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Exposure Assessment Approaches for Engineered Nanomaterials

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Products based on nanotechnology are rapidly emerging in the marketplace, sometimes with little notice to consumers of their nanotechnology pedigree. This wide variety of nanotechnology products will result (in some cases) in unintentional human exposure to purposely engineered nanoscale materials via the dermal, inhalation, ingestion, and ocular pathways. Occupational, consumer, and environmental exposure to the nanomaterials should be characterized during the entire product lifecycle—manufacture, use, and disposal. Monitoring the fate and transport of engineered nanomaterials is complicated by the lack of detection techniques and the lack of a defined set of standardized metrics to be consistently measured. New exposure metrics may be required for engineered nanomaterials, but progress is possible by building on existing tools. An exposure metric matrix could organize existing data by relating likely exposure pathways (dermal, inhalation, ocular, ingestion) with existing measurements of important characteristics of nanoscale materials (particle number, mass, size distribution, charge). Nanomaterial characteristics not commonly measured, but shown to initiate a biological response during toxicity testing, signal a need for further research, such as the pressing need to develop monitoring devices capable of measuring those aspects of engineered nanomaterials that result in biological responses in humans. Modeling the behavior of nanoparticles may require new types of exposure models that individually track particles through the environment while keeping track of the particle shape, surface area, and other surface characteristics as the nanoparticles are transformed or become reactive. Lifecycle analysis could also be used to develop conceptual models of exposure from engineered nanomaterials.

KEY WORDS: Exposure assessment; nanomaterials; nanoparticle

1. OVERVIEW

Products based on nanotechnology are rapidly emerging in the marketplace, sometimes with little notice to consumers of their nanotechnology pedigree. Uses of this emerging technology range from the mundane to those of great importance to society.[1–3] The wide variety of nanotechnology products in use and under development could result (in some cases) in unintentional human exposure to purposely engineered nanoscale materials via the dermal, inhalation, ingestion, and ocular pathway.[4,5] Intentional exposure to nanomaterials—such as targeted drugs—may result in nanomaterial transport to organs and tissues usually protected from the material in bulk form. Engineered nanomaterials may also be transported into the environment where additional exposure may occur.

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The emergence of nanotechnology-based consumer products signals an urgent need to examine pathways of exposure to products of nanotechnology and quantify these exposures with toxicologically relevant metrics. Conventional exposure monitoring techniques may not adequately characterize nanomaterials. Analysis of traditional exposure pathways may not provide adequate data for risk characterization and, ultimately, risk management.

Not all nanotechnology-enabled products will lead to exposure, and not all exposures will lead to new risks. For instance, modern semiconductors that are fabricated at the nanoscale are a clear product of nanotechnology, but their use is unlikely to lead directly to nanomaterial exposure. Materials and products of most concern are those with the potential to release nanoscale materials into the environment that may lead to biologically relevant exposure.[6] These include aerosols, powders, and suspensions of engineered nanometer-diameter particles (nanoparticles) and micrometer-scale agglomerates or aggregates of these particles. Products that may release nanostructured materials into the environment during manufacture, use, and disposal are also potentially of concern, if the released material has a biologically active nanostructure.[6]

Exposure assessment plays a critical role in a risk assessment by providing an estimate of the contact with a chemical, physical, or biological hazard by a receptor. The mere presence of a hazard is not enough to support a finding of risk—without exposure to the hazard, the human or environmental receptor is not directly at risk. Estimation of exposure requires that the unit of measurement match the toxicologically relevant aspects of the contact between the hazard and the receptor. Toxicologically relevant aspects of contact with a nanoparticle may include particle size, particle number, surface area, surface chemistry, charge state, degree of agglomeration, and shape.[7,8] Unique characteristics of nanomaterials that may become toxicologically relevant include the surface to mass ratio, strength, durability, conductivity, reactivity, solubility, and the ability to adsorb and carry other chemicals.[7]

Exposure should be measured in a manner consistent with the metric used to characterize the hazard of the nanomaterial. Multiple exposure events, as well as multiple exposure pathways, may need to be considered. Exposure measurements should be collected at the spatial and temporal scale relevant to the effect on the receptor. Exposure durations could range from short-term exposures measured in seconds or minutes to lifetime exposures measured in years and may include acute, subchronic, chronic, and lifetime exposures. A time-weighted average over the relevant duration may be more meaningful than the cumulative concentration for some classes of nanomaterials. Exposure of nonhuman organisms will vary based on habitat. Transfer of nanomaterials between trophic levels in the food chain must be considered when developing ecological exposure metrics.

A part of exposure assessment is describing the fate and transport of the hazardous material or agent through the environment. Transformations of the material into other chemical or physical forms may affect the distribution or toxicity of the material. Agglomeration of nanoparticles into larger structures is one example of a physical transformation that may affect transport, fate, and hazard.[6] The environmental persistence or durability of a chemical or physical form of the material should also be considered.

2. SPECIAL IMPLICATIONS OF NANOTECHNOLOGY FOR EXPOSURE ASSESSMENT

The characteristics of nanotechnology that make it such a powerful new tool also lead to novel mechanisms by which humans and ecological receptors may become exposed to some engineered nanomaterials. Not only does the size of engineered nanoparticles (for example) influence the distribution of these materials in the environment, but the shape, the coating, and other surface characteristics also control the fate and environmental transport of these materials.[9] Some nanomaterials exhibit quantum effects, the discontinuous behavior due to quantum confinement effects in materials with delocalized electrons,[10] which can lead to abrupt size-related changes in physical, chemical, and biological behavior at the nanoscale. Transport and fate in the environment could potentially be affected by quantum effects. Heterogeneous nanomaterials contain an internal material that differs from the external core shell,[8] potentially allowing the internal material to be transported through the environment more like the material in the outer shell.

While nanomaterials exhibit unique properties that may increase their hazard potential, the design of the engineered materials and their use in products may reduce the likelihood of exposure in some instances. Nanoparticles fixed within a medium will not move through the environment and will not

result in human or environmental exposure while they remain fixed in place.[10] It should be noted, however, that these particles may be freed from the medium in which they are embedded if the medium is physically or chemically altered, in which case exposure to the nanoparticles is possible.

Manufactured nanoparticles can be homogeneous in shape and size, unlike nanoparticles incidentally produced in the environment.[7] Thus, exposure to manufactured nanomaterials may result in high doses of materials with biologically relevant characteristics (e.g., high surface area, reactivity), even when the dose in terms of material mass is relatively low. While this disconnection between the biologically relevant dose and mass of material also applies to naturally occurring nanoparticles, engineered nanoparticles may exhibit this characteristic more strongly because their size and shape are the result of a controlled manufacturing process.

The unconventional behavior of nanomaterials makes it difficult to predict in many cases the distribution and effect of these materials in the human body or the environment. Manufactured nanomaterials may be transported along traditional exposure pathways (ingestion, dermal, inhalation) but in a manner unlike conventional materials.[7,9] Nanoparticles can be engineered to overcome the blood-brain barrier that conventional materials do not cross.[11,12] Some nanoparticles may possibly penetrate skin to greater degree than conventional materials and translocate within the body, although further research is needed to establish when and how this might happen.[13–15] Further studies have shown the potential of nanoparticles once in the dermis to localize to regional lymph nodes.[16] However, several studies have shown no evidence of nanoparticle penetration through healthy skin.[17–19] Some nanoparticles may cross from the lungs to the bloodstream following inhalation,[20] and can be transported along nerve cells, such as those connecting receptors in the nose to the brain.[21] Nanoparticles can efficiently be translocated through the epithelial cells and mucosal lining of the gastrointestinal tract.[22] They can also be translocated through other mucosa, such as the nasal lining, the vagina, the lungs, and the oral cavity.[7]

Nanoparticles may form aggregates or agglomerates that influence their transport in the environment and human body. Nanoparticles that form agglomerates may simultaneously act at the nano- and microscale as do some nanopowders.[23,24] Agglomeration may influence whether and to what extent organisms in the environment are exposed to the nanomaterial.

3. MODIFICATIONS TO TRADITIONAL EXPOSURE ASSESSMENT TO ACCOMMODATE ENGINEERED NANOMATERIALS

3.1. Developing Better Conceptual Models of Exposure

Life-cycle analysis could be used to develop conceptual models of nanomaterial exposure. Taking a life-cycle approach to problem formulation could guide development of likely exposure scenarios and identify potential receptors.[25] Monitoring data and model simulations could be used to refine and validate these conceptual models. Several frameworks incorporate a life-cycle approach into risk assessment.[26–28]

Case studies of existing nanomaterials, such as the Organization for Economic Cooperation and Development's (OECD) Working Party on Manufactured Nanomaterials or Environmental Protection Agency (EPA) case studies,[29,30] will also provide exposure data to develop conceptual models of exposure for new nanomaterials. These detailed case studies examining the fate and transport of nanomaterials in the environment, including exposure to humans through occupational and nonoccupational settings, will increase our understanding and aid in development of conceptual models of exposure. Because the EPA case studies use the comprehensive environmental assessment framework, they will inform conceptual models incorporating a life-cycle approach to risk analysis.[26]

3.2. Developing New Exposure Scenarios

New human and environmental exposure scenarios over the product lifecycle are necessary to consider changes in exposure during manufacture, use, misuse, and disposal. Exposure is often application-specific. Better understanding of the lifecycle of these new products will result in a more comprehensive analysis of human and environmental exposure.[3]

The exposed population will change over the product lifecycle. Workers are perhaps at the greatest risk of exposure to nanomaterials currently as new products are undergoing research and testing; eventually workers will also be exposed during

commercial manufacturing[6,31] and recycling. Occupational studies have focused on inhalation exposure, but there is a need for examining exposure through contact with skin (dermal sensitization) and ocular exposure as well as evaluating incidental ingestion of the nanomaterial during manufacture.

Consumer exposure scenarios must address exposure pathways associated with the intended use of the product as well as misuse or use at higher application rates than anticipated.[3] Transformation of the nanomaterial and its persistence in the environment will be important consideration for consumer exposure. The type of exposure to the nanomaterial may change during its use. A nanomaterial incorporated in a textile product may result in dermal exposure, but may also include oral exposure to a child mouthing the cloth.[3] Washing, drying, and ironing textiles may alter the exposure to nanomaterials.[32] Exposure to light or abrasion may also affect the movement of the nanomaterials from the textile into other environmental media. Nanomaterials freed from the textile matrix may accumulate in dust.[33]

Nanomaterials in consumer products may become dislodged or freed from the product matrix during use or disposal.[3,32] Nanomaterials that are no longer contained in the product matrix may be transported throughout the environment or human body differently than the nanomaterials within the product, creating novel exposure scenarios. For example, nanomaterials originally in a textile matrix may be released into washwater during laundering[32] or nanomaterials used in packaging may present inhalation exposure if the nanomaterial is freed from the product matrix while the packaging is heated or torn off.[34]

Disposal of products containing nanomaterials creates the possibility of transport through the environment and possibly secondary exposure through contact with a waste stream. For example, nanosilver particles accumulated in biosolids at a waste water treatment facility, due to the laundering of textiles containing nanosilver, could be transported to aquatic environments or possibly to terrestrial systems if the biosolids are used as fertilizer.[32] The nanosilver particles from the textile could potentially be applied to a food crop if biosolids are approved for that use.

Exposure scenarios for nonhuman species must address nanomaterial transport through the environment following accidental release or disposal in a waste stream. The movement of nanomaterials in the food chain and potential bioaccumulation in some species will need to be examined through monitoring studies. At least one laboratory study demonstrated that quantum dots may be transferred to higher trophic levels in a simple aquatic invertebrate food chain.[35]

3.3. Collecting New Measurements of Exposure

Shape, surface area, surface chemistry, surface charge, size, chemical composition, crystal structure, porosity, and agglomeration state have all been suggested as characteristics to measure in nanomaterials.[7] In many cases, unconventional or new exposure metrics will be needed to characterize nanomaterials.[8] Exposure assessments based solely on the concentration or mass of a material in a particular environmental medium (food, water, air, soil, etc.) will not adequately measure exposure to functional or structural properties of the nanomaterial, in many cases. A standard set of potentially relevant measurements collected routinely during exposure studies is critical to understanding how nanomaterials are transported through the environment and to facilitate the development of mechanistically based exposure models.

The lack of clarity as to which characteristics are associated with the hazard potential of various nanomaterials creates uncertainty as to what monitoring measurements should be made. Monitoring studies are crucial to developing adequate exposure estimates, yet the tools to detect the products of nanotechnology are not well developed. In addition, without standard approaches to characterizing nanomaterials, it is difficult to compare studies and determine what attribute is associated with an adverse effect. Comparisons between studies using a standard set of measurements for 14 nanomaterials may soon be possible as results from the OECD nanomaterial testing program become available.[29]

The toxic effects of many chemical hazards can be related to the chemical concentration available in air, water, soil, food, a product, or a carrier or transport medium.[36] It is unlikely that a single measurement, such as concentration in an environmental medium, will adequately characterize the relevant attributes of many nanomaterials. The mass-based exposure assessment metrics traditionally used to evaluate exposure to chemical hazards (e.g., mg chemical/kg organism from *in vivo* toxicity studies) may miss the toxicologically relevant aspects of exposure to nanotechnology products.[23]

Since the mid 1900s, health-related measurements of airborne particles have been characterized in terms of the mass of material per unit volume of air. Yet as has been discussed, a number of studies have indicated that, on a mass for mass basis, certain nanometer-scale insoluble particles small enough to deposit in the alveolar region of the lungs may be more toxic than larger particles with a similar composition.[9,37–45] In addition, epidemiology studies relating ambient aerosol exposure to health conducted since the early 1990s have demonstrated an increase in health impact from particles smaller than 2.5 μm compared to those smaller than 10 μm on a mass for mass basis.[46–56] And while only limited data on the health impacts of occupational nanoparticles exist, there is some evidence to suggest that health effects associated with inhaling nanometer-scale particles generated in hot processes such as metal processing and welding are greater than mass-based exposures would indicate.[57,58]

Overall, it is clear that mass concentration will not always be a relevant exposure metric for engineered nanomaterials on its own. There is toxicology-based evidence that aerosol surface-area is an appropriate exposure metric for some low solubility particles.[40–42,59] However, it is clear that factors in addition to surface area also play a role, including surface chemistry.[41,60,61] There are also indications that in some instances particle number within specific particle size ranges may be important.[57] And recent studies on particle translocation within the body have further indicated a size-dependency on the likelihood of deposited particles moving from the respiratory system to other organs.[21,22,62]

This uncertainty makes it difficult to evaluate exposure to airborne nanostructured materials appropriately, whether in toxicity studies or whether while monitoring human exposure. Relying on mass concentration will clearly not be appropriate in all situations, and alternative measurement methods and approaches will need to be used. Selecting the right approach for a given situation is not trivial though, and is compounded by a general lack of suitable equipment for making such measurements.

Measurement methods are currently available that allow nanoparticle characteristics to be evaluated. These include techniques such as electron microscopy, particle mobility analysis, dynamic light scattering, and field flow fractionation.[8,63,64] Yet many of these techniques are associated with specialized research tools, and are not well suited for routine exposure monitoring. In the long run, practical exposure monitoring instruments will be needed that provide relevant information on airborne and waterborne nanoparticles and nanostructured particles, in an efficient and cost-effective way.[65] In the near-term, a universal aerosol monitor has been proposed for monitoring airborne exposures, which is capable of providing personal exposure measurements to all three metrics—number of particles in air, mass, and surface area—simultaneously, and is sufficiently inexpensive to encourage widespread use.[8,65] While not covering all relevant metrics, such an instrument would enable many potentially relevant metrics of exposure to be tracked.[8]

The identification of biomarkers associated with exposure to various types of nanomaterials will allow monitoring of exposure of internal dose. If biomarkers are developed, screening for past exposure in the population could occur. Reconstruction of past exposure events may be possible following detection of biomarkers in an individual. Guidelines for the interpretation of the biomarkers will also need to be developed although the basic requirements of stability and specificity apply here as they do in conventional biomarkers. The development of such biomarkers for engineered nanomaterials could be informed by the radiological exposure research and the identification of stable intrachromosomal biomarkers of past exposure to ionizing radiation using multiband fluorescence *in situ* hybridization techniques.[66]

3.4. New Fate and Transport Models

Models that only account for chemical concentration in the environment will be inadequate for nanomaterials if the environmental behavior or the relevant toxicological attribute of the nanomaterial is related to particle size, surface area, particle shape, porosity, or surface chemistry. Before much progress can be made refining existing fate and transport models or developing new ones, the processes that influence the fate and transport of nanomaterials will need to be elucidated.

Modeling the behavior of nanoparticles may require new types of exposure models that individually track particles through the environment while keeping track of the particle shape, surface area and other surface characteristics as the nanoparticles are transformed or become reactive. Some existing particle-based models may provide an approach that could be modified to address the movement of engineered nanomaterials through different types of

environmental media. These models include those that estimate the transport and deposition of air pollutants[67–69] and other nonintentionally produced nanoparticles, such as those generated by forest fires,[70–73] volcanoes, dust storms, diesel exhaust,[74] and other traffic pollutants.[75]

Some fate studies suggest that nanoparticles do not follow traditional particle dynamics established for larger particles.[76,77] The fate and transport of nanoparticles in natural environments may be influenced by the presence of natural organic matter that allows nanoparticles to deaggregate in model aquatic ecosystems.[78,79] Models to estimate the movement of particles that have formed agglomerates are under development.[80] Particle-based models for biofilm development may also be useful in modeling nanoparticles in the environment.[81]

3.5. Developing an Exposure Metric-Matrix to Organize Existing Information on Exposure

Identifying the most relevant exposure metrics for nanomaterials will be driven by the results of toxicological studies that determine the toxic mode of action of the engineered nanomaterials and by epidemiological studies that link adverse health outcomes with exposure to engineered nanomaterials. Until these studies have been conducted, especially the toxicological experimentation, there will be uncertainty over which exposure metrics are most appropriate. Organizing the existing studies into an exposure metric matrix that relates likely exposure pathways (e.g., dermal, inhalation, ocular, ingestion), measurements of physical and chemical characteristics (e.g., number of particles, mass, size distribution, charge, etc.), and biological responses in the study organism would highlight data gaps. Synthesizing information across categories of nanomaterials—single-walled carbon nanotubes, multiwalled carbon nanotubes, metals, and oxides, for instance—could lead to identification of patterns of biological response associated with levels of one or more of the exposure metrics and the possibility of extrapolating to other nanomaterials sharing similar physical or chemical attributes. The matrix could be expanded to include different life stages of humans or other organisms. Nanomaterial characteristics that are not easily measured outside the laboratory, but shown to initiate a biological response during toxicity testing, indicate the need for new exposure monitoring techniques.

4. MODIFICATIONS TO RISK MANAGEMENT AND COMMUNICATION DUE TO NEW EXPOSURE ASSESSMENT METHODOLOGIES FOR ENGINEERED NANOMATERIALS

Risk management and risk communication will require a clearer understanding of the mechanisms through which humans and environmental receptors could be exposed to engineered nanomaterials. Stakeholders will require explanations of the new exposure metrics used. Interpreting the meaning of new exposure metrics will present a challenge for risk communicators. It is likely that no single metric will completely characterize exposure. Risk managers and communicators will need to explain why there are not uniform metrics for all types of nanomaterials. Risk managers should understand the classifications and categories of nanomaterials and how they relate to likely exposure by humans or in the environment.

Risk managers will no longer be able to rely only on estimates of the mass concentration of a material in the environment but will need to consider other metrics depending upon the type of nanomaterial at issue. Familiar exposure estimates that risk managers currently rely upon to regulate chemical hazards—daily dietary intake and permissible exposure concentrations[31]—will need to be augmented with new exposure estimates.

As more diverse nanotechnology-based products appear in the marketplace, there is an increased likelihood that humans will be exposed to multiple types of engineered nanomaterials. The different types of nanoparticles may be transported along the same environmental pathways and use the same routes of entry into the human body. Or it may transpire that engineered nanoparticles with different physicochemical characteristics may follow completely different exposure pathways. Risk managers will need to examine exposure to multiple types of nanoparticles. An appropriate regulatory metric will be needed synthesizing the cumulative and aggregate exposure to multiple nanomaterials. Evaluating a series of alternatives to reduce exposure to multiple nanomaterials and environmental media may require the development of more complex decision analysis tools for the risk manager.[82,83]

Coordination between the federal agencies will become increasingly important to federal risk managers. The lifecycle of nanomaterial products will cause these products to fall within the purview of

many different agencies as the products are manufactured, packaged, distributed, purchased by consumers, and eventually disposed of or recycled. Risk mitigation will require coordination between agencies that may otherwise not have interactions with one another.

5. PRIORITIES FOR FUTURE RESEARCH

Monitoring of nanomaterials in the body and environment is critical. Before more refined exposure models can be constructed to estimate fate and transport, basic research is needed to increase our understanding of the processes controlling the distribution of these materials in the environment. A recent pilot study suggesting that some carbon nanotubes can induce precancerous growths similar to those preceding mesothelioma following asbestos exposure highlights the urgent need to collect more data on real-world exposures to nanomaterials.[84] An exposure baseline for nanomaterials will be useful in assessing cumulative exposure from existing materials.

Developing monitoring tools to measure nanomaterials in the environment across the spatial and temporal scales relevant to risk assessors is a top priority.[65] Uncertainty over what to measure may have resulted in few monitoring and exposure measurements—this trend will have to be reversed.[85] Standardizing the measurements collected during monitoring will advance our understanding of exposure.[86] An uncoordinated set of monitoring measurements does not facilitate comparisons between studies, exposure pathways, or nanomaterials. More complex monitoring devices will be needed in the future. In the short term, there is a need to develop indirect measurements of the appropriate exposure metrics when these metrics are not directly measurable with today's monitoring equipment.

Some pathways of exposure to engineered nanomaterials are poorly studied. Exposure through ingestion will be the most common pathway for exposure to nanomaterials in water, food, food additives, dietary supplements, and some drugs, yet there are few studies addressing this pathway.[87] Foods and dietary supplements containing engineered nanomaterials are not common.[88] The migration of engineered nanomaterials from packaging or food contact materials to food is another potential contributor to the ingestion exposure pathway. Characterizing nanomaterials in biological matrices, such as foods before and during digestion, may require new detection and quantification methods.

Incidental ingestion of nanomaterials from the skin via hand-to-mouth activity and from swallowing nanomaterials that have been cleared from the respiratory tract via mucociliary escalator is also poorly studied.[89] Hand-to-mouth ingestion exposure is just beginning to be addressed, as shown in the recent EPA case study on nanoscale titanium dioxide in water treatment and sunscreen.[30] Federal agencies are not devoting many resources to this important exposure pathway.[85,90–92] Exposure to nanomaterials via the inhalation pathway has been more thoroughly studied than exposure via other pathways,[80,93] but even with this pathway there is a need for more real-time monitoring studies.

Many exposure scenarios involving consumer products lack monitoring data. An important data gap is monitoring chronic exposure to nanomaterials through contact with consumer products that have a long expected use period, such as textiles.[3,91]

Implementing life-cycle approaches will require research on exposure to nanomaterials during recycling and disposal. Recycling of nanomaterials may result in new occupational exposures as materials are reformulated or recovered from the product matrix. Disposal of nanomaterials may result in environmental exposure if the nanomaterials are released from the disposal site.

By the U.S. government's estimate, only 2% of annual federal research and development projects addressing nanotechnology environment, health, and safety impacts are directed toward exposure assessment.[91] This has been criticized as being an overestimate of the true funding levels by some.[94] The paucity of exposure assessment studies currently being funded and the lack of standardization in monitoring are preventing risk assessors from conducting comprehensive and timely assessments of nanomaterials.

6. CONCLUDING REMARKS

Exposure assessment of nanomaterials will continue to be an exciting area of development within risk assessment. Although the unique characteristics of nanomaterials will continue to provide measurement and modeling challenges, the exposure assessor's toolbox is not empty. Much progress can be made by building on existing tools rather than designing an exposure assessment protocol *de novo*. Mass concentration is not likely to be the most

important metric for assessing exposure in many cases, but it can be used as a starting point to be used with other metrics as they are developed. Mass concentration, in combination with other information, may be used to estimate some of the other more biologically relevant attributes of the nanomaterial, such as surface area. Organizing the exposure measurements from existing studies by nanomaterial, measurement type, pathway, and effect on the organism will highlight data gaps and may identify possibilities for extrapolation from one class of material to another.

There is a pressing need to develop monitoring devices capable of measuring those aspects of engineered nanomaterials that result in biological responses in humans. It is important to collect the measurements that can be made with today's generation of monitoring devices even if the exposure metric of interest can only be indirectly measured. Development of better monitoring techniques and exposure assessment methods for nanomaterials will advance the risk management of these materials.

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