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The Future in Nanosafety

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The last 20 years have brought significant progress in developing methods and knowledge about the safety of nanomaterials. Yet, sustained investment and focus is needed in service of responsible research and innovation of commercially relevant forms of nanomaterials. This requires dedication to safety assessments across the product life cycle by evaluating health and environmental impacts under realistic exposure conditions, improved focus on the next generation of advanced materials and technologies, and advancement of New Approach Methods (NAMs) that promote safer by design in the development of novel nanomaterials and nanoenabled technologies. Once a barrier toward regulatory and market acceptance, the relatively rapid efforts to address safety have reduced uncertainty sufficiently to allow commercial adoption of nanoenabled technologies. These innovations are often safer and more sustainable than currently used materials because they are specifically engineered for their properties.

> The current infrastructure and resources in nanosafety have been critical to advancing nanomaterial applications and now require adaptation toward the next generations of nanoenabled technologies that will refine methods, advance knowledge, and accelerate commercial adoption.

Through coordinated efforts of the National Nanotechnology Initiative (NNI) and related international coordination over the last 15 years, there has been deliberate focus and investment on advancing knowledge and methods about environmental health and safety of novel nanoscale materials. There is now significant infrastructure, networks, policy developments, a multidisciplinary international nanosafety community, as well as methods and a knowledge base from which to draw on to advance the responsible innovation of novel materials and advanced technologies (nanomaterials). Nanosafety research and policy efforts adapted existing approaches for conventional substances to address the nanoscale and particulate aspects of nanomaterials, setting the path for future investigations into more advanced materials and technologies. The rapid and real-time development of the field of nanotoxicology in step with developments in nanoscience is novel, unique, and replicable.

One key benefit of these international investments is the collaborations that have developed into an interdisciplinary field, creating some congruence toward requirements for safety demonstration and methods for more complex materials with advanced properties. The most pressing issues relate to:

(1) Evaluation of health/environmental risks across the product life cycle. Occupational exposures to airborne particulates are demonstrated to be highly controllable by conventional engineering approaches,[1] while downstream user exposures remain less investigated.[2] Safety research that addresses realistic exposures to nanomaterials beyond workplace inhalation in products is critical to commercial acceptance.

(2) The need for future orientation toward safety evaluation of more advanced materials. Current nanosafety research assesses the biological impacts of basic nanomaterial properties such as size, solubility, charge, and to some extent, shape. However, there is a need to address newer dose metrics.[3] Critical dosimetry and characterization metrics for assessing the safety of advanced materials, including active, self-assembled, and convergent (nano, bio, intelligent) technologies, are largely unexplored.

(3) The development of reliable and relevant NAMs that evaluate safety with reduced mammalian testing. NAMs will prove particularly useful for classes of materials with many variants, where differences in biological effects can be explored in faster and more efficient screening evaluations to advance concepts of safety by design. These alternative testing strategies rely on methods not yet validated for nanomaterials and in many cases do not yet have regulatory acceptance even for conventional materials. Investment is needed to advance the state of practice for NAMs in responsible research and innovation and regulation.

Critiques of the investments in safety research include: assertions that the resulting methods and extensive data sets are for relatively few materials, studies generally use unrealistically high concentrations and delivery methods, focus is mainly on inhalation exposure, and differences in sample preparation and testing protocols limit comparisons. These issues contribute to limitations for use in health and environmental risk assessment. In one analysis, ~45 materials were identified in ~1000 publications.[4] Most of the studies were not of adequate quality for risk assessment.[5] They did reveal, however, that with little exception, the nanomaterials entering commerce do not bring novel biological effects. Rather, the differences between nanoscale and conventional materials relate to the considerations of the nature and extent of exposure. That is to say that nanomaterials can behave differently than conventional substances in environmental media and within organisms (e.g., inhaled smaller particles move more deeply into lungs). Due to insolubility, nanomaterials may be more persistent or cause effects such as oxidative stress due to physical exposure. Thus, while there are numerous studies of nanomaterial safety, the data are of variable quality for risk assessment, yet have still provided significant insights.

One caveat is that the extensive number of publications and data sets generally exist for so-called first generation nanomaterials,[6] that is, passive nanomaterials and nanostructures. With the emergence of two-dimensional materials such as graphene, new metrics are developing. However, there is significantly less investigation on safety aspects in emerging areas of nanotechnology such as active structures, nanosystems, and convergent technologies. At the same time, funding agencies are shifting their focus away from nano to "advanced" materials and technologies, many of which build on nanoscience but may be manufactured using additive or biological approaches. While now more established after over 15 years, it is still early enough in the nanosafety realm that some fundamental questions remain unanswered; predictive models of biological behavior based on physical and chemical properties are not transferable from one type of material to the next, and continued focus and investment is required to develop nanoscale and advanced materials that are safer by design.

The current infrastructure and resources in nanosafety require adaptation toward next generations of nanoenabled technologies that will refine methods, advance knowledge, and accelerate commercial adoption. Critical challenges that need to be addressed include: more reliable and reproducible measurement techniques and standards, creating curated and publicly accessible data sets, especially from publicly funded projects,[7] increased focus on more realistic and less evaluated aspects of safety in the product life cycle, and especially, focus on advancing NAMs for regulatory and market acceptance.

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Notes

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REFERENCES

(1) NIOSH. Current Strategies for Engineering Controls in Nanomaterial Production and Downstream Handling Processes. DHHS (NIOSH) Publication No. 2014-102; U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health: Cincinnati, OH, 2013, https://www.cdc.gov/niosh/docs/2014-102/pdfs/2014-102.pdf.

(2) CPSC. Quantifying Exposure to Engineered Nanomaterials (QEEN) from Manufactured Products Addressing Environmental, Health, and Safety Implications. Workshop Proceedings. 2016, https://www.cpsc.gov/s3fs-public/qeenworkshopreport2016.pdf.

(3) Schmid, O.; Stoeger, T. Surface area is the biologically most effective dose metric for acute nanoparticle toxicity in the lung. *J. Aerosol Sci.* **2016**, *99*, 133−143.

(4) Kühnel, D.; Marquardt, C.; Nau, K.; Krug, H. F.; Paul, F.; Steinbach, C. Environmental benefits and concerns on safety: communicating latest results on nanotechnology safety research—the project DaNa 2.0. *Environ. Sci. Pollut. Res.* **2017**, *24* (12), 11120−11125.

(5) Krug, H. F. Nanosafety Research: Are We on the Right Track? *Angew. Chem., Int. Ed.* **2014**, *53*, 12304−12319.

(6) Roco, M. C.. Environmentally Responsible Development of Nanotechnology. In *Special Issues of Environmental Science and Technology*; Karn, B., Zhang, H., Eds.; ACS: 2004.

(7) Comandella, D.; Gottardo, S.; Rio-Echevarria, I. M.; Rauscher, H. Quality of physicochemical data on nanomaterials: an assessment of data completeness and variability. *Nanoscale* **2020**, *12*, 4695.

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