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Bridging the gap between exposure assessment and inhalation toxicology: Some insights from the carbon nanotube experience

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ABSTRACT

The early incorporation of exposure assessment can be invaluable to help design, prioritize, and interpret toxicological studies or outcomes. The sum total of the exposure assessment findings combined with preliminary toxicology results allows for exposure-informed toxicological study design and the findings can then be integrated, together with available epidemiologic data, to provide health effect relevance. With regard to engineered nanomaterial inhalation toxicology in particular, a single type of material (e.g. carbon nanotube, graphene) can have a vast array of physicochemical characteristics resulting in the potential for varying toxicities. To compound the matter, the methodologies necessary to establish a material adequate for *in vivo* exposure testing raises questions on the applicability of the outcomes. From insights gained from evaluating carbon nanotubes, we recommend the following integrated approach involving exposure-informed hazard assessment and hazard-informed exposure assessment especially for materials as diverse as engineered nanomaterials: 1) market-informed identification of potential hazards and potentially exposed populations, 2) initial toxicity screening to drive prioritized assessments of exposure, 3) development of exposure assessment-informed chronic and sub-chronic *in vivo* studies, and 4) conduct of exposure- and hazard-informed epidemiological studies.

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1. Introduction

As formulated in the National Academy of Sciences/National Research Council for risk assessment/risk management (NRC, 1983, 2009), risk assessment itself has four integral parts including hazard identification, dose-response assessment, and exposure assessment that lead to risk characterization. In schematic representations of the paradigm, the dose-response and exposure assessments contribute to the risk characterization but are oftentimes treated independently. For well-defined xenobiotics this would seem adequate, but with regard to the complexity of the physicochemical characteristics of

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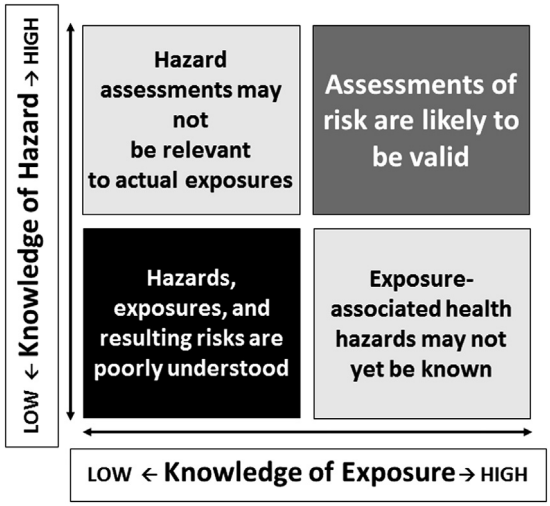

Fig. 1. View of the influence of knowledge-of-exposure and knowledge-of-hazard on the relevance and reliability of risk assessments. Adapted from the approach previously described (Hoover et al., 2014, 2015).

engineered nanomaterials, an integration between exposure and toxicological assessments is a necessity. An early review of nanotoxicology as an emerging discipline indicated that exposure assessment could be informative for dose-response assessments (Oberdorster, Oberdorster, & Oberdorster, 2005).

2. Risk and exposure assessments

2.1. Knowledge-of-exposure and knowledge-of-hazard influence the relevance and reliability of risk assessments

Risk, in reference to particle toxicology, is an evaluation of the relative hazard of a material taking into account the exposure, or more specifically, the delivered dose. If little to no knowledge exists for the hazard and exposure then the risk will be poorly understood. Having only thorough knowledge of the hazard without any exposure data will also limit the interpretation of the findings. Conversely, knowing all facets of the exposure with little hazard information provides no indication of the risk. Once both detailed exposure assessments are performed in association with properly designed and executed toxicological evaluations using relevant exposure metrics then assessments of risk are likely to be valid (Fig. 1). An additional need is for an understanding of the factors involved in transferring risk observed from animal toxicology studies to human exposures and health effects (NIOSH, 2013). Ideally, epidemiologic studies would be available as a source of hazard identification or dose-response information, or to corroborate risk projections from toxicology and exposure assessment studies and to serve, potentially, as an additional data source for risk assessment (Vermeulen et al., 2014).

2.2. A framework to integrate exposure and toxicity assessments for engineered nanomaterials

In the adaptive risk assessment paradigm, risk characterization arises from hazard identification and subsequent dose-response assessments as well as exposure assessments. With regard to engineered nanomaterial inhalation toxicology, a single type of material (e.g. carbon nanotube, graphene) can have a vast array of physicochemical characteristics resulting in the potential for varying toxicities. To compound the matter, the methodologies necessary to establish a material adequate for *in vivo* exposure testing raises questions on the applicability of the outcomes. The early incorporation of exposure assessment can be invaluable to help design, prioritize, and interpret toxicological studies or outcomes (Fig. 2). Initially there needs to be an identification and prioritization of hazards and exposed populations (Schubauer-Berigan, Dahm, & Yencken, 2011). The decision should be market-informed with a reasonable anticipation of potential toxicity. Toxicity screening then drives prioritized assessments of exposure. The exposure assessments provide information about routes of exposure, levels of exposure, and material characteristics. When feasible, there should be congruence among exposure metrics being used, or reasonable extrapolations from the workplace to toxicology studies may be unreliable. While surface area of particles has significant relevance when considering toxicological outcomes, particularly for engineered nanomaterials, there is no reliable way to measure this metric in the workplace for materials such as carbon nanotubes (Dahm, Evans, Schubauer-Berigan, Birch, & Deddens, 2013). In addition, a recent study of various graphite nanoplates showed an inverse relationship between surface area and toxicity.

To make informed interpretations between toxicological and exposure assessments the evaluation of the toxicant should be categorically representative. This is important for engineered nanomaterials that may have varying