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Workshop Report

Workshop report: Strategies for setting occupational exposure limits for engineered nanomaterials

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ABSTRACT

Occupational exposure limits (OELs) are important tools for managing worker exposures to chemicals; however, hazard data for many engineered nanomaterials (ENMs) are insufficient for deriving OELs by traditional methods. Technical challenges and questions about how best to measure worker exposures to ENMs also pose barriers to implementing OELs. New varieties of ENMs are being developed and introduced into commerce at a rapid pace, further compounding the issue of OEL development for ENMs. A Workshop on Strategies for Setting Occupational Exposure Limits for Engineered Nanomaterials, held in September 2012, provided an opportunity for occupational health experts from various stakeholder groups to discuss possible alternative approaches for setting OELs for ENMs and issues related to their implementation. This report summarizes the workshop proceedings and findings, identifies areas for additional research, and suggests potential avenues for further progress on this important topic.

1. Introduction

Certain engineered nanomaterials (ENMs) such as amorphous silica, zinc oxide, carbon black, and titanium dioxide have been used for many years, and considerable progress has been made in understanding and managing their occupational health risks. Over the past decade, however, many new, increasingly complex ENMs have been developed and introduced into commerce including those having unique chemistries (e.g., CdSe quantum dots, ZnGaN), surface modifications (e.g., organosilane- and acrylate-treated silicas), shapes (e.g., carbon nanotubes, Silica Nanosprings™) and other properties. Evaluation of the potential health risks posed by these "second-generation" ENMs is made difficult by, yet is important because of, their rapid pace of development.

Occupational exposure limits (OELs) are widely recognized as valuable tools for managing worker exposure to chemicals and other hazards in the workplace. Most OELs are time-weighted average (typically 8-h) air concentrations believed to represent a safe level of exposure for most workers over their working lifetime. Worldwide, OELs have been established by government regulatory agencies, non-regulatory authoritative bodies, and chemical manufacturers for approximately 6000 substances. In contrast, no regulatory OELs and only a handful of non-regulatory and manufacturer OELs have been published for ENMs, the main reason being the lack of long-term animal inhalation toxicity data and epidemiology data which have traditionally served as the bases for setting OELs.

For an OEL to be useful, a validated and practical method for measuring airborne concentrations in the workplace must be available. Although instruments and techniques are available to measure airborne ENMs, they tend to be less portable, more complicated to

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operate, and more expensive than equipment used to monitor other substances. These and other technical issues, including uncertainties about the most relevant exposure metric and how to distinguish the ENM of interest from other particles in the workplace air, pose additional barriers to establishing and implementing OELs for ENMs.

A Workshop entitled "Strategies for Setting Occupational Exposure Limits for Engineered Nanomaterials" was held in September 2012 to provide an opportunity for occupational health experts and other interested stakeholders from industry, academia, government, and non-governmental organizations to discuss possible alternative strategies for setting OELs for ENMs and issues related to their implementation. The workshop agenda and invited speaker's slides are available at http://nanotechnology.americanchemistry.com/OELWorkshop.

This report is a summary of the workshop proceedings. It is not a comprehensive review of the scientific literature on OELs for ENMs, although citations are provided for the reader interested in additional details about specific approaches for setting OELs and other topics discussed at the workshop. Ideas and concepts for which there appeared to be general agreement among workshop attendees were identified, but no effort was made to reach group consensus on any topic. Therefore, this report should not be viewed as reflecting the opinion of all workshop participants, their affiliated organizations, or the workshop sponsors or organizers.

2. Workshop findings

2.1. The need for occupational exposure limits for ENMs

There was broad agreement on the need for OELs for ENMs and that they should be established before health effects might begin to emerge among exposed workers. Standard industrial hygiene measures such as ventilation, containment, respirators, and other personal protective equipment (PPE) are considered effective for controlling occupational exposures to ENMs and can be employed in the absence of OELs. However, unnecessary use of these measures is costly, reduces worker efficiency, and, in some instances, may paradoxically increase the likelihood of workplace injuries such as musculoskeletal disorders associated with the use of glove boxes (UKHSE, 2012). Due to the rapid pace at which new ENMs are being developed, setting OELs for them cannot be a process driven solely by government agencies, nor can non-regulatory authoritative bodies such as NIOSH and ACGIH be expected to fill the void. Rather, OEL development for new ENMs will need to be a collaborative effort between manufacturers, regulatory agencies, and non-regulatory organizations. In light of the limited published hazard data available for most new ENMs, a conservative approach is warranted in setting and using OELs for them.

2.2. Barriers to developing OELs for ENMs

The lack of adequate published toxicity data, especially from long-term animal inhalation and worker epidemiology studies, is the primary barrier to developing OELs for most ENMs. Exceptions are the substantial quantities of toxicity data available for certain "first generation" ENMs such as titanium dioxide, amorphous silica, carbon black, and zinc oxide, and for some carbon nanotubes (CNT). Due to the number and varieties of new ENMs being developed and the time and resources required to perform long-term inhalation and epidemiology studies, it appears unlikely that these types of data will be generated for most new ENMs. There is a clear need for faster, more cost-effective methods for assessing the toxicity of new ENMs and for new strategies for deriving OELs based on more limited toxicity information.

Developing OELs for ENMs is also hampered by our limited current understanding of how the physicochemical properties of ENMs influence their *in vivo* kinetics and toxicity relative to that of their larger counterparts. A challenge in comparing ENMs to their larger counterparts or to other ENMs in a similar physicochemical class is that more than one property is sometimes changed at the same time as size, e.g., surface chemistry, surface area, or crystal phase. At a fundamental level, the properties considered to be most relevant to the toxicology of ENMs include size, size distribution, shape, agglomerate/aggregate state, density, surface area, surface charge, surface reactivity, solubility, and crystalline phase. The combined interactions of these properties, and undoubtedly others, determine the dose–response patterns observed in toxicology studies with ENMs. While quantitative property–toxicity relationships have been reported for certain ENMs under specific experimental conditions, no general rules have yet been established by which the chronic toxicity of ENMs can be accurately predicted based on physicochemical property information alone. Nonetheless, measuring and reporting appropriate physicochemical property information for ENMs evaluated in toxicity studies is considered essential to developing a deeper understanding of property–toxicity relationships for ENMs and for comparing findings among studies and laboratories.

A third factor impeding the development of OELs for ENMs is uncertainty concerning the most relevant dose or exposure metric. With the exception of fibrous materials such as asbestos, virtually all existing OELs for particulate materials are mass-based with units of mg/m^3, and they are usually based on toxicity data in which doses are expressed as an airborne mass of material. In the case of ENMs, however, animal inhalation and intratracheal instillation studies have found correlations between toxicity and administered doses expressed as particle mass, surface area, number, density, and volume. This diversity of dose metrics is perhaps not surprising considering the diversity of study designs, ENMs, and toxicity endpoints evaluated in these studies, but it creates uncertainty in interpreting toxicity data and in developing methods for measuring workplace exposures. Ongoing research may eventually clarify this matter, but, in the meantime, mass-based sampling and related analytical methods are viewed, at least within the U.S., as the most practical means for routinely monitoring airborne particulates in the workplace, and this is expected to drive OEL development for ENMs towards mass-based values, as least in the near-term.

Finally, the lack of standardized and validated methods for monitoring workplace concentrations of ENMs hinders the development of OELs and vice versa. Not only must such methods be capable of size- and substance-specific detection of low airborne concentrations, they must also be able to distinguish the ENM of interest from background levels of other particles which are almost always present in the workplace air. Conversely, the lack of OELs against which air monitoring data can be interpreted lessens the impetus for conducting air monitoring and for developing practical methods for measuring ENMs.

2.3. Strategies for setting OELs for ENMs: traditional and alternative approaches

Various approaches for setting OELs for ENMs have been used or proposed (reviewed in Schulte et al. (2010) and van Borekhuizen et al. (2012)). These approaches fall into two broad categories based primarily on the availability of toxicity data. When adequate toxicity data for the ENM are available, traditional quantitative risk assessment (QRA) methods have been used to set specific numerical OELs. When toxicity data for the ENM are limited, as is more often the case, alternative pragmatic approaches based on general principles and professional judgment have been used. Examples of