OECD Alternative Testing Strategies in Risk Assessment of Manufactured Nanomaterials: Current State of Knowledge and Research Needs to Advance Their Use (Workshop Report)

Recommends alternative testing strategies in risk assessment of manufactured nanomaterials.

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WHAT IT DOES

The Organization for Economic Co-operation and Development (OECD) under the guidance of the Working Party on Manufactured Nanomaterials (WPMN) held a workshop, in 2016, for Alternative Testing Strategies in Risk Assessment of Manufactured Nanomaterials (MNs): Current State of Knowledge and Research Needs to Advance Their Use. The WPMN workshop published an online report on January 30th, 2017, to suggest alternative testing strategies as a replacement for animal testing models, which:

- Determine how MNs are similar to, and differ from, conventional chemicals – Adapt models to describe how MN toxicity profiles differ from their bulk counterparts and determine how current toxicity models can be applied to MNs;
- Harmonize testing procedures and reporting – Standards of Operation (SOPs) regarding MN characterization must converge among international standardizations and scientific disciplines, so that MN descriptors become uniform. Realistically, this harmonization may not be attainable, so selection of specific MN categories and characterization techniques will be key;
- Perform occupational and environmental exposure monitoring – Environmental sampling for MNs should accompany their increasing use in consumer products. Computational (in silico) and other simulation techniques, such as microfluidics, will be a critical component for enhancing detection limits and improving predictive accuracy;
- Develop appropriate MN groupings – Methods to group MNs based on bioactive and toxicity profiles, such as heat maps, structure activity relationships (SARs), and quantitative structure-activity relationships (QSARs) can be improved through data mining to create a hierarchy;
- Develop Adverse Outcome Pathway frameworks – Risk assessment strategies that use existing and novel in vitro data to associate potential chains of events to MNs based on factors, such as exposure pathways, particle transformations, and their endpoints;
- Consider complex conditions – Experimentation with MNs must shift from idealistic to realistic settings wherein transformations and lifecycles can be contextualized. Routes of exposure and corresponding human dosages should be identified with an emphasis on chronic exposure studies; and
- Advance MN safer-by-design principles – Preemptively incorporating risk assessment and MN prioritization into the decision-making process before use in products. Producers should account for lifecycle data and toxicity profiles developed by research to provide safer products.

Based on this OECD workshop, parties concluded that the current best means of MN alternative testing strategies are those that are based upon the Integrated Approaches to Testing and Assessment (IATA) and that must include:

- Evaluation and organization of existing data – The utilization of tools, such as Adverse Outcome Pathways (AOPs), which depict a chain of causally-linked events that result in adverse consequences.
- Measurement of physicochemical properties – Characterization of physical and chemical traits dependent on the nanoscale size of the MNs (e.g. crystal structure or electron localization).
- Evaluation of the lifecycles and biokinetics of MNs – Understanding how the determined physicochemical properties of MNs interact with biological and environmental molecules and particles.
- Selection of context-specific toxicity tests – Many of the current risk assessment approaches try to generalize physicochemical interactions to a variety of contexts. Rather, physicochemical interactions should be attributed to exclusive biological and

environmental contexts.
- Application of a weight-of-evidence analysis – Incorporating the findings of each exclusive study and prescribing preference to studies with stronger experimental designs. This is in contrast with previous approaches that only selected a subgroup of studies that were considered to have strong experimental design.

To this end, the meeting experts acknowledge and support the following:

- Research must account for several routes of exposure rather than solely focus on inhalation. Dosages are generally attributed to inhalation exposure, whereas other routes of exposure, such as oral or dermal exposure, are neglected.
- Experimental design must be adapted to account for physical conditions of the environment. For example, many studies do not account for light exposure, which can alter the photoexcitation of electrons to the MN surface and subsequent reactivity.
- The need to identify relevant, human-based dosages resulting from exposure is prevalent as toxicity profiles are commonly obtained for model organisms (e.g. zebrafish assaying). Furthermore, many bacterial-based assays are inappropriate for MN modeling because of the limited particle uptake.
- Studies will benefit from a multiple-models approach, wherein similar outcomes from different assays are tested. Additionally, the false positive rates of analytical methods must be improved in order to increase the statistical viability of in vitro and in vivo modeling.

This workshop determined that the benefits of alternative testing strategies include:

- Improving the relevance of toxicological data;
- Providing better models for computational predictions and microfluidic simulations;
- Prioritizing the use of nontoxic MNs in modern products;

Facilitating positive industrial decision-making actions and forging robust regulatory frameworks through accurate and precise diagnostics.

RELEVANT SCIENCE

Chemical substances with structures that measure approximately 1 – 100 nanometers (nm, 10^{-9} meters) along at least one dimension are often referred to as nanomaterials, or nanoscale materials, yet some experts contend that this definition is too narrow and propose a definition that is not based on a specific metric. In either case, the nanoscale size of manufactured nanomaterials greatly increases the surface area to volume ratios of the materials relative to their larger, bulk counterparts that result in novel physical phenomena. For example, quantum dots, sometimes referred to as artificial atoms, exhibit unique electronic and optical properties that are not observed in their bulk complements and are dependent on the enhanced surface area to volume ratio wherein electrons become confined. Novel effects that arise from manufactured nanomaterials make them strong candidates to advance products to overcome limitations of current technologies, particularly in relation to enhancing the mechanical properties of materials, providing rapid and accurate medical diagnostics, guiding drug delivery to improve therapeutic efficacy, and going beyond binary computation.

The properties and behaviors of nanomaterials are widely variable, modifiable, and remarkable and have spawned innovations that benefit societies and modern economies. Although nanomaterials are widely utilized in commercial products, nanomaterial reactivity is less widely studied and currently thus remains difficult to predict. Titanium dioxide nanoparticles serve as an excellent example. TiO_2 nanomaterials can absorb UV energy, and it is this property that has led to their usage in sunscreen products. Moreover, the resulting spike in chemical reactivity from energy absorption enables their use in self-cleaning products where the reactivity is used to degrade microbes and surface chemicals. However, how the chemical reactivity of TiO_2 nanomaterials interact with biological and environmental systems throughout their lifecycles, which are associated with each product's industrial niche (e.g. beaches or pools, industrial window cleaning products, milk whitening agent, powdered donuts, and solar cells) require much more study as do other manufactured nanomaterials. Thus, there is a need to evaluate effects of manufactured nanomaterials in multiple contexts and through a variety of techniques. For collected data to be applicable, fundamental research is tailored to reflect the complex

conditions to which manufactured nanomaterials that are contained within consumer products are exposed and subsequently released. To achieve this, scientists are interested in: collaboration and integration across scientific disciplines, well-developed nanomaterial classifications, advancing characterization techniques to be used in versatile environments, and designing environmentally - and clinically - relevant experiments. By accounting for these factors, members of the scientific community and policymakers can work together to better manage risk and safe use of manufactured nanomaterials.

WHY IT MATTERS

The ability to describe and predict nanomaterial properties as they progress through their lifecycles will be critical to how regulators allow and restrict fundamental nanomaterial research and subsequent translation into viable, nano-enabled products. Testing strategies that are currently used are inadequate for complete nanomaterial characterization, therefore making it difficult for experts and policymakers to create optimal policy frameworks for the progression of MN research. The nanostructure of MNs – if released from their nano-enabled products – ultimately undergoes physicochemical changes, such as agglomeration and the addition of surface molecules adsorbed from the environment, as the nanomaterials interact with minerals, microbes, and other organisms. Alternative strategies that consist of a battery of context-specific texts, will allow researchers to develop descriptions that enable researchers to determine adverse MN outcomes that can guide policies based on prioritized risks rather than conferring uniform risks that may lead to excessive regulation.

More than 23 billion dollars has been invested in nanotechnology research since the birth of the National Nanotechnology Initiative (NNI) in 2001. The NNI has outlined the goals of nanotechnology investment that are based on the premise that mature nanotechnologies can lead to a technological revolution. Much of this research has been at the university level, with technology transfer from the university to small businesses acting as one of the primary vehicles through which this technological revolution will occur. However, many small businesses will have strategic and monetary difficulties in assessing the risk and toxicological fates of their nanomaterials because excessive or unforeseen costs can be a burden. For this reason, the plan for alternative testing strategies in this workshop can direct technology transfer efforts at the small and large business levels through its suggestions for experimental designs. Additionally, the workshop can be used to direct governmental and academic toxicological research that can be used as supplementary information to business leaders and the regulators they work with. In conclusion, the proposed alternative testing strategies should help to minimize high risk outcomes and maximize society's investment into nanotechnology.

RELEVANT EXPERTS

Mark Wiesner, Ph.D., Professor in the Duke University Pratt School of Engineering, Director of the Center for the Environmental Implications of NanoTechnology (CEINT) Duke University.

Mike Hochella, Ph.D., University Distinguished Professor of the Virginia Tech Department of Geosciences; Director of the Virginia Tech National Center for Earth and Environmental Nanotechnology Infrastructure (NanoEarth); Affiliate Professor of the Center for the Environmental Implications of NanoTechnology (CEINT) Duke University.

BACKGROUND

The Organization of Economic Co-operation and Development (OECD) is a global entity that strives to harmonize national and international policies through collaboration wherein 35 different countries are represented. In 2006, the OECD established the Working Party on Manufactured Nanomaterials (WPMN) to study the current state of MNs active in industry and to assess their properties to guide nanomaterial-associated policies. This is intended to promote responsible development of nanotechnology-enabled products with an emphasis on the human health and environmental safety sectors. The WPMN has provided a series of workshops that aim to provide better frameworks for description and prediction of the toxic effects of nanomaterials as they interact with biological and environmental systems throughout their lifecycles. Because MNs have the potential to impact standards of living and quality of life through a variety of processes such as, catalysis in chemical production, energy efficiencies of devices, advanced

delivery of therapeutics, and through other means, their implementation will result in many complex chemical and physical interactions that can be context-dependent. Despite the growing scientific evidence of MN applicability for new industrial applications, efforts to define the risk of using MNs has been unable to parallel this growth. This deficiency can be attributed to the unique physicochemical properties of MNs, which make them difficult to analyze in dynamic environments. To exacerbate this problem, the potential for MN release from current products integrating MNs, and their specific lifecycles, remains largely unknown. Additionally, the unique properties of MNs makes them distinct from traditional, macroscale particles, thus rendering many of the analytical techniques used to describe MN toxicity ineffective. Thus, the present workshop was one in a series of workshops conducted that served to facilitate discussion through expert panels and to direct the development of effective policy frameworks, metrological standards, and assessment techniques that accompany the growth of the manufactured nanomaterials industry.

ENDORSEMENTS & OPPOSITION

The University of California Center for Environmental Implications of Nanotechnology seeks (CEIN) "to ensure the responsible use and safe implementation of nanotechnology in the environment", wherein this mission is pursued by furthering alternative testing strategy methodologies, such as high throughput screening for SAR explorations and the implementation of in silico techniques as decision-making tools. Andre Nel, a leader at CEIN and expert in nanotoxicological testing strategies, has stated that alternative testing strategies can provide a framework wherein "an initial decision tree for whether a material poses a hazard and whether it is necessary to conduct further tests", but fulfillment of this vision will require "transparency, a lot of discussion, and a patient step-by-step implementation of the program."

No opposition has been published about this subject by nanomaterials' scientists.

ORGANIZATIONS

Members and sponsoring agencies for this workshop were not explicitly included in the document; however, contributing references can be found here (p. 32-36)

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RECOMMENDED CITATION

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