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Characterizing risk assessments for the development of occupational exposure limits for engineered nanomaterials

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ABSTRACT

The commercialization of engineered nanomaterials (ENMs) began in the early 2000's. Since then the number of commercial products and the number of workers potentially exposed to ENMs is growing, as is the need to evaluate and manage the potential health risks. Occupational exposure limits (OELs) have been developed for some of the first generation of ENMs. These OELs have been based on risk assessments that progressed from qualitative to quantitative as nanotoxicology data became available. In this paper, that progression is characterized. It traces OEL development through the qualitative approach of general groups of ENMs based primarily on read-across with other materials to quantitative risk assessments for nanoscale particles including titanium dioxide, carbon nanotubes and nanofibers, silver nanoparticles, and cellulose nanocrystals. These represent prototypic approaches to risk assessment and OEL development for ENMs. Such substance-by-substance efforts are not practical given the insufficient data for many ENMs that are currently being used or potentially entering commerce. Consequently, categorical approaches are emerging to group and rank ENMs by hazard and potential health risk. The strengths and limitations of these approaches are described, and future derivations and research needs are discussed. Critical needs in moving forward with understanding the health effects of the numerous EMNs include more standardized and accessible quantitative data on the toxicity and physicochemical properties of ENMs.

1. Introduction

Risk assessments are conducted to estimate the risk following exposure to hazardous substances. Few risk assessments have been performed to date on engineered nanomaterials (ENMs) due to limited data. However, there is a growing body of data that raises concerns about potential adverse health effects from exposure to ENMs (Hristozov et al., 2012; Kreyling et al., 2004; Kuempel et al., 2012; MaHock et al., 2009; Nel et al., 2013; Oberdörster et al., 1995, Sargent et al., 2009; Savolainen and Vartio, 2017; Schmid and Stoeger, 2016). The commercialization of nanotechnology generally began in the early 2000s and precautionary guidance followed soon after (Hett, 2004; HSE, 2004; NIOSH, 2005; The Royal Society and The Royal Academy of Engineering, 2004). By 2005, 54 consumer products were reported to contain nanomaterials, while today that number is over 1800 products (Vance et al., 2015). Workers are involved in all aspects of ENM production from research to production, use, and disposal, and are potentially exposed to nanomaterials. Employers, workers, insurers, government decision-makers, and other stakeholders all need information on the hazard of nanomaterials and the health risk to workers. In response, there has been a concerted effort to identify the hazards of nanomaterials and the underlying mechanisms of action, determine exposures, assess risks, and provide guidance on managing those risks.

Quantitative risk assessment (QRA) methods for ENMs generally have been consistent with those in the standard risk assessment paradigm (NAS, 1983, 2009; OECD, 2012). When quantitative dose-response data are available, risk assessment for ENMs and other substances involves the following five steps: 1) evaluating available data; 2) selecting an appropriate adverse response; 3) determining the critical dose; 4) calculating the human equivalent dose; and 5) determining the working lifetime exposure concentration that would result in that dose (Jarabek et al., 2005; Kuempel et al., 2006; Oberdörster, 1989; Schulte et al., 2010; U.S. EPA, 1994). QRA involves estimation of a point of departure (POD), which is a point on the dose-response curve that identifies the dose associated with an adverse response at a low level or a level that is not biologically or statistically different from background. A POD based on animal data is extrapolated to humans by estimating an equivalent dose (e.g., using interspecies adjustments) to lower risk levels based on quantitative modeling and/or uncertainty factors. OELs, critical tools in risk management, then are derived from estimates of the

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airborne exposure concentrations associated with no or low risk of adverse health effects in workers. Additionally, consideration is given to specific factors pertaining to the nanoscale, such as potential differences in the uptake and distribution of nanoscale and microscale particles in the body, and potential differences in the hazard potency of nanoscale vs. microscale particles of the same composition on a mass basis. When quantitative dose-response data are not available, other methods are needed, including read-across methods based on knowledge about the underlying biological mechanism of action, and grouping based on similar physicochemical properties, or comparative potency using shorter-term data in animals or cell systems (Arts et al., 2014, 2015; Gordon et al., 2014; Kuempel et al., 2012; Maier, 2011; NAS, 2017; Nel et al., 2013; Schoeny and Margosches, 1989; Sobels, 1977, 1993; Stone et al., 2014).

It is possible to characterize the trajectory of risk assessments of ENMs according to approaches that have been used in the past. This characterization requires seeing the trajectory in the context of the natural history of the development of commercial nanotechnology. The risk assessment of ENMs builds on earlier work with ultrafine particles and fine dusts (Dankovic et al., 2007; Donaldson et al., 1990; Driscoll et al., 1990; Kreyling et al., 2013; Oberdörster et al., 1992; Stone et al., 2016b; Tran et al., 1999; Tran and Buchanan, 2000; Wichmann and Peters, 2000). Fig. 1 shows the trajectory for risk assessment of ENMs in terms of the approaches used. In the early 2000s, concern about the potential hazards of ENMs was great. While there were preliminary data (air pollution epidemiology, health effects of welding fumes, and some studies of nanoparticle translocation from nose to brain), generally there was a major lack of information about hazards, risks, and exposures of ENMs. Consequently, the initial approach to risk assessment was based on precautionary appraisal to fill the pressing need for any kind of guidance to anchor risk management decisions (The Royal Society and The Royal Academy of Engineering, 2004; BSI, 2007; IFA, 2009). For ENMs with sufficient data, quantitative risk assessment methods have been used to develop OELs (e.g., NIOSH, 2011; NIOSH, 2013). Given the challenges in developing individual OELs for all ENMs – many of which have limited data – methods have been developed to prioritize or group ENMs based on the available subchronic or chronic dose-response data for benchmark materials and the utilization of shorter-term *in vivo* data for many ENMs (e.g., Arts et al., 2016; Hristozov et al., 2016; Drew et al., 2017). No OELs have been developed based on these methods to date, and efforts are underway to further develop quantitative methods to categorize ENMs by hazard potency, as well as to evaluate the use of data from alternative test systems including *in vitro* models.

Fig. 2 shows the trajectory of risk assessments for selected ENMs related to the development of OELs. While there are thousands of ENMs in commerce, only a minute fraction of those has an OEL. A recent

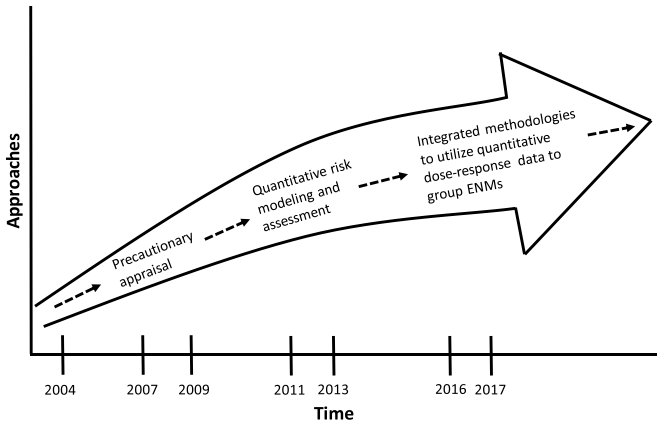

Fig. 1. The eras of risk assessment and development of occupational exposure limits for engineered nanomaterials.

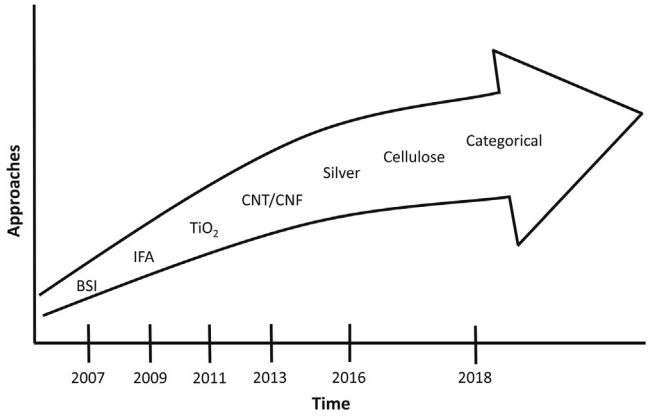

Fig. 2. Trajectory of risk assessments and development of occupational exposure limits for engineered nanomaterials.
Abbreviations:
BSI: British Standards Institute
IFA: Institute for Occupational Safety and Health of the German Social Accident Insurance
TiO_2: Titanium dioxide
CNT/CNF: Carbon nanotubes and carbon nanofibers

systematic review study cited 56 OELs that have been developed for ENMs, although many of these are for the same set of ENMs, and this number includes both individual and categorical OELs (Mihalache et al., 2017). The first two examples, the British Standards Institute (BSI) and the German Occupational Safety and Health authority (IFA), utilized professional judgement to describe broad categories of ENMs, called benchmark exposure levels (BSI, 2007; IFA, 2009). The categories were selected to utilize size, density, shape, and biopersistence and the exposure levels were derived as fractions of the OEL for benchmark bulk material of the same composition or physical chemical characteristics as the ENM. For fibrous materials, such as carbon nanotubes (CNTs), the benchmark exposure level was one-tenth of the asbestos or 0.01 fibers/ml (BSI, 2007; IFA, 2009). OELs based on quantitative risk assessments have been developed for titanium dioxide (TiO_2), carbon nanotubes and nanofibers, and silver, as discussed in Section 2. No OELs have been developed to date for nanoscale cellulose given the limited dose-response data, and methods to develop categorical OELs for ENMs are under development, as discussed in Section 3.

2. Protoypic nanomaterial risk assessment

2.1. Titanium dioxide

One of the first QRAs of a nanomaterial was on titanium dioxide (TiO_2). (Dankovic et al., 2007). A QRA is a systematic process to assess risks, in this case from chemical substances. The assessment procedure involves the four main steps of hazard identification, dose-response assessment, exposure assessment and risk characterization (NAS, 1983; NAS, 2009). Ultimately, it is the process of extrapolating from a range of direct observation to a lower potentially safer range for which there are few or no data (NRC, 1987; Schulte et al., 2002). While TiO_2 has been used in commerce for decades, it has been increasingly formulated with a greater proportion of primary particle sizes in the sub-100 nm range. The dose-response data available for the TiO_2 risk assessment included subchronic (13-week) and chronic (104-week) inhalation studies. Benchmark dose (BMD) and BMD lower confidence limit (BMDL) estimates (Crump, 1984) were derived from the dose-response data of pulmonary neutrophilic inflammation or lung tumors in rats, using the total particle surface area retained dose in the lungs to normalize across particle sizes. The BMDL estimate was used as the POD in this risk assessment. Extrapolation of the animal doses to humans utilized data and models to account for the inter-species differences in