Engineered Nanomaterials
Learning from the Past, Planning for the Future

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Objective: The ongoing explosion in creation and use of engineered nanomaterials leaves stakeholders in government, industry, and labor uncertain of how best to proceed in protecting worker health. Methods: A synopsis is presented of the conference Nanomaterials and Worker Health, along with considerations of prior, analogous challenges in occupational health. Results: Progress has been made in defining and addressing the occupational threat of engineered nanomaterials, but future success demands coordinated effort. Conclusions: The conference Nanomaterials and Worker Health laid necessary groundwork for collaboration to proactively and preemptively address the occupational health effects of engineered nanomaterials.

Engineered nanomaterials (ENM) represent a potentially transformative challenge to public health, and the earliest health impacts of these tiny materials may be found among the workers involved in their manufacture, processing, and disposal. The National Institute for Occupational Safety and Health (NIOSH) and the Mountain and Plains Education and Research Center sponsored the conference “Nanomaterials and Worker Health” in Keystone, Colorado, on July 21 to 23, 2010, to address three key components of an occupational health response: medical surveillance; exposure registries; and epidemiologic research. The conference brought together various ENM stakeholders to share information, identify gaps in knowledge, examine successful approaches, and explore future strategies for each element of this three-part response, the importance of which has been previously articulated by conference cochairs Trout and Schulte. The conference fostered thoughtful and spirited discussion toward a comprehensive plan for ENM worker safety as the exciting potential of these novel materials was realized.

An important lesson from the conference is that cooperation between stakeholders will be crucial to the success of occupational health efforts in the field of ENM. The breadth of the challenges will thwart any piecemeal approach, and unilateral regulation enforced by a single government would be insufficient to address what is already a global industry. Partnership is necessary for meaningful progress. An inspirational example was given of the Asphalt Paving Industry Partnership, a joint effort between labor, management, and government to prevent and control exposure-related illness. Another example of a coordinated approach was the European response furthering the pace of new materials is breathtaking. The NIOSH nanotechnology field research team is defining the state and limitations of ENM stakeholder must learn quickly from the successes and stumbles of such collaborations, as the diversity of exposures from ENM is growing at an exponential pace. Also importantly, the “triatite approach” of government, industry, and labor coordinating to address occupational health is built into NIOSH legislation. The conference was a milestone on the long journey of bringing together these stakeholders to develop a comprehensive ENM public health strategy based on shared concerns and common values.

From diverse stakeholders came diverse perspectives, some reassuring about progress made so far and some unsettling regarding the challenges ahead (Table 1). Reports from toxicologists warned about the hazards of carbon nanotubes and nano-scale metal oxides in animal models, sometimes at far lower doses than comparable particles of larger size. We learned that the measurement of ENM exposure lacks standard methods or validated metrics, and further, we learned that we do not have information about how many and where workers are exposed to ENM. Monitoring may join existing screening tests to identify early disease. And despite the dearth of easily accessible data, epidemiologic researchers have already made progress identifying cohorts of workers with potential exposure for future studies.

Coordination of efforts is facilitated by a systematic approach. A useful systematic approach to such public health challenges is modeled by the cascade of occupational health prevention (Fig. 1). Each step along the cascade represents an opportunity for intervening to prevent exposure-associated illness. One feature of the cascade is that success at “higher” levels of prevention can reduce the burden “downstream.” For example, substitution and elimination of toxic chemicals make personal protective equipment less important; early detection of pathologic changes by preclinical medical examination may prevent the need for rehabilitation. Another element of the cascade is surveillance, which provides feedback to “upstream” processes. Data from environmental monitoring guide engineering controls, and clinical diagnoses inform biological monitoring. Working from a framework like the cascade for occupational health prevention is valuable, because it brings together disparate efforts into a cohesive system greater than the sum of its parts.

The conference illuminated work being done at several steps along the prevention cascade, as well as opportunities for improvement. Premarket testing of ENM toxicology is ongoing, although the pace of new materials is breathtaking. The NIOSH nanotechnology field research team is defining the state and limitations of environmental monitoring of ENM exposure. Presentations were given on the effectiveness of and progress in personal protective equipment, biological monitoring, and preclinical medical examination. Lacking, yet, is the integration achieved by incorporating surveillance feedback along every step of the cascade. A collaborative conference, such as this one, lays good groundwork for such coordination.

EXPOSURE REGISTRIES AND MEDICAL SURVEILLANCE: THE CASE FOR STARTING NOW

Much of the conference dealt with the related questions of whether the time is right for instituting ENM exposure registries and regular medical surveillance of workers. Such registries would be a source of data and hypothesis generation for epidemiologic research as well as work in toxicology, biological monitoring, and exposure assessment and control. Appreciation of the value of starting to
TABLE 1. Impressions of Conference Presentations

| Presenter  | Topic       | Impression | Presenter  | Topic       | Impression |
|------------|-------------|------------|------------|-------------|------------|
| Nasterlack | Surveillance| Challenges | Busnaina   | Application | Motivation |
| Sing       | Surveillance| Example    | Castranova | Toxicology  | Concerning |
| Lichty     | Surveillance| Example    | Kuempel    | Toxicology  | Concerning |
| Gause      | Surveillance| Example    | Ellenbecker| Exposure    | Concerning |
| Kosnett    | Surveillance| Promising  | Geraci     | Exposure    | Concerning |
| Marchant   | Registries  | Challenges | Monteiro-Riviere | Exposure | Concerning |
| Cassidy    | Registries  | Example    | Erdely     | Biomarkers  | Concerning |
| Wambach    | Registries  | Example    | Li         | Biomarkers  | Promising  |
| Cone       | Registries  | Example    | Sayre      | Regulation  | Concerning |
| Kosnett    | Registries  | Example    | Sayre      | Regulation  | Concerning |
| Groth      | Registries  | Example    | Trout      | Systematic Approach | “Unique workplaces require unique applications of standard principles.” |
| Peters     | Epidemiology| Concerning  | Riediker   | Illustrated Shewhart cycle |
| Harthorn   | Epidemiology| Challenges | Melius     | Illustrated tripartite approach |
| Eisen      | Epidemiology| Challenges | Roisman    | State government involvement |
| Schubauer-Berigan | Epidemiology | Promising | Kreibel    | “When do we know enough to act ‘as if’ an association is causal?” |

FIGURE 1. The cascade of occupational health is a model that illustrates the interacting roles of prevention and surveillance in keeping workers safe.

As a “worst-case scenario” analogy for the risks of and for the ENM industry, consider the explosion of the Zeppelin Hindenburg in 1937. Not only was this incident a tragedy for the individuals who died in the crash, but it was likely disastrous for lighter-than-air travel, particularly hydrogen based. Although political factors and advances in airplanes certainly contributed to the decline of the industry, the dramatic footage of the burning Hindenburg (“Oh, the humanity!”) signaled the end of an era of commercial dirigibles. The possibility of a similarly high-profile, “game-changing,” preventable incident occurring to the nascent nanotechnology industry—or perhaps for a defined segment of it like, say, carbon nanotubes—does not far stretch the imagination. Provided our imagination is primed by our prior experiences with other fibers such as asbestos.
The Hindenburg crash is an example of a “true positive” catastrophe, one in which the adverse effect is actually associated with the exposure. In contrast, we can describe a “false positive” event that could similarly cripple a growing industry. Call these possibilities type 1 and type 2 disasters, respectively. In a type 2 disaster, a cluster of adverse health outcomes is found in association with an exposure of interest, but the cluster is random and the association is just unlucky. Epidemiology and toxicology can reveal type 2 disasters to be nothing but statistical chance, but the research process can take time that may cost an industry and society dearly.

An illustration of a type 2 disaster is the case of video display terminals (VDT). Several clusters of spontaneous abortion were reported in 1980 in suspected connection with very- and extremely-low-frequency electromagnetic fields from cathode-ray tubes in VDT. Initial types of studies of occupational exposure to VDT were inconclusive. Conduct of a proper epidemiologic study, with an appropriate control cohort defined and exposure to electromagnetic fields quantified in the field, took time. Fortunately for exposed workers, an appropriate control cohort was defined and exposure to electromagnetic fields was monitored. Conclusions of the study were reported in 1991\(^1\); the time to mount the study and obtain an answer took a full decade. A decade is a long time to a VDT user who has suffered the adverse effect. Because the adverse effect is largely preclinical, the interval between observation of the first signs of a cluster and definitive assessment will be a time of great uncertainty for industry, workers, and society that will inevitably impede the growth or unnecessarily increase the cost of this new and important technology.

A type 3 disaster is a public concern over an exposure due to fear of adverse events even in the absence of an outbreak. Consider the struggles of the genetically modified organisms industry. Promise for modern genetically modified organism technology has at times been comparable in breathlessness—a cure for world hunger and malnutrition—to that for ENM. Exciting products have been developed, such as “golden rice” containing β-carotene and “Bt-corn” that kills pests without synthetic insecticides. The most likely biological risks of the technology are similar to those for other agricultural techniques, such as cross-pollination or adverse effects on local ecosystems. Nevertheless, widespread public concerns have arisen about direct health effects on human consumers, concerns that, some say, are out of proportion to presently observed or reasonably expected effects. The innovation and development of this technology has been retarded by bad public relations, even in the absence of a safety failure. Given the impressive novelty of ENM, similar scares are possible for its industry and should be preemptively addressed.

The public health challenge from ENM comes not only from its potential for diverse toxicologic effects\(^1\) but also from its predicted ubiquity throughout industry and society. Given enough manufacturers, enough users along the value chain, enough consumers of ENM, eventually a high-profile cluster of health events will occur that can be plausibly linked in time and proximity to ENM exposure. This cluster may reveal an adverse effect of ENM exposure, previously unrecognized or underappreciated, a Hindenburg-like type 1 disaster that might have been prevented with more forethought and risk management. Alternatively, the cluster may be a “false positive” type 2 disaster like VDT, simply a chance grouping of unrelated health events that is statistically inevitable as the industry grows. Yet another possibility is that the cluster will happen in a movie or be a prediction of protesters, and the chilling effect of a type 3 disaster on industry may be no less severe for the outbreak being imagined. Whether the adverse effect is fact, fluke, or fiction, the human and commercial impact will grow until epidemiologists are able to precisely define the risk.

The considerable costs to establishing and maintaining exposure registries can be justified if the registries will protect workers and industry against type 1, 2, and 3 disasters. A specific example in occupational health that illustrates the value of registries is that of dioxin. In 1980, Centers for Disease Control and Prevention epidemiologists were asked by Department of Defense to study the alleged adverse effects of the herbicide “Agent Orange” used by military forces in Vietnam. To augment studies of soldier exposure in the field, NIOSH proposed a study of civilian production workers exposed to a related industrial compound (2,3,7,8-tetrachlorodibenzo-p-dioxin). The epidemiologists located chemical plants where exposure could be assessed, enrolled study cohorts of workers, and prospectively monitored exposure and health outcomes. Conclusions of the study were reported in 1991\(^2\); the time to mount the study and obtain an answer took years. A registry of workers could have provided a clear answer within months to years of preparation necessary for finding appropriate industry cohorts to study an event cluster, is reported. The more detailed alternative proposed by many participants of this conference is a registry of workers: a list of individuals with their contact information, personal exposure history, and record of health outcomes obtained through regular surveillance. Examples were presented from the US Air Force and French Alternative Energies and Atomic Energy Commission (CEA). Such a registry would enable epidemiologists not only to design cohorts but also to immediately begin analyzing differences in exposure-controlled morbidity and mortality. After an event cluster, a preexisting worker registry would save the years to decades needed to prospectively follow individuals exposed to the suspected hazard. The savings in human health and public relations from quickly defining a “true positive,” exonerating a “false positive,” or assuaging nonspecific fear would easily justify the effort to build and maintain the exposure registry.

Although the future value of exposure registries is substantial, their implementation raises several nontrivial challenges, described in detail during this conference\(^2\) that must be addressed. Issues of access, usability, and standardization of the registry database are crucial and will require coordination and commercialization among manufacturers. Agreements must satisfy industry needs regarding proprietary information and legal liability, needs that may otherwise be barriers to willing participation. In addition, a common understanding must be reached on the methods and appropriateness of medical surveillance of workers in the registry; such detailed consensus building might be the topic for a near-future workshop.

The contention surrounding medical surveillance centers on the clinical value to the worker of currently available screening tests. Concerns about the hazardous nature of ENM—supported by varying degrees by toxicology studies with animal models\(^1\) and epidemiologic studies of ultrafine particles in diesel exhaust\(^3\)—focus on diseases that are fairly common: restrictive pulmonary disease; cardiovascular disease and its diverse sequelae; malignancy of unspecified type; and systemic manifestations of chronic inflammation. These nonspecific endpoints, coupled with our biological malfeasance of ENM burden, make individual screening a troublesome proposition from a clinical standpoint. Abnormal findings on pulmonary function tests, chest radiographs, or serum C-reactive protein may not be interpretable for the individual worker.\(^6\) This uncertainty may be due to operating characteristics of the test (such as sensitivity and specificity) or due to potentially confounding risk factors (like smoking, diabetes, and other exposures). Clinically, uninterpretable test
results are particularly problematic as exposure-related pathology may impact employability or have legal repercussions. Nevertheless, even a test that is experimental, insensitive, or nonspecific can have occupational health value for comparing cohorts. Different average results in two comparable groups may suggest an engineering control flaw, resulting in higher than expected exposure, for example, or may reflect an unexpected biologic response at exposure levels previously thought safe. In addition, careful informed consent procedures can obviate the problems of test results that are not actionable at the individual level. A major precept of medical screening in nonoccupational settings is that test results must have therapeutic or prognostic value to the patient; occupational health screening in exposed workers, however, may be justified despite an indeterminate clinical value of the test. Occupational screening can detect early indicators of adverse effects and thereby lead to reduction of exposure. Such research can save worker health costs. Exposures registries of workers can provide data—the accumulation of “paralysis of analysis” or “letting the perfect be the enemy of the good.” It is true that we do not yet know enough about ENM to look back in pride at the proactive steps taken in Keystone. The broad array of presentations and discussions helped to define the state of the art and lay foundation for future consensus and standardization. Stakeholders in government and industry together are accepting their ethical obligation to share the costs of this wondrous new technology with the workers who will inevitably bear the brunt of exposure. The challenge is where to go hence. Clearly, industrial innovation will be raging forward. This conference presented clear messages that we must hasten our pace along numerous fronts, including toxicology, assessment of potential occupational exposure, and detection of biological effects. Although we yet need agreement on certain crucial details, we have from this conference, a path on which to proceed with epidemiologic studies and exposure registries. The efforts of this conference and the meetings to follow it reduce the chances of widespread adverse health effects and commercially crippling uncertainty as we enter the brave new world of ENM.

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ACKNOWLEDGMENT

Expenses for travel and lodging paid by National Institute for Occupational Safety and Health.

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