and effect offer approaches to study occupational groups. **Conclusions:** Potential exists to assemble cohorts to study the human health effects associated with nanomaterial exposure. Stakeholder partnerships are critical to the success of these studies and international partnerships hold great potential.

The potential adverse health consequences of exposure to engineered nanomaterials have yet to be elucidated. However, a growing body of toxicologic research suggests that exposure to some forms of engineered nanomaterials has the potential to cause serious adverse human health outcomes. Given the evidence to date, it is generally accepted that precautionary measures are important to prevent human exposure to nanoparticles. Despite this agreement, it remains unclear whether exposure to nanomaterials has in fact resulted or will result in any cases of human morbidity or mortality. Epidemiologic studies are needed to adequately address the extent to which exposure to nanomaterials is associated with adverse health outcomes and to quantify the risk of specific health outcomes in subsets of workers currently exposed to nanomaterials.

In July 2010, the National Institute for Occupational Safety and Health (NIOSH) and the Mountain and Plains Education and Research Center sponsored a conference on Nanomaterials and Worker Health: Medical Surveillance, Exposure Registries, and Epidemiologic Research. Following the panel of speakers describing epidemiologic design challenges, exposure assessment, use of biomarkers, and risk assessment for nanomaterials, approximately 120 attendees participated in breakout sessions to consider four key questions as follows:

1) Which epidemiologic design strategies are most promising?
2) How do we encourage companies to collect and retain the necessary information?
3) Are there international networks for research collaboration?
4) What are immediate opportunities for epidemiologic studies?

The ideas generated about these topics during the breakout session and group discussion are summarized below.

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EPIDEMIOLOGIC DESIGN STRATEGIES

No epidemiologic studies of workers exposed to engineered nanomaterials have yet been conducted, primarily because of feasibility issues such as access to exposed populations and exposure characterization.[1] However, the lessons learned from studies of other particulates (eg, asbestos, fine particulates in air) suggest that early attention to health effects in the context of epidemiologic studies should at the very least be considered.[2–6] Epidemiologic studies have the potential to be quite valuable in determining links between different types of occupational exposure to nanomaterials and the development of health problems. In addition, if properly designed, these studies could provide the ability to identify adverse health outcomes much earlier than if not conducted.

Several participants suggested that the time is right to begin cohort studies, while others suggested that at the present, small cross-sectional or panel studies might be more appropriate and feasible. These two approaches could be done separately or, combining these ideas, one could start by enumerating a cohort and then use smaller, transitional studies to validate biomarkers within the framework of the cohort study. Some participants suggested that, on the basis of animal toxicology data, studies of pulmonary fibrosis in the carbon nanotube (CNT) workforce might be most promising at this time. Others felt that studies of cardiovascular effects would be most informative.

Important challenges to designing a successful epidemiologic study of nanomaterial workers were identified by the participants and will be summarized in this article.

Challenges in Defining and Recruiting an Appropriate Study Population

A major challenge in conducting an epidemiologic investigation is finding a study population to assemble for a cohort study. The industry is not well defined and there are distinct challenges in identifying groups of individuals exposed to nanomaterials (both manufacturers and end users) particularly with respect to exposure to similar types of nanomaterials.

To adequately design and conduct a study of nanomaterial workers requires a working definition of "nanomaterials worker." Because the types of nanomaterials and their uses are so diverse, accurately understanding the lifecycle of the typical nanomaterial and tracking through how many workers' hands that material may have passed is difficult. It is likely that the initial epidemiologic studies will be unable to adequately define every worker who may have been exposed to a given nanomaterial throughout the lifecycle of that material or the significance of such exposure. Therefore, to the extent possible, initial studies should focus on workers who are aware they are handling "raw" nanomaterials. These would include production, research and development, and laboratory workers. Although there are strengths to restricting the study population to production workers, there are also limitations. In studies of exposure and disease, misclassification of exposure is a legitimate concern. Any comparative health effect could be obscured if a segment of the production workforce defined as exposed to nanoparticles was actually unexposed through the adequate use of engineering controls or personal protective equipment.

Traditionally, companies involved in manufacturing have constituted the ideal study population, as their workers' exposures (which are often monitored in the workplace) may be higher than those of other workers. Nevertheless, the numbers of employees involved in manufacturing may be insufficient for long-term follow-up studies. It was suggested that workers involved in nanoparticle research at federal laboratories (eg, department of energy, department of defense) could be important groups to study. The extensive health registries already existing for these federal employee cohorts and detailed information on coexisting exposures also make these populations attractive for study. University populations could also be a potential source for recruitment of occupational cohorts. Given the small numbers of workers in any given occupational site, novel techniques to recruit study participants may be required and could include the use of mass media to invite individual workers, or the recruitment of recent nanotechnology technician graduates from community colleges. Small companies are also quite ephemeral; startups will lose out to or be acquired by larger producers. Workers from small companies may move to larger companies that will be able to conduct medical surveillance programs and within which epidemiologic studies might be easier.

Once an occupational cohort is identified the numbers of individuals to be recruited will depend on the type of health endpoint to be examined. The minimum latency after exposure may be short for some diseases, such as the sarcoidosis observed in workers involved in cleanup after the World Trade Center disaster on September 11, 2001.[7] However, a worker registry consisting of thousands of workers who are followed-up repeatedly would likely be necessary to detect this type of endpoint. To obtain thousands of nanomaterial workers might take a 10- to 20-year timeframe, which would be a strong downside to this design. It was also noted that, in ambient air pollution studies, a long-term (eg, 20-year) follow-up study with thousands of subjects is typical for cardiovascular and respiratory diseases. Even given these limitations and the possibility that an assembled cohort will be insufficient to detect rare outcomes, it seems prudent, given the current uncertainties, to begin to assemble cohorts of workers in order to be able to adequately examine health outcomes in the future.

Challenges in Exposure Assessment

At present, measurement of nanoparticulates is difficult, and in many real-world settings the levels of exposure are likely transient or very low. Nevertheless, lack of ideal measures of exposure does not prevent the design and initiation of epidemiologic studies.

Methods for measuring nanomaterials exposure are rudimentary at present. Exposure concentrations are not known, and potentially important metrics such as surface area and size are difficult to measure using available equipment. Methods are also needed for personal exposure monitoring because area samples may not provide enough specificity or accuracy. For certain types of nanoparticles, such as CNTs, particle number by size may be an important metric, as it has been for coal dust and asbestos.

Ideally, exposures could be assessed over specified times (eg, 15 minutes, hour-long, 40-hour work week). One could use a combination of measures, particle counting, and subjective impression of work activities to classify activities at greater risk for exposure. This would allow the classification of workers into high, medium, and low categories. However, requiring this amount of data could unduly limit participation in a cohort study. Participants from different industries agreed that broad categories were reasonable at this point, and that methods of exposure assessment will probably improve with time. In a given work site, workers' job functions (eg, packaging, material harvesting, and clean-up) are starting points for classifying exposure. However, job classifications will not always determine exposure levels because there are human risk factors that confound that relationship. Still, uncertainty around exposure levels should not preclude the design and initiation of studies.

Novel technologies, such as use of access card records or global positioning system technology could allow researchers to combine the worker's distance from the source with an area sample to estimate exposure; however, such tracking may be unacceptable to the worker or infeasible in practice.

Challenges in Defining Appropriate Endpoints

A key feature of most epidemiologic studies is a clear statement and understanding of the disease or health outcome being assessed. For case-control designs this is through establishing a case definition. Similarly for cross-sectional studies, at least some *a priori* knowledge of the expected disease is required. It is currently unknown whether exposure to engineered nanoparticles increases one's risk for developing any health outcome. Nevertheless, evidence from animal studies indicate that it is biologically plausible. Also, important information can be gleaned from epidemiologic studies of air pollution and of workers exposed to welding fumes, diesel fumes, and ultrafine carbon particles. By analogy, these studies coupled with animal studies implicate respiratory and cardiovascular diseases outcomes as the most important endpoints of concern.

No specific biomarker of early effect for nanomaterials exists at this time, but workshop participants discussed several promising markers and agreed that additional studies should be conducted. In the case of CNT exposure, pulmonary endpoints (eg, early markers of pulmonary fibrosis or lung cancer) may be the most sensitive. Once workers are classified according to exposure, the development of interstitial lung disease should be monitored. Some participants felt that it will be difficult to determine the most useful biomarker until it is certain that there will be disease development in exposed populations. Nevertheless, others disagreed that knowledge of the disease endpoint was required prior to initiating studies of biomarkers of effect. Epidemiologic studies, including biomarkers, will help determine what diseases are of concern. Biomarkers used in epidemiologic studies (particularly for hypothesis-generating studies) would require less stringent standards for validation than those used clinically for disease screening but would ideally be affordable, accessible, and noninvasive.

There was substantial discussion of the need to incorporate markers of early cardiovascular effect, such as heart rate variability, reperfusion rate with blood pressure cuff, and markers of oxidative stress, given the substantial data from ultrafine particle exposures. The design of studies should incorporate the possibility that individuals with preexisting cardiac conditions may be more susceptible to the effects of nanoparticle exposure. In addition, the many confounding factors associated with cardiac endpoints would need to be accounted for in the design of epidemiologic studies.

Some other potentially useful markers of early effect identified by participants include exhaled breath condensate, serum markers of early interstitial disease, and high-resolution computed tomography or spiral computed tomography. Concerns identified with these biomarkers include lack of specificity, unclear clinical significance, potential harm from radiation exposure, and lack of clinical validation.

Summary: Epidemiologic Study Designs

The general conclusion from the participants was that prospective cohort studies may be useful, but for many nanomaterials, workforce size has not been determined and it is likely that for a given site, the numbers of individuals working with nanoparticles may still be quite small. In addition to cohort designs, cross-sectional or small-panel studies could be useful to detect early markers of disease from nanoparticle exposure and to provide preliminary evidence for larger hypothesis-testing studies. Smaller studies would permit the collection of more detailed information related to exposure, the

use of exposure controls, and personal protection. However, the limitations of a cross-sectional study design, including representativeness and inability to establish causality, are important to consider. With the uncertainty associated with accurate classification of exposure and the uncertainty related to what endpoint is most relevant to measure, it may be that cross-sectional studies are inherently more susceptible to spurious associations than other study designs.

Clearly, the gold standard epidemiologic study design would be a large prospective cohort. Nevertheless, the feasibility of such an endeavor is questionable and much discussion still needs to occur between interested stakeholders (eg, employer, worker, medical, academic, governmental, and international communities) to initiate such a process. One potential approach for amassing an adequately sized cohort would be for investigators to assemble smaller study cohorts in multiple locations, but to participate in common protocols determined by a consortium agreement that would include common laboratory and exposure determination methods. So while there are different design approaches that the scientific community could take to begin to provide empirical evidence of the risk of nanoparticle exposure to worker health, both long-term and short-term studies are necessary and it is important to begin these investigations.

STAKEHOLDER PARTNERSHIPS NECESSARY FOR OCCUPATIONAL STUDIES

As described earlier, epidemiologic studies of nanomaterials workers will be important in answering questions regarding the human health impacts of these exposures. Nevertheless, participants expressed concern that information needed for epidemiologic studies is not routinely being collected by employers. Barriers were identified, including concerns about sharing "business sensitive" information in the private sector. Incentives may be needed to encourage companies to assist in determining potential health effects associated with the materials their personnel are producing or using. It was also pointed out that most researchers do not have right of entry into companies; therefore, time and great effort will be required to build trust with the industry. There may also be concerns on the part of companies about potential legal ramifications of study findings. The cost of participating in a study is also a potential concern for industry, particularly for small manufacturers.

The participants identified several methods to increase the availability of employment data. One idea was to require any recipients of federal nanoparticle research and development funds to address this need in their applications for funding and to agree to participate in registries or health studies. It was expressed that government nanomaterial research entities should be at the forefront of this effort. Participants noted that department of energy and department of defense facilities already have worker registry systems. This may provide incentive to private industry if information could be pooled from multiple sources of both primary and secondary manufacturers. It was noted that department of defense, in particular, may have thousands of workers exposed to nanomaterials in grinding, sanding, and spray-painting operations.

Other possible avenues to encourage participation include working through insurance companies, which were not represented at this meeting. Insurance companies might be encouraged to turn down coverage for nanoparticle workers compensation claims if companies do not agree to participate in research on health effects. It was also suggested that companies participating in health studies be awarded some benefit (eg, reduced legal liability, tax incentive, or workers compensation relief). Analogy was made to the asbestos industry, which has seen many bankruptcies as a result of findings of adverse health effects from exposure.

Some of the information needed for occupational epidemiology studies consists of rosters of workers handling nanomaterials, along with their job histories. It was pointed out that US law requires companies that go out of business to offer their personnel and exposure records to National Institute for Occupational Safety and Health for future epidemiologic studies. This is important for the nanomaterials industry, which has a high attrition rate, but many nanotechnology companies may be unaware of this requirement. Effort should be made to inform these industries and solicit these records from expiring companies.

Participants advocated the need to engage industry about health, safety, and environmental aspects of nanotechnology and to encourage them to value a healthy workforce. The need for health studies should be put on the agenda of big industry conferences so that trade associations become aware and will put together programs on this topic. A partnership among all the stakeholders (government, employers, etc) was suggested as a key component in overall feasibility. These may be critical in developing a centralized registry, which could serve as the starting point for a cohort.

POTENTIAL INTERNATIONAL NETWORKS FOR RESEARCH COLLABORATION

It was pointed out by participants that international collaborations are already occurring on many aspects of nanotechnology; occupational health studies would be a valuable and natural addition. Possible populations or research opportunities could include those presented in Table 1.

It was recommended that participants in this conference work together with international contacts (eg, International Agency for Research on Cancer) and share information. Multinational companies may be a particularly good source population for epidemiologic studies. It was stated that many individual companies already require collaboration between factories. Working model consortia have been established in other industries (eg, cobalt, nickel) that could be models. It was pointed out that some countries (eg, France) require extensive documentation that may be useful for epidemiologic research. In the end, participants agreed that international cooperation was needed to combine resources and link together small studies.

IMMEDIATE OPPORTUNITIES FOR EPIDEMIOLOGIC STUDIES

Upon discussing the challenges and barriers to conducting epidemiologic studies (outlined earlier) the session participants considered what immediate opportunities for epidemiologic studies were

TABLE 1. Potential Populations or Research Opportunities to Target for Occupational Health Studies of Nanomaterial Workers

A proposed NIOSH study of all US carbon nanotube producers and users
Registries of nanomaterials users at US Department of Energy facilities
International studies of nanoparticle exposures among military workers in Taiwan
Identification (and possible epidemiologic study) of nanotechnology workers in France
Other medical monitoring and biomarker work being conducted in Taiwan, Singapore, and elsewhere in Southeast Asia
The United Kingdom Nanotechnology Safety Forum is considering studies
Studies of nanomaterials workers in Scotland
The REACH program, a new European Community Regulation on chemicals and their safe use, may require health-effects studies for nanomaterial producers or users in Europe[8]
The NanoimpactNet, a multidisciplinary European network on the health and environmental impact of nanomaterials is consolidating information on health effects and exposure, which could serve as a collaborative platform

most reasonable. Although broad consensus was not reached on specific actions or study designs, consensus was reached with regard to one point-–something should be done. Although the limitations of all the study designs discussed were highlighted throughout the session, the overriding conclusion was summed up by invoking Voltaire's "let not the perfect be the enemy of the good." Session participants were in agreement that a proactive approach was necessary and that it would be ill-advised to not pursue epidemiologic research of some form among nanomaterial workers.

However, because of the many unknowns that exist, the question of what can be done immediately is not easily answered. Some favored small incremental approaches while others advocated large-scale international cohort studies. The session concluded with Dr Paul Schulte[1] of National Institute for Occupational Safety and Health proposing a specific nested hybrid design that could potentially allow for a number of different study designs to occur simultaneously as part of a larger cohort or registry.

In general, given a strong enough exposure/disease relationship and/or adequate sample size, an observational cohort design would not necessarily require *a priori* knowledge of a specific disease endpoint if a population of exposed individuals could be adequately identified and observed over time. In addition, a large observational cohort design would not preclude sampling within the cohort or recruiting new worker populations to conduct panel studies, case-control studies, cross-sectional studies, or studies focusing on biomarkers.

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