NATIONAL NANOTECHNOLOGY INITIATIVE ENVIRONMENTAL, HEALTH, AND SAFETY RESEARCH STRATEGY: 2024 UPDATE

A Report by the

NANOTECHNOLOGY ENVIRONMENTAL AND HEALTH IMPLICATIONS WORKING GROUP

SUBCOMMITTEE ON NANOSCALE SCIENCE, ENGINEERING, AND TECHNOLOGY

COMMITTEE ON TECHNOLOGY

of the

NATIONAL SCIENCE AND TECHNOLOGY COUNCIL

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The NSET Subcommittee created the Nanotechnology Environmental and Health Implications (NEHI) Working Group in 2005 to provide for exchange of information among agencies that support nanotechnology research and those responsible for regulation and guidelines related to nanomaterials and products incorporating nanomaterials; facilitate the identification, prioritization, and implementation of research and other activities required for development, utilization, and oversight of nanotechnology; promote communication of information related to research on environmental, health, and safety (EHS) implications of nanotechnology to other government agencies, non-government parties, and the general public; and adaptively manage the development and implementation of interagency nanotechnology EHS research strategies. More information is available at https://www.nano.gov/about-nni/working-groups/nehi.

About this Document

This document updates the 2011 NNI EHS Research Strategy. It describes the progress made in advancing the research goals set out in 2011 and strategic needs for ongoing, unmet, and new challenges for the responsible development of nanotechnology.

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Jay Vietas, NIOSH
Andrew R. Schwartz, DOE

NSET Subcommittee Executive Secretary:
Stephanie Mack, NNCO Staff

National Nanotechnology Coordination Office:
Branden Brough, Director
Quinn Spadola, Deputy Director

NSET Subcommittee Participants

Office of Science and Technology Policy (OSTP)
Branden Brough

Office of Management and Budget (OMB)
Danielle Jones
Thomas Libert
William McNavage

Consumer Product Safety Commission (CPSC)†
Joanna Matheson
Treye A. Thomas

Department of Agriculture (USDA)

Agricultural Research Service (ARS)
Jonn Foulk

Forest Service (FS)
Kenneth Zwick

National Institute of Food and Agriculture (NIFA)
Hongda Chen

† An independent commission that is represented on NSET but is non-voting

Department of Commerce (DOC)

Bureau of Industry and Security (BIS)
Kelly Gardner

International Trade Administration (ITA)
Tracy Gerstle

National Institute of Standards and Technology (NIST)
Stephanie Hooker
J. Alexander Liddle
Angela Hight Walker

Patent and Trademark Office (USPTO)
Tariq Hafiz
Matthew W. Such

Department of Defense (DOD)
Konrad Bussman
Jeffrey DePriest
Eric W. Forsythe
Mark H. Griep
Aisha Haynes
Michael Holthe
John Kamp
Akbar Khan
Antti J. Makinen
Heather Meeks
Brian D. Pate
Wooddy Miller
Victor Pugliano
David M. Stepp

Department of Energy (DOE)
Linda Horton
Tina M. Kaarsberg
Harriet Kung
Andrew R. Schwartz

Department of Health and Human Services (HHS)

Agency for Toxic Substances and Disease Registry (ATSDR)/National Center for Environmental Health (NCEH)
Custodio V. Muianga
Max Zarate-Bermudez

Biomedical Advanced Research and Development Authority (BARDA)
Sandeep Patel

Food and Drug Administration (FDA)
Anil Patri

National Institute for Occupational Safety and Health (NIOSH)
Vladimir V. Murashov
Jay Vietas

National Institutes of Health (NIH)
Piotr Grodzinski
David Rampulla
Luisa M. Russell

Department of Homeland Security (DHS)
Laura Parker

Department of the Interior (DOI)

Bureau of Reclamation (USBR)
Kenneth Nowak

Bureau of Safety and Environmental Enforcement (BSEE)
Candi Hudson

Geological Survey (USGS)
Jeffery Steevens

Department of Justice (DOJ)

National Institute of Justice (NIJ)
Greg Dutton
Kyle Fox
Mark Greene

Department of Labor (DOL)

Occupational Safety and Health Administration (OSHA)
Janet Carter

Department of State (State)
Andreea Paulopol
Kathleen E. Stevens
Maher Tadros

Department of Transportation (DOT)
David Kuehn

Department of the Treasury (Treasury)
Heather Hill

Environmental Protection Agency (EPA)
Annette Guiseppi-Elie

International Trade Commission (USITC)[†]
Elizabeth R. Nesbitt

National Aeronautics and Space Administration (NASA)
Tiffany S. Williams

Nuclear Regulatory Commission (NRC)[†]
Steve Ruffin

U.S. National Science Foundation (NSF)
Khershed Cooper
Fred Kronz
Richard Nash
Mihail C. Roco
Nora Savage
Birgit Schwenzer
Thomas Woodson

[†] An independent commission that is represented on NSET but is non-voting

Nanotechnology Environmental and Health Implications (NEHI) Working Group

NEHI Working Group Co-Chairs:
John Howard, NIOSH
Max Zarate-Bermudez, NCEH

NEHI Working Group Executive Secretary:
Rhema Bjorkland, NNCO Staff

NEHI Working Group Participants

Consumer Product Safety Commission (CPSC)
Joanna Matheson
Treye A. Thomas*

Department of Agriculture (USDA)
National Institute of Food and Agriculture (NIFA)
Hongda Chen

Department of Commerce (DOC)
International Trade Administration (ITA)
Tracy Gerstle
National Institute of Standards and Technology (NIST)
Vincent A. Hackley
Elijah Petersen
John Pettibone

Department of Defense (DOD)
U.S. Army Corps of Engineers Engineer Research and Development Center (USACE-ERDC)
Alan J. Kennedy
Igor Linkov
Benjamin Trump
Office of the Secretary of Defense (OSD)
Natalia Reyero Vinas

Department of Energy (DOE)
Anita Street

Department of Health and Human Services (HHS)
Agency for Toxic Substances and Disease Registry (ATSDR)/National Center for Environmental Health (NCEH)
Custodio V. Muianga
Max Zarate-Bermudez
Food and Drug Administration (FDA)
Anil Patri
National Institute for Occupational Safety and Health (NIOSH)
Vladimir V. Murashov
Jay Vietas
National Institutes of Health (NIH)
Piotr Grodzinski
Luisa M. Russell
Srikanth (Sri) Nadadur
Lingamanaidu (Ravi) V. Ravichandran

Department of the Interior (DOI)
Bureau of Reclamation (USBR)
Kenneth Nowak

Department of Labor (DOL)
Occupational Safety and Health Administration (OSHA)
Janet Carter

Environmental Protection Agency (EPA)
Annette Guiseppi-Elie
Iris Camacho-Ramos
Holly Mortensen

International Trade Commission (USITC)
Elizabeth R. Nesbitt

U.S. National Science Foundation (NSF)
Mihail C. Roco
Nora Savage
Thomas Woodson

* Former NEHI co-chair (September 30, 2024)

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Abbreviations and Acronyms[1]

2D	two-dimensional
3D	three-dimensional
AI	artificial intelligence
AOP	adverse outcome pathway
CEA	comprehensive environmental assessment
CEIN	Center for Environmental Implications of Nanotechnology (University of California Los Angeles)
CEINT	Center for the Environmental Implications of Nanotechnology (Duke University)
CNF	carbon nanofiber
CNT	carbon nanotube
COR	Community(ies) of Research
DIIG	Database and Informatics Interest Group (NEHI)
EHS	environment(al), health, and safety
ELSI	ethical, legal, and social implications
ENM	engineered nanomaterial
FAIR	findability, accessibility, interoperability, and reusability (data standards)
GD	guidance document (OECD)
IDEA	inclusion, diversity, equity, and access
IVIVE	*in vitro* to *in vivo* extrapolation (IVIVE)
ISO	International Organization for Standardization
JRC	Joint Research Centre (European Commission)
LCA	life cycle assessment
MGI	Materials Genome Initiative
MSI	minority-serving institution
nanoEHS	nanotechnology environmental, health, and safety
Nano WG	Nanotechnology Working Group (National Cancer Informatics Program)
NASEM	National Academies of Sciences, Engineering, and Medicine
NCI	National Cancer Institute
NEHI	Nanotechnology Environmental and Health Implications (Working Group, NSET)
NEP	Nanotechnology-enabled product
NIEHS	National Institute of Environmental Health Sciences (NIH)
NKB	NaKnowBase (EPA database)
NNC	National Nanotechnology Challenge
NNCI	National Nanotechnology Coordinated Infrastructure (NSF)
NNCO	National Nanotechnology Coordination Office
NNI	National Nanotechnology Initiative
NP	nanoparticle
NSET	Nanoscale Science, Engineering, and Technology (Subcommittee, NSTC)
NSI	Nanotechnology Signature Initiative
NSTC	National Science and Technology Council
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit

[1] See list of NSET and NEHI participants in the front matter of this report for abbreviations of participating agencies.

OWL web ontology language

PBPK physiologically based pharmacokinetic

PNC particle number concentration

PPP public-private partnership

QEEN Quantifying Exposure to Engineered Nanomaterials (CPSC/NNI conferences)

R&D research and development

RECR responsible and ethical conduct of research

RFI request for information

RRI responsible research and innovation

spICP-MS single-particle inductively coupled plasma mass spectrometry

STEM science, technology, engineering, and mathematics

TDME transport, distribution, metabolism, and excretion

TG test guideline (OECD)

TRUST Transparency, Responsibility, User focus, Sustainability, and Technology (data principles)

UFP ultrafine particle

VOC volatile organic compound

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Elijah Petersen
NIST
Lead Editor

Benjamin Trump
DOD/USACE-ERDC
Lead Editor

Rhema Bjorkland
NNCO
Staff Lead

Contributors:*

Souhail Al-Abed, EPA
Jason Borenstein, NSF
Branden Brough, NNCO/OSTP
Robert Burgess, EPA
Iris Camacho-Ramos, formerly EPA
Janet Carter, DOL/OSHA
Jason Delborne, formerly AAAS Science and Technology Policy Fellow, NNCO
Aaron Erdely, HHS/CDC/NIOSH
Doug Evans, HHS/CDC/NIOSH
Annette Guiseppi-Elie, EPA
Kay Ho, (retired), EPA
Huixiao Hong, FDA
John Howard, HHS/CDC/NIOSH
Annie Jarabek, EPA
Eileen Kuempel, HHS/CDC/NIOSH
Igor Linkov, DOD USACE-ERDC
Todd Luxton, EPA
Jeffrey Mantz, NSF
Joanna Matheson, CPSC
Morgan Miller, NASA
Jeff Morris, EPA
Holly Mortensen EPA
Custodio Muianga, HHS/CDC/ATSDR
Vladimir Murashov, HHS/CDC/NIOSH
Srikanth (Sri) Nadadur, NIH/ NIEHS
Vivian Ota Wang, NIH
Anil Patri, FDA
Elijah Petersen, NIST
Lingamanaidu (Ravi) V. Ravichandran, NIH/NIEHS
George Richter-Addo, NSF
Nora Savage, NSF
Paul Schulte, (retired), HHS/CDC/NIOSH
Keana Scott, NIST
Jordan Smith, DOE
Quinn Spadola, NNCO
Aleksandr Stefaniak, HHS/CDC/NIOSH
Anita Street, DOE
Treye Thomas, CPSC
Benjamin Trump, DOD USACE-ERDC
Jay Vietas, NIOSH
Natalia Vinas, DOD/OSD
Max Zarate-Bermudez, HHS/CDC/NCEH

* Affiliations as of September 2024

Executive Summary

The responsible development of nanotechnology is foundational to the National Nanotechnology Initiative (NNI). This focus, which includes research into the ethical, legal, and social implications (ELSI) of nanotechnology, led to the creation of the Nanotechnology Environmental and Health Implications (NEHI) Working Group within the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council. Through NEHI's leadership on behalf of the NNI, and with input from intensive stakeholder engagement, the NNI Environmental, Health, and Safety (EHS) Research Strategy was published in 2011. Building an EHS infrastructure to address the research questions identified in the 2011 strategy has led to significant advancements in understanding and proactively addressing the human and environmental impacts of engineered nanomaterials (ENMs).

This NNI EHS Research Strategy: 2024 Update continues the United States' leadership in advancing the responsible development of nanotechnology. This strategy lays out a comprehensive, integrated approach that builds on the initial 2011 strategy and reflects current opportunities to enable responsible nanotechnology innovation to flourish, benefiting human health, the environment, the economy, and society.

The knowledge gained since the 2011 strategy has led to the availability of tools, standards, and models to detect, characterize, and quantify ENMs; models of flow and uptake of ENMs through environmental and biological systems; and life cycle assessment methodologies. However, opportunities remain in areas such as translating the data from pristine nanoparticle studies to environmentally relevant materials and at chronic, real-world exposure levels. This work relates to identifying and modeling scenarios for emerging applications in areas like electronics, agriculture, and biomedicine. Additionally, the NNI EHS Research Strategy: 2024 Update highlights the importance of applying the existing nanotechnology environmental, health, and safety (nanoEHS) infrastructure built around engineered nanomaterials to understanding emerging nanoscale contaminants of concern.

As the nanotechnology landscape evolves and diversifies, utilizing the NNI's nanoEHS research to nurture innovation without creating unnecessary impediments will lead to the further commercialization of new technologies. At the same time, it is important to foster this conceptual framework of responsible development within the broader research community. Mechanisms to do so include educational initiatives that focus on ELSI, responsible conduct of research, environmental sustainability, green engineering design principles, and safe-by-design approaches.

Realizing the potential of engineered nanomaterials and nanotechnology-enabled products to solve pressing global challenges, while protecting human and environmental health, necessitates addressing unmet and new needs in nanoEHS through coordinated, collaborative action. Key areas for action in the strategy's 2024 update include:

- Addressing the remaining EHS knowledge gaps for engineered nanomaterials in commerce.
- Monitoring and evaluating emerging nanotechnology applications.
- Investigating emerging nanoscale contaminants of concern.
- Strengthening the collaborative informatics infrastructure.
- Increasing engagement with the international nanosafety community.
- Expanding public engagement in the responsible development of nanotechnology.

The NNI EHS Research Strategy: 2024 Update fosters collaborations, capabilities, and discoveries that address ELSI and catalyze the field's next decades of achievement. The challenges and opportunities outlined in this document build on the past two decades' advances and, as nanotechnology has grown from an emerging field to one that permeates much of engineering and the sciences, these lessons can also inform new areas of scientific progress.

Introduction

Nanotechnology, the science and engineering of matter at the nanoscale, has broad applications and underpins many fields, including artificial intelligence (AI), quantum information science, and advanced materials.[2] In 2000, President Clinton announced the National Nanotechnology Initiative (NNI), and in 2003, President Bush signed the law that authorized the NNI to coordinate and accelerate the multiagency U.S. government investment in nanotechnology research and development (R&D). Since then, the NNI has been the platform for U.S. government agencies to work toward a shared vision of a "future in which the ability to understand and control matter at the nanoscale leads to ongoing revolutions in technology and industry that benefit society."[3] The NNI has provided the framework for a collaborative nanotechnology R&D infrastructure to advance economic growth and prosperity, national security, and societal wellbeing. The NNI mission has been organized around the goals of supporting world-class R&D, commercialization, creating an accessible R&D infrastructure, public engagement and workforce development, and ultimately, the responsible development of nanotechnology. In 2011, the Obama-Biden Administration published an NNI EHS research strategy, after extensive public consultation. The Biden-Harris Administration is publishing this updated 2024 NNI EHS research strategy to guide nanotechnology R&D, which is foundational to the aims of the landmark CHIPS and Science Act to responsibly revitalize the semiconductor industry. The strategy also addresses the Administration's commitment to environmental justice, health equity, and the safety of emerging technologies such as AI.

From its inception, the NNI emphasized responsible development, including research to understand the ethical, legal, and social implications (ELSI) of nanotechnology. The NNI's nanotechnology environmental, health, and safety (nanoEHS) research and coordination activities were initially driven in part by concerns within the EHS community about the health implications of engineered nanomaterials (ENMs) as new forms of ambient ultrafine particles (UFPs), with aerodynamic diameters less than 100 nm. For example, early nanoEHS research studies indicated that size, surface area, surface chemistry, and other physicochemical properties might be predictors of particle toxicity.[4] The NNI was proactive in developing a research agenda to understand the safety implications of nanotechnology. The NNI, through the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council, established the Nanotechnology Environmental and Health Implications (NEHI) Working Group to coordinate these activities, among which were the publication of strategy documents in 2006 and 2008. Responding to recommendations to include public input in the EHS strategy, NEHI, on behalf of the NNI, launched an intensive process of stakeholder engagement, culminating in the 2011 NNI EHS Research Strategy.[5] The collaboration within U.S. government agencies and the nanotechnology community to develop the overall NNI strategy, and the NNI EHS strategy as an integral part of that, has been cited as a successful model for coordination across the federal R&D landscape.[6]

Progress in achieving the research needs set out in the 2011 strategy relied on building a durable EHS infrastructure. Measurement infrastructure, real-world assessment capability, and methods for robust risk analysis and decision-making are central elements of this infrastructure. This 2024 update of the NNI EHS research strategy is informed by the advances and evolution in nanotechnology since 2011. An

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2 https://www.nano.gov/2023BudgetSupplement

3 NNI Strategic Plan, 2021, https://www.nano.gov/sites/default/files/pub_resource/NNI-2021-Strategic-Plan.pdf

4 https://www.nano.gov/interagencynanoEHSresearchcollaboration

5 https://www.nano.gov/2011EHSStrategy

6 https://www.nano.gov/interagencynanoEHSresearchcollaboration

important goal for NEHI is that the revised strategy should continue to be a north star that guides research activity in the field, in the conduct of laboratory studies, and in the development of nanotechnology-enabled products, devices, and systems. Acknowledging that the United States led the way with the 2011 NNI EHS Research Strategy, NNI member agencies have built international collaborations and partnerships that have been important in the successes that are mentioned throughout Part A of this document. The NNI and the European Commission (EC) have collaborated since 2012 on building a transatlantic nanoEHS research community, the U.S.-EU NanoEHS Communities of Research (CORs).[7] The CORs are a unique platform for exploring transnational, cross-disciplinary approaches to responsible development and the application of nanotechnology and nanomaterials. As more and more nations invest in nanotechnology R&D, the United States will leverage its experience to provide continued leadership in the responsible development of nanotechnology as an area of global interest and focus.

Process of Developing the NanoEHS Research Strategy Update

NEHI's efforts to prepare this updated EHS research strategy began with the review of the 2011 NNI EHS Research Strategy. NEHI participants led focused interagency teams that evaluated the six core research areas described in the 2011 NNI EHS Research Strategy along with their respective 26 research needs and 120 sub-needs and ELSI considerations.

The review team also analyzed many other reports and scientific articles when developing this document. For instance, the team revisited a 2014 NNI report assessing progress toward the 2011 research needs[8] and another report published in 2017 summarizing highlights of federal nanoEHS research from 2014 to 2017.[9] The 2017 update provided select examples of important milestones and new knowledge gained from recent nanoEHS research and updated the 2014 progress review. NEHI also extracted the annual investments of NNI agencies in EHS research, as reported in the NNI supplements to the President's Budget (2019–2023).[10] The annual reports and metrics provided by agencies via the NNI supplements to the President's Budget have proven invaluable in documenting the strides made toward realizing the research goals outlined in 2011. This 2024 update to the NNI's EHS strategy shares key findings and observations, as well as the activities that made them possible, emerging from the NNI EHS research enterprise since 2011.

The process of revising the 2011 strategy has also relied heavily on expert input and perspectives on the NNI's progress, as well as recommendations for next steps. This process has involved significant collaboration and coordination across 13 federal agencies and between the interagency community and other interested and affected parties over many in-person and virtual meetings and webinars. The revision process also included input from the NNI's 2021–2022 EHS public webinar series, which solicited the perspectives of a diverse group of experts on progress made in nanoEHS research, especially with respect to the needs identified for the 2011 strategy's six core research areas.[11]

Beginning in August 2022, NEHI led the federal nanosafety community in developing a framework and timeline for drafting the revised strategy, including opportunities for public input and comments. In April 2023, the White House Office of Science and Technology Policy (OSTP) published a Request for

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7 https://us-eu.org/
8 https://www.nano.gov/2014-EHS-Progress-Review
9 https://www.nano.gov/Highlights-Federal-NanoEHS-Report
10 https://www.nano.gov/NNIBudgetSupplementsandStrategicPlans
11 https://www.nano.gov/PublicWebinars

Information (RFI)[12] seeking input from the public and the research community. A public meeting to gather comments was held on May 31 and June 1, 2023, with participation from academic institutions, private individuals and businesses, and the federal community. NEHI representatives leading the strategy refresh introduced each session and shared highlights of previous discussions on each of the six core research areas from the 2011 strategy. NEHI published the draft strategy on regulations.gov as a final point of public input.[13] The comments received from the EHS research community and the public are accessible in the regulations.gov docket. The comments, perspectives, and ideas gathered throughout this process have been thoroughly reviewed and informed this EHS strategy document.

Organization of the Revised Strategy

The 2024 update of the NNI EHS research strategy identifies the needs and priorities of the NNI community in order to align the responsible development of nanotechnology with economic and societal goals. The document is organized into the following major sections:

- Part A, "Progress toward the 2011 EHS Research Strategy Goals." This section assesses the progress and current research needs for the following six core research areas: (1) nanomaterial measurement infrastructure; (2) human exposure assessment; (3) human health assessment; (4) environmental hazard assessment; (5) risk assessment and risk management methods; and (6) informatics and modeling. Additionally, this strategy introduces a separate, ELSI-specific review to consolidate ELSI considerations across all the research areas.
- Part B, "Future Directions." This section addresses the scope of the research strategy going forward, expands on the unmet needs from Part A, adding specific actions to support the new needs and challenges identified in the first section. It also identifies topics and themes that require integrated approaches and cross-disciplinary strategies that merit prioritization for nanotechnology EHS research into the future.

[12] https://www.federalregister.gov/documents/2023/05/23/2023-10958/request-for-information-national-nanotechnology-initiative-environmental-health-and-safety-research

[13] https://www.regulations.gov/document/OSTP-POLICY-2024-0002-0001

Part A: Progress toward the 2011 EHS Research Strategy Goals

Nanomaterial Measurement Infrastructure

Overview

The need to conduct measurements of ENMs across all media increases the complexity in instrumentation design and handling of test materials. Real-time field measurement of exposure in complex media continues to require new instrumentation. In 2011, these goals were formulated as: (a) "develop measurement tools to detect and identify engineered nanoscale materials in products and relevant matrices and determine their physicochemical properties throughout all stages of their life cycles," and (b) "develop measurement tools for determination of biological response, and to enable assessment of hazards and exposure for humans and the environment from engineered nanomaterials and nanotechnology-based products throughout all stages of their life cycles." The 2011 strategy identified the following research needs to meet these goals:

1. Develop measurement tools for determination of physicochemical properties of ENMs in relevant media and during the life cycles of ENMs and nanotechnology-enabled products (NEPs).
2. Develop measurement tools for detection and monitoring of ENMs in realistic exposure media and conditions during the life cycles of ENMs and NEPs.
3. Develop measurement tools for evaluation of transformations of ENMs in relevant media and during the life cycles of ENMs and NEPs.
4. Develop measurement tools for evaluation of biological responses to ENMs and NEPs in relevant media and during the life cycles of ENMs and NEPs.
5. Develop measurement tools for evaluation of release mechanisms of ENMs from NEPs in relevant media and during the life cycles of NEPs.

Progress and Advances Since the 2011 EHS Research Strategy

One key area of advancement has been in the measurement tools for determining the physicochemical properties of ENMs in relevant media and during the life cycles of the particles themselves and NEPs. International collaborations and dialogue on documentary standards, which include test methods and definitions of agreed-upon terminology in a given field, led to the publication of prioritized standards needed for research and regulatory purposes in 2016.[14] Building on this and previous feedback, many standards have been published on a broad range of techniques through ASTM International Committee E56, International Organization for Standardization (ISO) Technical Committee (TC) 229, and the Organisation for Economic Co-operation and Development (OECD) Working Party on Manufactured Nanomaterials (WPMN).[15] A list of the key standard methods for toxicity testing has recently been published.[16] Many (standard) reference materials and representative test materials have been put forth by different national metrology institutes such as the National Institute of Standards and Technology

[14] https://gcrsr.net/downloads/GSRS16_Final_Report.pdf
[15] https://doi.org/10.1016/j.yrtph.2021.104885
[16] https://doi.org/10.14573/altex.2105041

(NIST), the European Commission's Joint Research Centre (JRC), and the National Research Council of Canada (NRC). These materials include particles of titanium dioxide (TiO_2), silicon, gold nanoparticles, silver nanoparticles, polystyrene nanoparticles, carbon nanotubes, cellulosic nanocrystals, and lipid nanoparticles.[17]

The ability to measure ENMs in relevant exposure media is a key objective for toxicity evaluation and life-cycle assessment (LCA). For metal and metal oxide particles, measuring the mass concentration of ENMs in a matrix is now well developed;[18] however, dissolution can make interpretation of these measurements more challenging in some matrices, such as soil, sediment, and biological tissues/cells. Two key advances since 2011 have been the broader usage of single-particle inductively coupled plasma mass spectrometry (spICP-MS) and microwave methods. The spICP-MS technique can measure individual, suspended metal, and metal oxide particles, achieve very low detection limits (parts per billion or parts per trillion), and is supported by a published documentary standard.[19] A second key advance in this area is the development of the microwave method to detect carbon nanotubes (CNTs).[20] This approach can detect CNTs in complex media such as biological tissues and soil. However, the type of CNT needs to be known to produce a calibration curve, and the instrumentation for the microwave method is custom-built and not broadly available. The development of the *in vitro* sedimentation, diffusion, and dosimetry (ISDD) model represents another key advancement.[21] The ISDD model enables various estimates of nanoparticle dose metrics, mass, number, or surface area, among others.

The capacity to measure transformations of ENMs in different media has also advanced. For example, OECD has published a test guideline (TG) 318 on the dispersion stability of ENMs and a guidance document (GD) 318 on testing the environmental behaviors of particles.[22] While TG 318 describes a method for testing the dispersion stability of particles, a corresponding TG for measuring dissolution is under development. Methods are available for testing speciation changes of inorganic ENMs in complex matrices at synchrotron user facilities,[23] but methods are not yet available for more widespread usage. Dispersion and dissolution testing for nanomaterials in various media remain challenging.

Numerous advancements have occurred in toxicity testing across the life cycle of ENMs and NEPs. An ecotoxicology testing guidance document (GD 317) was published, describing how to apply OECD ecotoxicity TGs for use with ENMs and providing clear recommendations on how to adapt these tests for ENM evaluation to reduce uncertainties in conducting ecotoxicity testing. In addition to the ISDD model described above, numerous advancements have occurred for testing the toxicity of ENMs using *in vitro* test methods. For example, an ISO TC 229 standard was published in 2017 on cell viability measurements after ENM exposure using submerged cultures.[24] This standard includes results from successful inter-laboratory comparison studies for two-dimensional (2D) adherent cells exposed to particles pipetted into the overlying cell media. Key sources of variability for *in vitro* inhalation toxicity

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17 https://doi.org/10.1016/j.yrtph.2021.104885
18 https://doi.org/10.1038/s41565-021-00889-1
19 https://www.iso.org/standard/82209.html
20 http://dx.doi.org/10.1016/j.scitotenv.2012.12.037; https://doi.org/10.1016/j.carbon.2012.05.022
21 https://doi.org/10.1038/nprot.2016.172; https://doi.org/10.1186/s12989-015-0109-1; https://doi.org/10.1186/1743-8977-7-36
22 https://one.oecd.org/document/env/jm/mono(2020)9/en/pdf; https://doi.org/10.1787/9789264284142-en
23 https://doi.org/10.1021/ac4024439; https://doi.org/10.1016/j.watres.2018.01.009; https://doi.org/10.1039/C6EN00095A; https://doi.org/10.3233%2FBSI-130041
24 https://www.iso.org/obp/ui/#iso:std:iso:19007:ed-1:v1:en

test systems have been recently described, potentially improving the inter- and intra-laboratory agreement of *in vitro* inhalation test results. [25]

Significant advancements in methods development also have occurred for *in vitro* exposure systems (flow-through or closed-box systems) to aerosolized ENMs. Significant advancements in biological test models for ENM exposures have been made. For example, numerous three-dimensional (3D) tissue constructs, composed of multiple cell types and designed to model human tissues, have been developed for different parts of the inhalation exposure route, as well as other tissues.[26] Substantial advancements also have occurred for organ-on-a-chip technologies that use microfluidics and cell culturing to model different organ systems and achieve human-relevant results.[27] Efforts to identify the steps in adverse outcome pathways (AOPs) have begun to uncover the progression from key initiating events to adverse outcomes in humans.[28] Multiple *in vitro* methods that test different steps along an AOP can potentially be used in combination to yield similar information as could be obtained during *in vivo* testing. While not specific to ENM evaluation, frameworks have recently been provided to increase the technical quality of, and the scientific confidence in, *in vitro* test methods.[29]

Another key measurement need is the evaluation of particle release from NEPs during their life cycles. The NanoRelease project, supported by U.S. and Canadian government agencies as well as industry and nonprofit organizations, focused on the development of nanomaterial release measurement methods.[30] A pilot inter-laboratory study on nanomaterial releases from composite materials found that particle concentration data were consistent across analytical methods, but inter-laboratory particle concentration and temporal correlation was poor.[31] At the end of the project, NanoRelease collaborators concluded that "much of the current research literature regarding hazard of nanomaterials does not appear to be related to what is being emitted from actual uses of nanomaterials."[32] ISO TC 229 provides information about the methods that can be used to assess release from polymer nanocomposites.[33] Standards also have been published in ASTM E56 related to measuring release of silver nanoparticles from textiles.[34] CPSC, EPA, FDA, and NIOSH have collaborated on the measurement of silver nanoparticle release from consumer products and food contact materials.

Ongoing Research Needs

Significant measurement challenges raised in the 2011 NNI EHS Research Strategy remain largely unresolved for nanomaterials in complex biological and environmental media. Metrology tools and protocols for quantification of nanoparticle physicochemical parameters—such as dissolution rate, surface reactivity, and particle number concentration in real-world samples—still require development. For example, dissolution in biological media remains a subject of interest and inquiry, which, if resolved, could help predict toxicity in a manner aligned with Integrated Approaches to Testing

25 https://doi.org/10.1021/acs.chemrestox.1c00080
26 https://doi.org/10.1021/acsnano.9b06860
27 https://onlinelibrary.wiley.com/doi/10.1002/smll.202003517
28 https://doi.org/10.1039/D1EN01127H; https://doi.org/10.1186/s12989-020-00344-4
29 https://doi.org/10.14573/altex.2205081; https://doi.org/10.14573/altex.2205081;
30 https://nanorelease.org/welcome-2/funding/
31 http://dx.doi.org/10.1016/j.carbon.2016.11.011
32 https://nanorelease.org/
33 https://www.iso.org/standard/73049.html
34 https://www.astm.org/e3025-22.html

and Assessment (IATA) ongoing at OECD.[35] Additionally, reference materials for emerging 2D and 3D nanomaterials need development. Characterization techniques to distinguish engineered nanomaterials from background particles of a similar size in food, tissue, and environmental samples remain inadequate. Improved analytical methods are also needed to probe nanomaterial transformations arising from synthetic processing, geochemical processes, biological interactions, photo-oxidation, and other aging processes across the life cycle.

Human Exposure Assessment

Overview

Human Exposure Assessment was identified as a core research area in the 2011 EHS Research Strategy. Specific goals for this research area were to: (a) "identify, characterize, and quantify exposures of workers, the general public, and consumers to nanomaterials," and (b) "characterize and identify the health outcomes among exposed populations to determine safe levels of exposures." The specific needs to address these goals were stated as:

1. Understand processes and factors that determine exposures to nanomaterials.
2. Identify population groups exposed to engineered nanomaterials.
3. Characterize individual exposures to nanomaterials.
4. Conduct health surveillance of exposed populations.

Progress and Advances Since the 2011 EHS Research Strategy

Since 2011, advancements in assessment of human exposure to ENMs represent significant milestones in nanotechnology research. The development of robust methods to characterize and quantify nanomaterials in a wide range of media and *in vivo* has resulted in the establishment of exposure limits for a wide array of ENMs.[36] The NNI, led by NIOSH, has developed sampling and quantification methods for workplace exposures, including in-the-field testing methods at more than 140 manufacturing and research sites.[37] Achieved through meticulous and comprehensive investigations with the use of tiered approaches to workplace evaluation over the past 15 years,[38] these activities have provided a comprehensive understanding of worker exposure, including mixed exposures.[39] This research has been critical in dispelling initial concerns regarding the potential hazards posed by ENMs and fostering confidence in their deployment across various applications. Survey data also indicate that engineering and administrative controls as well as personal protective equipment are being deployed in carbonaceous-ENM manufacturing facilities, indicating implementation of exposure controls and risk management measures.[40]

In addition to safety assurance, the research landscape has seen the progression of studies probing the factors that significantly impact the release of nanomaterials from products. These studies have

35 https://www.oecd.org/en/topics/sub-issues/assessment-of-chemicals/integrated-approaches-to-testing-and-assessment.html

36 https://doi.org/10.1080/17435390.2016.1262920

37 https://www.cdc.gov/niosh/nano/field/?CDC_AAref_Val=https://www.cdc.gov/niosh/topics/nanotech/field.html

38 https://doi.org/10.1080/15459624.2016.1167278; https://doi.org/10.1093/annhyg/meq015; https://doi.org/10.1093/annhyg/mer073; https://doi.org/10.1093/annhyg/mer110; https://doi.org/10.1093/annhyg/mes079; https://doi.org/10.1093/annhyg/mev020; https://doi.org/10.1016/j.envint.2018.04.004; https://doi.org/10.1186/s12989-018-0258-0

39 https://doi.org/10.1016/j.ijheh.2018.01.006

40 https://doi.org/10.1080/15459624.2017.1376252

contributed to aligning potential exposure with nanomaterials' toxicity. Research has been conducted on the exposure potential from diverse products, including fine and nanoscale powders,[41] treated lumber,[42] treated fabric,[43] plastics containing multiwalled carbon nanotubes,[44] food-contact materials,[45] and conductive films containing silver nanowires.[46] Researchers have meticulously characterized these releases, deriving vital insights into the characteristics of the materials encountered by exposed populations using NEPs. For example, international inter-laboratory studies have evaluated test protocols to measure the impact of weathering and environmental variables on releases from polymer matrices, providing insights into the extent to which releases from nanocomposites can be estimated from measurements of the neat (lacking fillers, reinforcements, or pigments) matrix.[47] Also, research has resulted in improved methods to quantify the release and characterization of ENMs from NEPs in occupational environments, including techniques to characterize and measure worker breathing zone samples.[48] These results and other research findings indicate limited release of unbound multiwalled CNTs.[49]

The rise of 3D printing has led to a significant focus on the potential hazards of exposure to materials and emissions from printing operations.[50] For example, NIOSH has taken a multipronged approach that includes (1) field studies of emissions in 3D printing workplaces as well as schools, makerspaces, and other indoor environments; (2) laboratory studies of factors that influence emissions in well-controlled settings; and (3) toxicology studies of emissions using *in vitro* and *in vivo* models. Field studies in workplace settings have enabled a better understanding of work practices in real-world environments. Research has demonstrated the effectiveness of engineering controls in managing the risk of exposure and has led to the development of novel engineering controls.[51] Research on the factors that influence the number, size distribution, and characteristics of emissions of particulate and volatile organic compounds (VOCs) from 3D printers is essential to informing risk assessment.[52] Recent studies on particulate and VOC emissions from 3D printers delivered similar exposure concentrations, allowing for a comparison of *in vitro* cell culture and animal model health effects. The study concluded that minimal respiratory and systemic changes were observed in animal models exposed to lower particle deposition than that delivered in the *in vitro* study.[53]

The Quantifying Exposure to Engineered Nanomaterials (QEEN) conferences brought together scientists from the United States and the European Union to understand the relationship between exposure and toxicity and discuss the importance of exposure in assessing risk and the need to develop

41 https://doi.org/10.1093/annhyg/mes060
42 https://doi.org/10.1016/j.scitotenv.2017.09.050
43 https://doi.org/10.1016/j.impact.2019.100160
44 https://doi.org/10.1021/acs.est.0c02015; https://doi.org/10.1016/j.impact.2023.100486
45 https://doi.org/10.1080/19440049.2018.1529437; https://doi.org/10.1080/19440049.2019.1654138
46 https://doi.org/10.1016/j.impact.2020.100217
47 https://doi.org/10.1016/j.carbon.2016.11.011; https://doi.org/10.1016/j.impact.2016.01.001; https://doi.org/10.1016/j.impact.2018.10.002
48 https://doi.org/10.1016/j.impact.2018.10.002
49 https://doi.org/10.1016/j.jhazmat.2017.06.057
50 https://doi.org/10.1093/annweh/wxaa146; https://doi.org/10.1016/j.jchas.2018.11.001
51 https://doi.org/10.1007/s11051-020-04844-4
52 https://doi.org/10.1080/15287394.2016.1166467; https://doi.org/10.1016/j.taap.2017.09.016; https://doi.org/10.1021/acs.est.9b00765; https://doi.org/10.1016/j.envint.2018.12.014
53 https://doi.org/10.1016/j.toxlet.2019.09.013; https://doi.org/10.1080/08958378.2020.1834034

robust exposure methods.[54] The exploration of these topics has led to the development of a platform that facilitates a holistic understanding of the potential risks associated with ENMs and the development of occupational safety measures and guidelines.[55] While pulmonary effects have been the major targets of studies of nanomaterial exposure via the inhalation route, cardiovascular effects have been a more recent focus and extend to printer-emitted nanoscale particles.[56]

The commercialization of a wide range of new technologies, including those incorporating ENMs into consumer products, also provides challenges for exposure and risk assessment. For example, additive manufacturing/3D printing is an emerging technology that allows small manufacturers and consumers to create a wide range of products. Some feedstocks that incorporate nanomaterials into the matrix are commercially available. Additionally, since the 2017 EHS highlights review, the greatest focus of federally supported researchers has been on printing with plastic feedstocks that emit UFPs, which might be derived from the feedstock plastic, into the indoor air environment.

Ongoing Research Needs

A comprehensive understanding of human exposure, and attendant risk, to all classes of nanomaterials, including incidental nanomaterials released to the environment (air, soil, and water) is still needed. Major gaps persist in identifying and modeling exposure scenarios for novel nanotechnology applications that have emerged over the past decade. These gaps include nanotechnology-enabled pharmaceuticals, agricultural products, coatings, sensors, and electronics. Biomonitoring tools to systematically assess exposed occupational, consumer, and environmental populations to NMs and NEPs are still lacking. Further work is needed in dosimetry, with a specific focus on developing robust methodologies for translating various exposures to internal doses in target organs and tissues. These methodologies must cover respiratory tract and systemic tissues and the development of *in vitro* to *in vivo* extrapolation (IVIVE) strategies. Developing these methodologies will allow improved integration in risk assessment approaches, enabling a more reliable assessment of potential health risks associated with nanomaterial exposure. This is linked to developing comprehensive databases for health surveillance and route-specific exposures.

Generating quality data on external exposure levels throughout product life cycles, as input for models, remains difficult due to limitations in monitoring methods. The Exposure through Product life COR of the U.S.-EU NanoEHS CORs is investigating the potential for indoor air cleaning devices for assessing exposures. Understanding and evaluating the exposure and risk associated with the evolving additive manufacturing/3D printing machinery, processes, and feedstocks is an important research goal going forward. Mixture toxicity approaches to evaluate combined exposures require further development and validation.

Human Health Assessment

Overview

In 2011, the NNI EHS Research Strategy for human health was “designed to systematically examine exposure, uptake, distribution, metabolism, excretion, and effects of nanomaterials in *in vitro* and *in vivo* models and relate their physicochemical properties to nanomaterial biological response at the

54 https://www.nano.gov/QEENWorkshopReport; https://www.nano.gov/qeen2presentations

55 https://doi.org/10.3109/08958378.2014.908987; https://doi.org/10.26616/NIOSHPUB2019116

56 https://doi.org/10.5271%2Fsjweh.3800; https://doi.org/10.1080/17435390.2017.1416202; https://doi.org/10.1186/s12989-019-0335-z

molecular, cellular, tissue, and whole-organism levels." The goals arising from this core research area were: (a) "understand the relationship of physicochemical properties of engineered nanoscale materials to *in vivo* physicochemical properties and biological response," and (b) "develop high-confidence predictive models of *in vivo* biological responses and causal physicochemical properties of ENMs." The 2011 NNI EHS Research Strategy listed six focal areas for human health research:

1. Identify or develop appropriate, reliable, and reproducible *in vitro* and *in vivo* assays and models to predict *in vivo* human responses to ENMs.
2. Quantify and characterize ENMs in exposure matrices and biological matrices.
3. Understand the relationship between the physicochemical properties of ENMs and their transport, distribution, metabolism, excretion (TDME), and body burden in the human body.
4. Understand the relationship between the physicochemical properties of ENMs and uptake through the human port-of-entry tissues.
5. Determine the modes of action underlying the human biological response to ENMs at the molecular, cellular, tissue, organ, and whole-body levels.
6. Determine the extent to which life stage and/or susceptibility factors modulate health effects associated with exposure to ENMs and nanotechnology-enabled products and applications.

Progress and Advances Since the 2011 EHS Research Strategy

Significant advancements have been made in the six research needs that were identified under these two major goals for the Human Health Assessment research area. Some of the major activities include: NNI agencies' intramural and extramural research support laying the foundation for exposure assessment and the effects on human health; NNI agencies providing a platform to fund extra-agency research through grants, interagency agreements, and contracts; and the development of EHS research infrastructures such as centers, scientists, and equipment.

Important progress has been made toward developing tools and approaches to predict *in vivo* human responses to ENMs.[57] Investments supporting these advances include the Nano Grand Opportunity (Nano GO) Grant Program consortium (supported by NIH's National Institute of Environmental Health Sciences, NIEHS) to promote/advance development of standardized protocols to link *in vitro* measurements to *in vivo* responses.[58] These and other efforts have led to progress in multiple areas: *in silico* (including computational modeling) and alternative methods for high-throughput screening, and developing alternative test strategies to reduce reliance on animal testing. Significant advancements have occurred in understanding the role of the surface coating of transformed ENMs in biological media (excluding dissolution of metal nanoparticles), and methods have been developed to determine toxicity of CNTs with differing physicochemical properties, carbon nanofibers (CNFs), and nanotechnology-enabled devices, for example, medical devices.[59]

Initial research efforts on the quantification and characterization of ENMs in exposure matrices and biological matrices were focused on development of quantitative tools to measure key physicochemical parameters such as size distribution and concentration of ENMs in biological systems.[60] These efforts are continuing to contribute to the development of the necessary tools and

[57] https://doi.org/10.1021/acsnano.9b02774
[58] https://www.niehs.nih.gov/research/supported/exposure/nanohealth; https://doi.org/10.1289/ehp.1306866
[59] https://doi.org/10.1007/s40089-017-0221-3
[60] https://www.futuremedicine.com/doi/10.2217/nnm.15.129

complement the recent focus on developing more specific exposure metrics related to this need.[61] In addition, activities toward development of biomarkers of exposure to ENMs (including more complex mixtures) are gaining interest, indicating that the need has expanded beyond quantification and characterization of ENMs and toward understanding the biological implications of such exposures and developing required tools for such analyses.[62]

Significant advancements have also been made in understanding of the relationship between the physicochemical properties of ENMs and uptake.[63] For example, an interdisciplinary program funded by NIEHS from 2010 to 2020 has facilitated characterization efforts among grantees who worked with a set of defined ENMs at each of their respective labs.[64] The work of the three NIEHS consortia—Nano GO, the NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR), and Nanomaterials Health Implications Research (NHIR) Consortium—led to the development of physiologically based pharmacokinetic (PBPK) models and hierarchical risk aggregation and dose-response *in vitro* models.[65] Similarly, another effort at the NSF-supported Center for Environmental Implications of Nanotechnology (CEIN) led to the development and application of zebrafish assays on diverse ENMs such as metal and metal oxide nanoparticles and CNTs.[66] This model fits between the traditional cell culture and mammalian models.

Progress in understanding the relationship between physicochemical properties and uptake by the human body also includes advancements in the following:

1. Using comparative physiological approaches and *in vitro* methods to examine differences in the bioavailability and the behavior of functionalized ENMs in the human body.
2. Developing alternative models to determine relationships between toxicity and physicochemical properties.
3. Developing state-of-the-art physicochemical characterization, determination of appropriate exposure protocols, and reliable methods for assessing ENM uptake and their kinetics in living organisms.
4. Understanding the fate and transport of ingested ENMs.
5. Establishing inhalation research in an academic-industrial manufacturing environment with the goal of quantitatively assessing the relationships between *in vitro* nanotoxicity and physicochemical characteristics of CNTs and CNFs.
6. Evaluating chronic pulmonary CNT exposure studies with longer post-exposure evaluation periods in multiple organ systems, including lungs, heart, brain, liver, spleen, and kidneys.

These developments in understanding nanomaterial human health effects are also useful for safety testing of nanomedicines, as reflected in the growth of nanomaterial and nanotechnology use in medical therapeutics and diagnostic applications.

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61 https://doi.org/10.1021/acs.est.6b00608; https://www.sciencedirect.com/science/article/abs/pii/S0003267015013677?via%3Dihub; https://onlinelibrary.wiley.com/doi/10.1002/jbio.201600125

62 https://pubs.rsc.org/en/content/articlelanding/2014/AN/C3AN01644G; https://pubs.acs.org/doi/10.1021/acs.nanolett.8b05172; https://www.nature.com/articles/s41467-022-31609-5

63 https://www.annualreviews.org/doi/full/10.1146/annurev-pharmtox-032320-110338

64 https://doi.org/10.1289/ehp.1206091

65 https://doi.org/10.3390/toxics10050232; https://doi.org/10.1021/acsnano.2c07312; https://doi.org/10.1021/acsnano.5b04420

66 https://doi.org/10.1002%2Fsmll.201202115

Researchers have made progress in understanding biological responses to ENMs at cellular, tissue, and whole-body levels since the publication of the 2011 strategy, but a complete understanding of the underlying modes of action that govern nanotoxicity is still needed. While still limited, there has been an expansion in the use of a variety of testing approaches to understand the link between the physical and chemical properties and biological responses of high-priority ENMs and newly developed ENMs.[67] Research has identified the toxicological response to ENMs leading to the identification of potential biomarkers that could be used in epidemiological studies.[68]

Over the past few years, there has been a significant research shift from investigating potential human and environmental exposures from nanotechnology-enabled consumer products and workplace exposures to better understanding the factors modulating ENMs' impacts. NIEHS has provided grant funding on topics such as for evaluating the effects on asthma and pregnancy outcomes. NIOSH has evaluated, and continues to evaluate, emissions from 3D printers and other additive manufacturing machines to understand the potential for exposure to workers, which will inform future epidemiological studies, as well as animal and *in vitro* toxicology studies.

Epidemiological investigations have confirmed the occurrence of a broad range of exposures to CNTs and nanofibers at manufacturing facilities.[69] These efforts represent first steps toward determining if exposures in the workforce have acute or long-term health effects. Even with the significant achievements made to date, continued leverage of the rich body of research on UFPs and ENMs can help both fields. For example, understanding the mechanism of toxicity of UFPs has aided the identification of plausible health effects of ENMs, while ENM inhalation studies have advanced understanding of the potential for UFP biopersistence and transport.[70]

Ongoing Research Needs

Several critical data gaps on nanomaterial impacts raised in the 2011 strategy remain. Acute and chronic toxicity data are still needed to understand short- and long-term risks of consumer exposures. Mechanistic studies that elucidate modes of action underlying biological response for novel 2D and 3D nanomaterials are lacking. Linking ENM properties to *in vitro* effects has been constrained by characterization limitations. Predictive models for extrapolating non-animal test results to humans remain inadequate due to insufficient validation. Additionally, assessment of vulnerable populations, developmental effects, and real-world low-dose co-exposures requires significant expansion. Epidemiological tools that can detect health signals from emerging applications with small, exposed populations are still absent.

67 https://tools.niehs.nih.gov/portfolio/index.cfm/portfolio/scienceCodeGrants/scode/78/topic/78
68 https://doi.org/10.1038/s41467-022-31609-5; https://pubmed.ncbi.nlm.nih.gov/26902652/
69 https://doi.org/10.1016/j.ijheh.2018.01.006; https://doi.org/10.1186/s12989-018-0258-0
70 https://doi.org/10.1016/j.jaci.2016.02.023; https://doi.org/10.1289/EHP424

Advances in Nanomedicine

There has been a gradual evolution of nanomaterial-based medical product development in recent years, with complex multifunctional and multimodal systems graduating from basic research into clinical development. Engineered nanomaterials integrated into medical products—e.g., drugs, vaccines, imaging agents, and devices—must undergo an extensive testing and a pre-market approval process, which includes appropriate quality control of the product, demonstrated pre-clinical and clinical safety, and efficacy assessment (Figure 1). Decades of research in this field with optimized nanomaterial carrier platforms, investigation into their physicochemical properties, and structure-activity and structure-function relationship studies, have provided insights into the safety of the medical products and the nanomaterial platforms. There have been many successes, including more than 77 drug products approved for clinical use so far and many others in clinical evaluation for therapeutic and vaccine applications. During the product development life cycles, the lessons learned from failures during the products' preclinical evaluations through federally funded research are resulting in novel products that have overcome prior pitfalls. Recent approval of lipid nanoparticle-based vaccines, such as those intended to provide protection against the SARS-CoV-2 virus, is a testament to the commercialization of products and devices based on decades of research and development arising from industrial and government investments.[71]

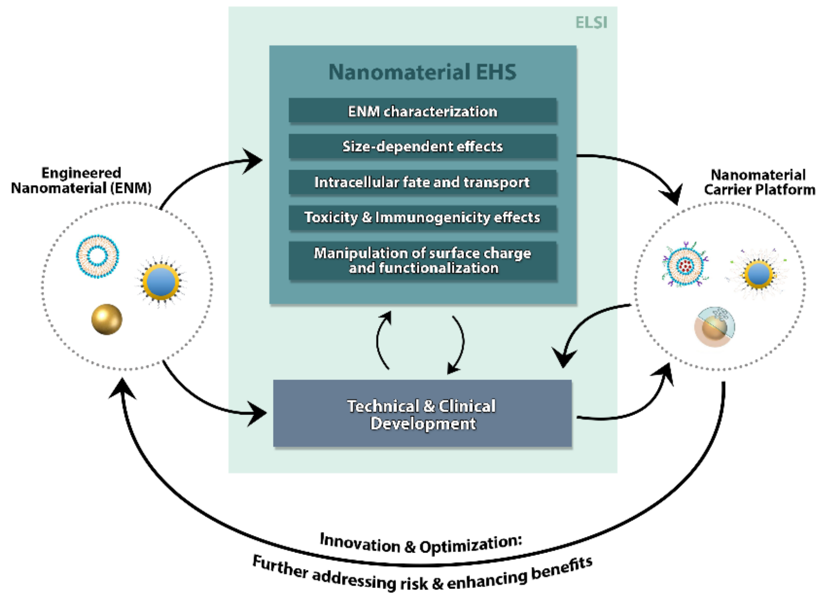

Figure 1: EHS research on the safety of ENMs in conjunction with the development of drug delivery platforms (nanomaterial carrier platforms) has accelerated advancements in nanomedicine. Graphics by G. Siharulidze (USACE-ERDC).

Environment

Overview

The EHS research within the Environment core research area examines the potential impacts of engineered nanomaterials on ecological receptors, such as fish, and their accompanying ecosystems. Concurrently, it delves into the fate, degradation, and transport mechanisms of these nanomaterials across diverse environmental media including air, water, soil, sediment, and tissues. The 2011 strategy outlined a single goal: to "understand the environmental fate, exposure, and ecological effects of engineered nanomaterials, with priority placed on materials with highest potential for release, exposure, and/or hazard to the environment." This goal was strategically addressed through five research needs:

71 https://doi.org/10.1007/s13346-021-00911-y

1. Understand environmental exposures through the identification of principal sources of exposure and exposure routes.
2. Determine factors affecting the environmental transport of nanomaterials.
3. Understand the transformation of nanomaterials under different environmental conditions.
4. Understand the effects of engineered nanomaterials on individuals of a species and the applicability of testing schemes to measure effects.
5. Evaluate the effects of engineered nanomaterials at the population, community, and ecosystem levels.

Progress and Major Advances Since the 2011 EHS Research Strategy

Substantial progress has been made in understanding the principal sources of ENM exposure in the environment. It has been determined that ENMs used in industrial processes and consumer products enter the environment primarily through wastewater streams.[72] In addition, the transformations of particles during product use have been evaluated. Examples include investigations of nanoparticle transformation during simulated usage and disposal of consumer products that contain the particles, the release of nanoparticles added to lumber, and nanoparticle release from commercially available sock fabrics during washing.[73] Advances have also been made in the detection of ENMs such as TiO_2 and graphene nanomaterials in the environment,[74] while models have been developed to estimate ENM release into the environment during different stages of product life cycles.[75] Members of the U.S.-EU NanoEHS CORs have conducted simulations and contributed to the development of predictive models of accidental environmental nanomaterial release.[76]

Progress has been made in understanding the key factors impacting the environmental transport of nanomaterials. Much of the focus of research has been on CNTs, other carbonaceous materials, and metals/metal oxides, with research shifting toward elucidating the mechanisms of fate and ecotoxicological effects of carbonaceous and metal nanomaterials.[77] Other topic areas have included chemical synthesis and characterization, nanomaterials as catalysts, ecotoxicity studies, and bioremediation. In addition to carbonaceous and metal nanomaterials, other materials studied have included quantum dots, nanomaterials released from 3D printing, carbon-metal nanohybrids, and nanomaterials in consumer products.[78] Environmental research at several NNI agencies is increasingly focused on nanoparticles formed by the degradation of plastics and tires to create micro- and nanoplastics and tire wear particles (see Part B Incidental Nanomaterials of Concern call-out box, p. 33).[79]

One key factor for the assessment of environmental impact is the rate of transformations. For carbon nanomaterials, substantial work has been performed to understand their photodegradation, biodegradation, and agglomeration.[80] This work has supported model development and model

72 https://doi.org/10.1016/j.watres.2015.03.003; https://doi.org/10.1021/acs.est.6b01910
73 https://doi.org/10.1039/C8EN00958A; https://doi.org/10.1016/j.scitotenv.2019.133669; https://pubs.acs.org/doi/10.1021/es7032718
74 https://doi.org/10.1039/C8EN01376D; https://doi.org/10.1016/j.jhazmat.2020.122335
75 http://dx.doi.org/10.1016/j.jclepro.2018.08.265
76 https://doi.org/10.1038/s41565-022-01290-2
77 https://doi.org/10.1029/2020RG000710; https://doi.org/10.1002/eap.1742; https://doi.org/10.1002/etc.4147
78 https://doi.org/10.1039/D1EN00712B
79 https://doi.org/10.1016/j.cotox.2021.09.004; https://doi.org/10.1038/s41565-022-01082-8; https://doi.org/10.1016/j.marpolbul.2019.06.061; https://doi.org/10.3389/fenvs.2022.1022697
80 https://doi.org/10.1039/C8EN01088A; https://doi.org/10.1016/j.carbon.2016.09.013; https://doi.org/10.1002/etc.2791

optimization for these particles, such as using the EPA Water Quality Analysis Simulation Program,[81] while other environmental fate models have also been published.[82] Additionally, recommendations have been set forward to harmonize testing media for environmental fate and toxicity measurements.[83] A framework has also been published related to environmental relevance for environmental fate and ecotoxicity studies.[84] Similarly, a decision-support framework was published for evaluating environmental health and safety concerns of ENMs.[85] Extensive research has been conducted using mesocosms by the NSF-supported Center for the Environmental Implications of Nanotechnology (CEINT),[86] which has provided insights into the likely environmental fate of ENMs after their release into the environment.[87] The development of the nanoinformatics knowledge commons has been instrumental in making progress in characterizing the spatial and temporal variability of nanomaterial fate and behavior in the environment.[88]

It is broadly recognized that ENMs will be transformed when released into the environment.[89] This transformation includes the formation of an ecocorona after adsorption of environmental macromolecules such as natural organic matter, heteroagglomeration with environmentally relevant particles, sedimentation, speciation changes, and the potential degradation of carbonaceous ENMs.[90] Some of these changes are known to reduce the toxicity of certain types of ENMs, for example, sulfidation of silver nanoparticles,[91] while others, such as sedimentation, can result in increased potential exposure to sediment organisms with reduced exposure to pelagic organisms.[92] Efforts have also focused on making intentional changes to an ENM or NEP to modify its fate or toxicity, such as coating silver nanoparticles with lipids to reduce their toxicity,[93] or silanizing a nanocellulose nanocomposite to reduce its biodegradability.[94]

Numerous studies (including several cited above) have been conducted to understand the potential effects of ENMs on individual species. As discussed in the Nanomaterial Measurement Infrastructure section, a significant advancement in this area with regard to testing for regulatory purposes was the publication of OECD GD 317 on applying OECD TGs for testing aquatic species for use with ENMs. These TGs were designed to test dissolved substances and to remove particulate substances prior to testing. Thus, their use for testing particulate substances required extensive deliberation of the many key factors for using them in a reproducible fashion. These factors include making a stable test material dispersion in the relevant media for the assay, determining how to maintain a consistent exposure concentration during the assay, and dosimetry and reporting considerations. One biologically relevant factor that can impact the environmental fate of ENMs is their potential for bioaccumulation. Reviews on the bioaccumulation potential of various engineered and incidental carbon nanomaterials suggest

81 https://doi.org/10.1016/j.impact.2018.11.001
82 https://doi.org/10.1021/es505076w
83 https://doi.org/10.1039/C9EN00448C
84 https://doi.org/10.1039/D1EN00162K
85 https://doi.org/10.1080/10408444.2017.1328400
86 https://ceint.duke.edu/node/85.html
87 https://doi.org/10.1039/C4EN00063C
88 https://doi.org/10.1016/j.impact.2021.100331
89 https://doi.org/10.1021/es300839e
90 https://doi.org/10.1002/etc.4147; https://doi.org/10.1029/2020RG000710
91 https://doi.org/10.1021/es2037405
92 https://doi.org/10.1002/etc.2529; https://doi.org/10.1002/ieam.1540; https://doi.org/10.1021/es502976y
93 https://doi.org/10.3390%2Fnano11061516
94 https://doi.org/10.1021/acsanm.8b01819

the potential for bioaccumulation and food chain transfer in unicellular organisms and plants and limited bioaccumulation in other multicellular organisms, for example, fish and *Daphnia*).[95] Strategies to improve the quality of bioaccumulation studies with ENMs in general have also been described at length.[96]

In addition to evaluating ENMs with individual organisms, it is important to understand their effects at the population, community, and ecosystem levels. Such effects have been investigated through the mesocosm experiments that have been conducted at CEINT, as described above. One area in which the impact of ENMs on communities has been investigated in depth is microbial communities.[97] For example, one study evaluated the impact of nanoparticle design on microbial communities through metagenomic analysis.[98] In addition, species sensitivity distributions have been constructed for many ENMs.[99]

The OECD report on the Safety Testing and Assessment of Manufactured Nanomaterials (the recommendations of which were adopted by the OECD Council in 2013 and amended in 2017)[100] showed much progress on how the safety testing and assessment of nanomaterials has been aligned with measures for the safety testing and assessment of traditional chemicals. That report also discussed developments of tools for testing and assessments and how existing regulatory systems were adapted to address nanomaterials. The report indicated that work that still needed to be done included developing and updating TGs and tools to support their implementation. The EU NanoHarmony Project (2020–2023) was designed to meet this latter need, i.e., producing scientifically reliable test methods and good-practice documents based on the interpretation of existing scientific knowledge and data.[101] Creating a framework and harmonized test methods for nanomaterials requires significant effort. This framework is coming to fruition with several reports and peer-reviewed publications that are now available. Also, several continuing activities under OECD's Working Party on Manufactured Nanomaterials will provide useful information for TG development and modification.[102]

Ongoing Research Needs

Despite the impressive progress of environmental research on ENMs, several research needs require further investigation. Environmental fate models that incorporate transformations, bioavailability, and food web transfers require additional development and validation. Whole-ecosystem studies tracking community impacts and recovery from ENM exposures are rare. Evaluation of synergies and antagonisms for nanomaterial mixtures is also rarely undertaken. Overall, progress has been limited in translating pristine nanoparticle lab studies to environmentally relevant conditions.

95 https://doi.org/10.1016/j.envint.2022.107650
96 https://doi.org/10.1039/C8EN01378K
97 https://doi.org/10.1039/D2EN00547F; https://doi.org/10.1021/es5031646
98 https://doi.org/10.1038/s41565-017-0029-3
99 https://doi.org/10.1021/acs.est.5b00081
100 https://legalinstruments.oecd.org/en/instruments/OECD-LEGAL-0400
101 https://nanoharmony.eu/
102 https://digital.csic.es/bitstream/10261/330149/1/NSC_N.pdf; https://doi.org/10.1186/s12302-022-00623-1; https://iopscience.iop.org/article/10.1088/2399-1984/abe560/meta

Informatics and Modeling

Overview

With rapid advancements in nanotechnology, the need to effectively manage the enormous volume of information produced has become critical. One of the core research areas identified in 2011 was Informatics and Modeling. Three broad focal goals were identified for this research area: (1) enhancements in data quality and availability; (2) expansion of theory, modeling, and simulation capabilities and development of computational models of ENM structure-property-activity relationships; and (3) creation of an interagency nanoinformatics infrastructure. These goals were formulated in 2011 into a single research need:

1. Develop computational models of ENM structure-property-activity relationships to support the design and development of ENMs with maximum benefit and minimum risk to humans and the environment.

A decade later, significant strides have been made in these areas. The U.S. nanoinformatics community has established significant international collaborative areas of work, including with the OECD.[103] At present, NEHI is exploring the different types and structures of nanoEHS data held by NNI agencies to facilitate access and sharing across the interagency community. There has been success in maintaining databases established at the time of and since the 2011 strategy. Examples include caNanoLab[104] and CEINT. NNI agencies agree that there is significant value in identifying mechanisms and approaches to reduce barriers to sharing data and to enhancing interoperability between nanoEHS databases, including the creation of formal interagency and interinstitutional agreements. Progress to date in nanoinformatics is summarized below.

Progress and Advances Since the 2011 EHS Research Strategy

Since 2011, the field of nanoEHS research has seen substantial improvements in data quality and availability. Progress can be gauged by the introduction of data standardization efforts, such as data standards that adhere to the principles of findability, accessibility, interoperability, and reusability (FAIR), and the establishment of sustainable data repositories. NNI agency efforts, coordinated through NEHI's Databases and Informatics Interest Group (DIIG), are working toward a common language approach, further improving data reproducibility and interoperability. Acknowledging the need for data sharing, DIIG participants are using diverse approaches that take advantage of a shift in nanomaterial- and nanotechnology-related nomenclature for data integration. This shift is manifest in the move from data integration, where datasets are linked in the same environment such as databases and repositories, toward the use of a "common language" like the Resource Description Framework (RDF).[105] The semantic or ontology mapping facilitated by RDF effectively overlays the data in the absence of common nomenclature. Additionally, this mapping can be used to query across datasets without integrating the datasets in a single repository. This shift in thinking is due to the several large, collaborative nanoEHS-focused projects in this area since 2011, both in the United States and

[103] https://one.oecd.org/document/ENV/CBC/MONO(2022)3/en/pdf
[104] https://cananolab.cancer.gov/#/
[105] https://www.w3.org/RDF/; https://ontogenesis.knowledgeblog.org/235

internationally,[106] as well as the consensus that nanotechnology-related data are unstructured, relatively abundant, rapidly generated, and dispersed across many different sources.[107]

The nanoinformatics community has grappled with the absence of a common, shared set of nomenclature standards for nanoEHS data. OECD has been working on an OECD harmonized template for various data types that would be supported by the International Uniform Chemical Information Database (IUCLID). Individual nomenclature efforts have been successfully defined for specific datasets (NSF-supported CEINT, EPA, international efforts).[108] However, while common vocabularies are being developed, the nanoinformatics community has not yet widely adopted or agreed on a "gold standard" for fundamental concepts and relationships. Data completeness, quality,[109] and interoperability[110] have been discussed. Steps toward the creation and curation of comprehensive databases of nanoEHS research findings include EPA's development of NaKnowBase (NKB), an initial publicly available version of a database on the environmental effects of nanomaterials.[111] The NKB collates EPA research data and corresponding tools that establish consistent nomenclature and automate semantic mapping based on an established ontologies project.[112] This project has led to efforts to promote interoperability of NKB with data from other NNI participating agencies, boosting data sharing and consolidation across various federal bodies. Figure 2 shows the data content contributed by each agency, corresponding databases used to store the siloed datasets, and a conceptual outline for data re-use. This simplified data flow was adapted from the EU-U.S. Nanoinformatics 2030 Roadmap[113] (see Figure 2 of the roadmap), whereby different data types are captured in databases and described using common descriptors, which can be fed into models and predictions. The roadmap is an example of a successful EU-U.S. collaboration, with members of the Databases and Computational Modeling COR participating in the production of the roadmap. NEHI has created the DIIG federal consortium to establish a standard protocol for the mapping of controlled vocabularies that is both consistent among the U.S. federal partner datasets and between U.S. and international efforts. DIIG will pursue plans to make these data available and will explore the feasibility and sustainability of a common infrastructure for federal nanoEHS data. In assessing progress in nanoEHS informatics and modeling since 2011, NEHI reviewed the NNI's activity in the following three areas:

Facilitating data integration and interoperability

The increase in nanomaterial-related research has led to an increase in nanotechnology-related databases, knowledge bases, web-based libraries, and registry repositories.[114] Nanoinformatics efforts in the United States have primarily been agency-specific, whereby datasets are not interoperable and, most often, not accessible outside of any given agency. Much work has been done, both manual and automated, to develop specific file formats and templates to achieve specific goals to improve data

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106 https://doi.org/10.1088%2F1749-4699%2F6%2F1%2F014008; https://doi.org/10.2147/ijn.s40722; https://doi.org/10.3762/bjnano.6.202; https://doi.org/10.1038/nnano.2015.338; https://doi.org/10.1002/ieam.1663

107 https://doi.org/10.5281/zenodo.1486012

108 https://ceint.duke.edu/research/nikc; https://doi.org/10.1038/s41597-021-01098-0; https://nanocommons.github.io/datasets/

109 https://doi.org/10.1039/C5NR08944A; https://doi.org/10.1038/nnano.2015.338;

110 https://doi.org/10.1016/j.impact.2017.11.002; https://doi.org/10.3762/bjnano.6.202

111 https://cfpub.epa.gov/si/si_public_record_Report.cfm?dirEntryId=354002&Lab=CPHEA

112 https://doi.org/10.1038/s41597-021-01098-0; https://doi.org/10.12688/f1000research.141056.1

113 https://zenodo.org/records/1486012#.W-zHK-j7TIW

114 https://doi.org/10.1016/j.impact.2020.100288

quality and enable data exchange,[115] but more work remains to make those improvements "fit for purpose," i.e., suitable in design to meet the intended purposes and objectives.

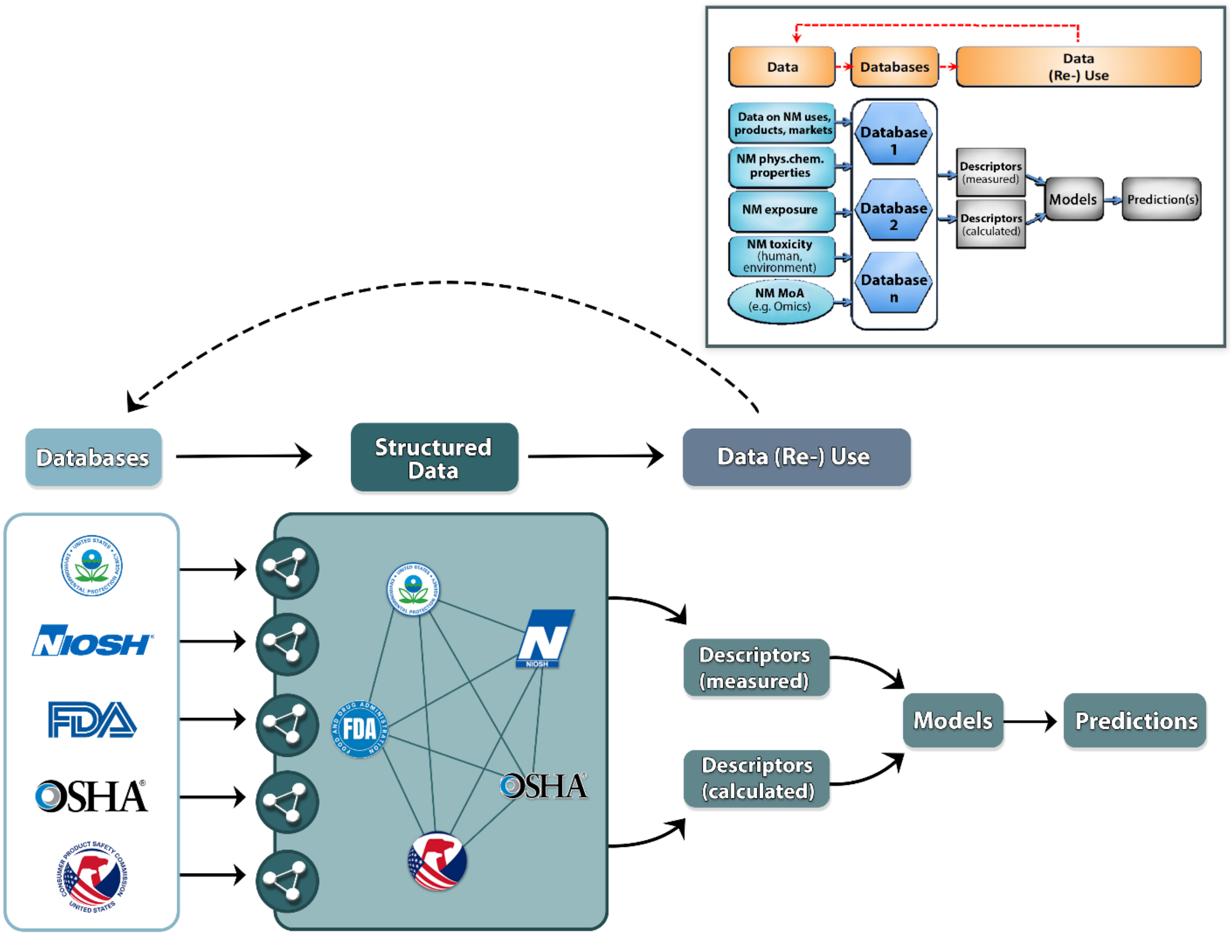

Figure 2: Individual agency databases (e.g., EPA's NaKnowBase) are available for computational modeling and prediction to support hazard and risk assessment and regulatory action for target NMs. Agency data are not combined by data type, as envisioned in the Nanoinformatics 2030 Roadmap (inset, upper right). The process of making the federal nanoEHS data machine actionable is a step towards a "virtual integration."[116] This would require databases to be standardized, structured, and interoperable for data sustainability and reuse, using approaches that include resource description framework (RDF) models, symbolized by the icon in structured data. Source: Holly Mortensen, EPA. Graphic editing by G. Siharulidze (Contractor, USACE-ERDC).

Many efforts to integrate databases, and to create knowledge infrastructures, have also occurred since 2011: physical infrastructure such as the National Cancer Institute (NCI) Nanotechnology Characterization Lab,[117] as well as the caNanoLab database,[118] the RTI International Nanomaterial Registry,[119] the NNI Nanotechnology Knowledge Infrastructure (NKI) Signature Initiative,[120] and the

115 https://doi.org/10.1039/C5NR08944A
116 https://doi.org/10.3389/fphy.2023.1271842
117 http://ncl.cancer.gov
118 https://cananolab.cancer.gov/#/
119 https://doi.org/10.2147/ijn.s40722
120 https://www.nano.gov/NKIPortal/About

Materials Genome Initiative.[121] Additionally, the semantic web[122] has been introduced as a useful tool for data integration and knowledge sharing for nanoEHS data, implementing web ontology language (OWL)[123] and RDF.[124] Semantic annotation facilitates interoperability and harmonization with other resources; recent examples include computational toxicology (EPA AOP-DB),[125] molecular processes (WikiPathways),[126] and clinical or pharmaco-epidemiological data (FDA's Adverse Event Reporting System[127] and EudraVigilance[128]). Several internationally funded nanoEHS-specific efforts that have recently been completed share common curation and ontological annotation standards[129] as part of the NanoSolveIT project. Concerted efforts like this, whereby large libraries of well-characterized nanomaterials and hazard and exposure datasets are curated and annotated, are essential for making nanoEHS data computer-interpretable, and instrumental for use in modeling and federation into knowledge commons. EPA and other federal partners, as part of DIIG, have proposed a federal nanoEHS consortium to create interoperable formats for federal nanoEHS data. Although results of this effort are forthcoming, substantial progress has been made in the creation of tools and training materials to jumpstart curation of federal partner data as part of this effort.[130]

Expanding theory, modeling, and simulation capabilities

Development of predictive models for nanomaterials depends on the availability of high-quality (complete, high quantity, robust) datasets,[131] especially with regard to regulatory risk assessment application.[132] Computational researchers face significant challenges in acquiring data needed for the development of robust models.[133] Extending the goals of nanoEHS data infrastructure beyond data retrieval and collection will enable data analyses, modeling, and subsequent theoretical advancements. In the 2011 NNI EHS Research Strategy, research needs for modeling played a key role in the development of ENM structure-property-activity models and training sets. This area of computational modeling has advanced substantially beyond the success of quantitative structure activity relationship (QSAR) methods.[134] Applications of statistical learning, machine learning, or AI methods have become popular and can be applied to a wide array of data sets. NIOSH is currently developing a technical report describing applications of statistical learning such as agglomerative clustering and random forests for developing occupational exposure limits (OELs) or occupational exposure bands (OEBs) for ENMs.[135]

Emerging tools and methodologies such as natural language processing (NLP) might assist with nanoinformatics and modeling development. NLP semi-automates the extraction of pertinent

121 https://www.mgi.gov/
122 https://www.jstor.org/stable/26059207
123 http://www.w3.org/TR/2012/REC-owl2-primer-20121211/
124 https://www.w3.org/RDF/
125 https://doi.org/10.3389/ftox.2022.803983
126 https://doi.org/10.1093/nar/gkaa1024
127 https://doi.org/10.1177%2F0018578718795271
128 https://doi.org/10.1007/s40264-018-0647-1
129 https://doi.org/10.1016%2Fj.csbj.2020.02.023
130 https://doi.org/10.1038/s41597-021-01098-0
131 https://doi.org/10.3762/bjnano.6.202; https://doi.org/10.3109/17435390.2014.952698
132 https://doi.org/10.3109/17435390.2015.1038661
133 https://doi.org/10.1016/j.csbj.2020.02.023
134 https://doi.org/10.1016/j.tox.2012.11.005; https://doi.org/10.1016/j.taap.2015.12.016
135 https://www.federalregister.gov/documents/2021/07/13/2021-14801/draft-approaches-to-developing-occupational-exposure-limits-or-bands-for-engineered-nanomaterials

information from various textual resources such as research papers, patents, and regulatory documents. This information often revolves around the properties, methods of synthesis, experimental conditions, and results associated with nanomaterials. EPA has applied NLP in its naming convention for NKB nanomaterials and currently tracks NKB nanomaterials and other chemicals using these methods in the EPA CompTox Chemical Dashboard.[136] Another invaluable application of NLP in nanoinformatics is the development of ontologies for nanomaterials.[137]

Cross-disciplinary approaches are gaining momentum. Nano-bioinformatics and the transatlantic Nanoinformatics 2030 roadmap efforts highlight the improvement and availability of nanoEHS data and the integration with types of data used in bioinformatics or systems biology approaches[138] such as transcriptomics, toxicogenomics, and even adverse outcome pathway datasets.[139] Currently, most of this work is limited to multiwalled carbon nanotubes; however, integration across these types of data is promising and highlights the possibility of computational inference of the biological effects of nanomaterials and ENMs in humans and other species, organisms, or cells.

Creating a collaborative informatics infrastructure

As mentioned above, there have been multiple efforts (some ongoing and others completed) to create knowledge infrastructures. In the United States, there has yet to be a shared data "warehouse" for federal nanoEHS data. Some concerns preventing the creation of such a shared location in a government cloud environment have been data security and vulnerability, data size and storage, and ongoing storage cost. Identifying a common location and coordinated, long-term agency support continues to be a challenge for such an effort. An alternative approach that NNI participating agencies are currently pursuing, coordinated through DIIG, is outlined in Figure 2.

Ongoing Research Needs

Since the publication of the 2011 strategy, significant gaps remain in accessing high-quality nanoinformatics data to support modeling. Ontologies and databases have been constructed in isolation, creating integration challenges. Cultural barriers between experimentalists and modelers constrain effective knowledge transfer, and training programs enabling scientists to leverage informatics tools remain limited. Infrastructure and incentives for sharing negative data, which are critical for model training, are deficient. Multiscale models linking molecular interactions to cellular, tissue, and organism responses require further research and validation. Efforts to connect *in vitro* assays to human health outcomes via modeling require substantial development. Overall, the quality of collected and cleaned datasets will remain a lingering challenge for nanoinformatics researchers and practitioners. Likewise, the informatics field is rapidly advancing in numerous scientific disciplines, and subsequent advances in the application of informatics to chemistry, manufacturing, and other fields can be leveraged to address needs and opportunities with nanoinformatics.

Future efforts, once data standardization has been met across federal partners' datasets, could include the creation of a "living" dataset, for example, or specific test datasets in a central location, depending on partner and general user needs. As the fields of nanotechnology and nanoinformatics continue to mature and evolve, it is vital that approaches to risk assessment and policy management evolve in tandem. The challenges outlined above and the current plans to address data and research needs at

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[136] https://doi.org/10.1038/s41597-021-01098-0; https://comptox.epa.gov/dashboard/chemical_lists/NAKNOWBASE

[137] https://doi.org/10.1016/j.jbi.2010.03.001; https://doi.org/10.1186/s13326-015-0005-5; https://doi.org/10.1126/science.aad0768

[138] https://doi.org/10.1080/15287394.2016.1159635; https://doi.org/10.1002/jat.3548

[139] https://doi.org/10.1002/em.21936; https://doi.org/10.3389%2Fftox.2021.653386

the agency level, in coordination with future research and policy efforts, are aimed at ensuring the safe and responsible development of nanotechnology.

Risk Assessment and Risk Management Methods

Overview

The strategic goal for the 2011 Risk Assessment and Risk Management Methods research area was to "increase available information for better decision making in assessing and managing risks from nanomaterials, including using comparative risk assessment and decision analysis; life cycle considerations; and additional perspectives such as ELSI considerations, stakeholders' values, and additional decision makers' considerations." The 2011 NNI EHS Research Strategy identified five research needs toward this goal:

1. Incorporate relevant risk characterization information, hazard identification, exposure science, and risk modeling and methods into the safety evaluation of nanomaterials.
2. Understand, characterize, and control workplace exposures to nanomaterials.
3. Integrate life cycle considerations into risk assessment and risk management.
4. Integrate risk assessment into decision-making frameworks for risk management.
5. Integrate and standardize risk communication within the risk management framework.

Over the past two decades, significant progress has been made in understanding and managing the potential risks associated with nanotechnology.[140] Research efforts have expanded knowledge of the properties and behavior of ENMs, as well as their potential impacts on human health and the environment.[141] Advances in measurement, exposure and hazard assessment, and predictive modeling have improved the ability to evaluate and mitigate risks throughout the life cycles of ENMs and NEPs in various feedstocks and product classes.[142] Moreover, collaborations among government agencies, academia, and industry have supported efforts to advance comprehensive risk assessment and risk management decision frameworks.[143]

This section summarizes the progress made since the publication of the 2011 NNI EHS Research Strategy and key meetings, such as the 2013 NNI Workshop on the Perception, Assessment, and Management of the Potential Risks of Nanotechnology,[144] and discusses the next steps for nanotechnology risk assessment and management. This section is placed after all the other core research areas to reflect the contribution, role, and reliance of robust risk assessment and risk management efforts on information from these other disciplines.

Progress and Advances Since the 2011 EHS Research Strategy

Significant progress has been made in risk assessment and risk management through collaborative efforts among the NNI agencies, academia, and private sector partners. For example, NIOSH has published a state-of-the-art overview on utilizing current hazard research data and risk assessment methods for ENMs to develop and implement effective risk management guidance.[145] NIOSH has published guidance for 3D printing in emerging settings, for example, schools, libraries, and

140 https://doi.org/10.17226/25729
141 https://doi.org/10.1126/science.aau8299
142 https://doi.org/10.1016/j.impact.2021.100365
143 https://doi.org/10.1111/risa.12581; https://doi.org/10.1039/C8EN00848E; https://doi.org/10.1201/9781315216799
144 https://www.nano.gov/r3workshoppresentations
145 https://www.cdc.gov/niosh/docs/2018-121/default.html

makerspaces,[146] and ongoing activities have focused on using an evidence-based strategy to develop OELs for various ENMs.[147] In 2013, OSHA published a "Working Safely with Nanomaterials" fact sheet that addresses OELs.[148] Additionally, a multistakeholder workshop involving some of the NEHI agencies evaluated the potential use of alternative testing strategy data such as *in vitro* and limited *in vivo* data in a tiered testing scheme in hazard assessment and toxicity prediction of ENMs.[149] OECD has released a document titled "Important Issues on Risk Assessment of Manufactured Nanomaterials" under its Series on the Safety of Manufactured Nanomaterials.[150] This document discusses the current practices and challenges faced when assessing the risks of manufactured nanomaterials, especially in scenarios in which data availability is limited. The need for extensive research to fill the gaps in specific risk assessment areas is emphasized, reflecting the nascent and evolving nature of nanotechnology and its associated risks. The intention is to clarify risk management practice in a manner applicable to member country regulatory practice, for common guidance across the OECD member and observer base. An integral part of the document is an overview of the chemical risk assessment paradigm, showcasing how various member countries have tailored their pre-existing regulatory frameworks to incorporate the nuances of nanomaterial assessment. By examining the adaptations made by different nations, one can gain insights into the diverse approaches taken to ensure the safety of these new materials.

Life cycle considerations have been integrated into risk assessment through case studies and the development of comprehensive environmental assessment (CEA) approaches, as exemplified by EPA.[151] The CEA meta-analysis approach integrates life cycle analysis, exposure assessment, hazard analysis, and risk characterization, and has been used in case studies on several ENMs, including nanoscale titanium dioxide, nanoscale silver, and multiwalled carbon nanotubes.[152] In terms of integrating risk assessment into decision-making frameworks, EPA's CEA approach provides both a framework for systematically organizing complex risk-relevant information and a process that uses collective judgment to evaluate such information for risk management planning. NIOSH has evaluated hazard banding as a method to categorize chemical risk, with references to ENMs, by hazard potential.[153] Investigations of life cycle considerations associated with ENMs, including best practices, were discussed at the 2015 and 2018 QEEN from Manufactured Products public conferences, co-hosted by CPSC and the NNI.[154]

Regarding risk communication, NSF-supported research has developed risk communication models and has integrated them into risk management frameworks at large university-based research centers where risk communication is a component of larger nanotechnology research programs.[155] NIOSH, CPSC, OSHA, and NSF have used communication tools, guidance documents, and other publicly available documents to disseminate knowledge about products that may contain ENMs or otherwise involve the application of nanotechnology.

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146 https://www.cdc.gov/niosh/docs/2024-103/default.html
147 https://doi.org/10.26616/NIOSHPUB2021112; https://www.cdc.gov/niosh/docs/2013-145/default.html
148 https://www.osha.gov/sites/default/files/publications/OSHA_FS-3634.pdf
149 https://doi.org/10.1111/risa.12683
150 https://one.oecd.org/document/ENV/CBC/MONO(2022)3/en/pdf
151 https://doi.org/10.1021%2Fes3023072
152 https://doi.org/10.1201/9781315216799
153 https://doi.org/10.26616/NIOSHPUB2019132
154 https://www.nano.gov/qeenworkshop; https://www.nano.gov/qeen2
155 https://doi.org/10.1016/j.nantod.2014.09.008; Priest. (2017). *Nanotechnology and the public: Risk perception and risk communication*. CRC Press.

Despite these achievements, areas remain where improvements in nanotechnology risk assessment and management are needed.[156] For example, gaps persist in understanding of the long-term hazards of ENMs and attendant human health risks, as well as the cumulative risks associated with multiple nanomaterials and their combined effects.[157] Additionally, more accurate and efficient methods to characterize and quantify exposures are needed, especially in occupational settings.[158] The integration of ELSI considerations into risk assessment and management frameworks is also an essential component for ensuring that risk management strategies align with societal values and expectations.[159]

Ongoing Research Needs

Even with the progress since 2011, risk assessment and risk characterization do not yet meet the demands of an evolving nanotechnology landscape. Existing methodologies may provide insights into primary exposure scenarios, but as ENM life cycles become more intricate and integrated into diverse applications, the emphasis must continue to be on capturing risk components across the entire material and product life cycles, especially in settings beyond initial occupational environments. While the NNI community has endeavored to expand risk management strategies, a comprehensive approach is needed that encompasses a wide array of ENMs and NEPs and accounts for different decision contexts. This broader lens will allow for the evaluation of cumulative risks posed by multiple ENMs, ensuring that risk management remains robust and adaptive.

Coordinated efforts to boost data accessibility and sharing remain paramount. With each novel nanomaterial and technological advancement, the call for interagency coordination and the ability to query data across platforms intensifies. A cohesive, transparent, and accessible data hub—aligned with both FAIR and TRUST (Transparency, Responsibility, User focus, Sustainability, and Technology) principles—becomes essential for streamlining risk assessment processes. This integrative approach can foster consistency in risk assessment methodologies and offer a platform for international collaboration, harmonizing global practices. Collaboration with and participation in international entities like OECD and ISO have paved the way for standardized risk assessment and risk management strategies. These collaborations can also serve to propagate best practices, ensuring a safe and systematic evolution of nanotechnologies.

Ethical, Legal, and Social Implications

Overview

The use of nanotechnology in society brings challenges and promises of new opportunities for improvements in health, environmental protection, and public welfare. However, the introduction of new technologies and materials carries with it a significant obligation to prevent and mitigate harmful or negative impacts. Nanotechnology's growth coincided with the rising expectations that research agendas be set in close collaboration with the social and human sciences and that the public be actively engaged in technological choices. The discourse surrounding this emerging technology was distinguished by its strong inclusive power and potential for social innovation.[160] The NNI has been proactive from its authorization in 2003 in promoting responsible development of nanotechnology

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156 https://doi.org/10.1016/j.impact.2020.100219
157 https://doi.org/10.1016/j.nantod.2018.09.002
158 https://doi.org/10.1016/j.yrtph.2018.03.018
159 https://doi.org/10.1016/j.nantod.2020.100989; Hussain, C. M. (Ed.). (2020). *The ELSI handbook of nanotechnology: risk, safety, ELSI and commercialization*. John Wiley & Sons.
160 https://doi.org/10.1007/s11569-021-00396-6

among its foundational goals. This commitment has included a need for ELSI to be investigated in parallel to the development and commercialization of new nanotechnology-enabled products and devices.

The 2011 NNI EHS Research Strategy noted that the responsible design and development of nanotechnology, including the design, deployment, and use of nanotechnology, encompasses a broad range of activities such as promoting public outreach and engagement. The responsible design and development of nanotechnology also includes the use of nanomaterials to solve environmental challenges such as ensuring potable water supplies; removing contaminants from air, soil, and water; and creating new sustainable clean energy sources. The NNI reiterated the importance of these activities in the 2014 progress review of the 2011 NNI EHS research strategy.[161] The 2011 strategy recognized that the six core research areas were "strongly interrelated and synergistic," as illustrated in Figure 1.4 of the 2011 strategy. While ELSI considerations were and remain integrally and inextricably interwoven into the other research categories (Figure 1.3), the development of this current strategy document included a separate review to highlight the NNI ELSI-related investments throughout this report and to outline common features with other disruptive (game-changing) technologies (biotechnology and synthetic biology, advanced materials, AI, and quantum science) and how these technologies may be integrated in the strategic themes and actions in Part B of this document. The actions and support mechanisms for ELSI and responsible research and innovation in this revised strategy include important research questions and gaps.

Progress and Advances Since the 2011 EHS Research Strategy

The 2011 NNI EHS Research Strategy called for the generation of ELSI knowledge primarily in understanding public perception of nanotechnology's benefits and risks. The 2011 EHS strategy aligned its goals with the 2011 NNI Strategic Plan,[162] noting that "ELSI considerations, as described previously in this document [the 2011 EHS Research Strategy], provide a perspective that guides decisions about the types of research needed and risk analysis and management decisions."[163] The 2011 NNI Strategic Plan proposed an objective "to develop tools and procedures for domestic and international outreach and engagements to assist stakeholders in developing best practices for communicating risk...." ELSI was thus treated as a consideration that would encircle all of the EHS research goals and be a key component of building public trust in nanotechnology innovation. Life cycle and ELSI considerations, as well as stakeholder values, were conceptualized as critical components of increasing and integrating the information available for risk assessment and emerging best practices for the risk management of nanotechnologies.[164] Effective risk communication grounded in the above themes (LCA, ELSI, and public engagement) was thus central in guiding risk management decisions. The NNI's efforts in ELSI include the following areas:

Creating an accessible and expert community

The 2011 NNI Strategic Plan called for increasing the capacity of federal agencies and ELSI communities to identify and address ELSI issues specific to nanotechnology by creating and maintaining a resource

[161] https://www.nano.gov/2014-EHS-Progress-Review
[162] https://www.nano.gov/2011StrategicPlan
[163] https://www.nano.gov/2014-EHS-Progress-Review
[164] *The ELSI Handbook of Nanotechnology: Risk, Safety, ELSI and Commercialization*. 2020; Taken from NSTC (2014). *Progress Review on the Coordinated Implementation of the NNI 2011 Environmental, Health, and Safety Research Strategy*. https://www.nano.gov/2014-EHS-Progress-Review; https://www.nano.gov/node/626; https://doi.org/10.1111/j.1539-6924.2011.01738.x

list of experts in ELSI and nanotechnology that is accessible to a broad range of users. The rise of peer-reviewed research platforms such as the *Journal of Nanoethics* and the *Journal of Responsible Innovation* reflects the growth in the ELSI and responsible research and innovation (RRI) research communities.

Ethical decision-making frameworks

Ethical issues, particularly regarding the balance between innovation and safety, data gathering capabilities of the technology, and personal privacy, are common features of modern technological innovation. With a rich research history and proactive EHS and ELSI stance, maturing, enabling fields such as nanotechnology can provide examples and frameworks for emerging technologies.[165] To address these concerns for nanotechnology, new ethical decision-making frameworks were devised to prioritize the protection of individual rights while fostering innovation. These frameworks support prioritization and screening of consumer products and serve as a guide for researchers and developers, ensuring that the deployment of nanotechnologies aligns with societal values, including attention to potential impacts on marginalized communities.[166] ELSI frameworks for emerging technologies such as quantum technology can be enriched by those developed for nanotechnology.[167]

Legal standards and regulatory protocols

As nanotechnology began to intersect with various facets of daily life, a pressing need emerged for policies and legal and regulatory oversight. The combination of potential, risk, and uncertainty that accompanies the development of nanotechnology is not unique; it applies to many other emerging technologies. In this regard, legal issues include transparency in how balance is achieved in developing regulatory limits and guidance, as well as concerns regarding liability, disclosure, and the protection of intellectual property. To generate further discussion and perspectives on this topic, the NNI hosted a public webinar on nanotechnology and the insurance industry in 2016.[168]

In the United States, manufacturers assume responsibility that their products satisfy safety and other legal standards and requirements, regardless of whether the regulatory framework requires pre-market approval or not. NNI participating agencies have used the extensive EHS research findings to inform the regulatory landscape and to develop guidance documents, voluntary standards, and exposure limits, largely within the framework of the broader agency statutory authorities. For example, the potential safety and health risks of nanomaterials—as well as other compounds that are incorporated into consumer products—can be assessed under existing CPSC statutes, regulations, and guidelines. CPSC reviews the potential health effects of consumer products under the Federal Hazardous Substances Act and the Consumer Product Safety Act. OSHA recommends exposure limits in occupational environments based on NIOSH recommendations. EPA has used its authority under Section 5(a) of the Toxic Substances Control Act to set conditions for the manufacture of new nanoscale materials, including carbon nanotubes, using consent orders or Significant New Use Rules.[169] FDA regulates nanotechnology products "under existing statutory authorities, in accordance with the specific legal standards applicable to each type of product under its jurisdiction." FDA's approach is

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165 P. Brey, Ethics of Emerging Technology, in *The Ethics of Technology: Methods and Approaches*. S.O. Hansson, Ed. (Rowman & Littlefield International, London, United Kingdom, 2017), pp. 175-191.

166 https://doi.org/10.1039/C8EN00848E; https://doi.org/10.1038/s41565-018-0120-4

167 https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3814422

168 https://www.nano.gov/PublicWebinars

169 https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/control-nanoscale-materials-under

thus focused on products and product classes such as drugs, cosmetics, biologics, and medical devices.[170]

Ethics and the product life cycle

The growth in nanotechnology-enabled products necessitates that ethical considerations should not be limited to just the product development phase. Life cycle ethics has emerged as a holistic approach to ensure that every stage of a product, from inception to disposal, considers the potential ethical, legal, and social consequences without compromising on values or causing undue harm.[171] For example, researchers have used the Principles of Green Chemistry and the Ashby material selection strategy in frameworks to design nanomaterials to maximize performance and minimize undesirable implications at all stages of the product life cycle.[172] This perspective aims to guide the design of next-generation applications with enhanced functional efficacy and minimized potential unintended environmental and human health consequences.[173]

Risk communication and public engagement

As advancements in nanotechnology surged, the NNI engaged in activities to facilitate transparent communication with the public.[174] NNI agencies have invested in making nanotechnology-related data more accessible and understandable, for example, through EPA's NKB, ensuring that stakeholders and the public can make informed decisions.[175] The maturing science and the increasing diversity of applications have placed nanotechnology largely beyond the fear of the potential for the most adverse impacts. The previously cited study (171) suggests the need for continued efforts to provide adequate information on health and safety hazards, including handling and storage of unbound ENMs. Public perception is divergent on this point; research presented at the 2022 NSF Nanoscale Science and Engineering Grantees Conference suggests that the U.S. public does not consider the gap between what it knows and what it needs to know about nanotechnology as a significant one.[176] However, research on international stakeholder perceptions reported a greater consensus on the crucial importance of having unbiased, scientific, and trustable information regarding the potential impacts of nanomaterials and nanotechnology-related products on the environment, health, and safety.[177] This research also cited an interest among stakeholders for greater internationally harmonized and robust regulation, improved scientific evidence on EHS effects, and guidance on the safe use of nanomaterials.

Ongoing Research Needs

Developing a research agenda

Stakeholders have called for the NNI's EHS research strategy to include a structured set of activities that supports a shift in research culture to one that increasingly emphasizes societal good while incentivizing innovation in the development and commercialization of applications, devices, and

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170 https://www.fda.gov/science-research/nanotechnology-programs-fda/fdas-approach-regulation-nanotechnology-products
171 https://dx.doi.org/10.2788/318544
172 https://doi.org/10.1039/C4CS00445K; https://doi.org/10.1038/s41565-018-0120-4
173 https://doi.org/10.1039/C4CS00445K
174 Stakeholder perspectives on the perception, assessment, and management of the potential risks of nanotechnology, http://www.nano.gov/R3Workshop
175 https://doi.org/10.1016/j.jchas.2018.10.002
176 https://www.nseresearch.org/2022/program.htm
177 https://doi.org/10.1007/s11051-019-4689-9

products.[178] Systematic efforts should be made to anticipate ELSI issues as research breakthroughs lead to the next generation of products, devices, and services. Efforts should be made to identify potential downstream and cascading effects of technological advancements, particularly those related to human health diagnostics and therapies.

Further research is needed to understand the impact of demographic factors on nanotechnology exposure and risk. Gaining a more granular and focused comprehension of stakeholder perceptions of nanotechnology benefits and risks furthers understanding of when and how public opinion about the potential of nanotechnology may be amplified or distorted, impeding or supporting the uptake of the application or product. This information may help to identify strategies for communicating the benefits and risks of nanotechnology in a manner that stakeholders are likely to comprehend. Such assessments should also reflect an understanding of public perception to bring stakeholders into a transparent governance process.

Public engagement and improved public education about laws pertaining to nanotechnology are critical for evaluating nanotechnology under existing legal structures. This includes facilitating transparent communication about potential benefits and risks, such as discussions on how current hazardous waste laws might apply to emerging concerns like nanoplastics. By promoting public understanding of the legal landscape, societal values and longstanding legislative concerns can be adequately considered in decision-making processes. This approach may lead to more valid and defensible decisions regarding the development, use, and regulation of nanotechnology.

Integrating ELSI into the NNI's expanded responsible development goal

Nanotechnology has also expanded from nanomaterials to systems, devices, and structures. As the nanotechnology community creates new materials and devices, a holistic and systematic approach should be undertaken to ensure that issues concerning the end of life of these new products have been researched and that sustainable paths forward for the new products can be envisioned. Discussion is ongoing in many sectors of civil society regarding the societal impacts of advanced technologies.[179] This discussion has created the need to understand where nanotechnology-specific considerations may exist and to share nanotechnology's lessons for other emerging technologies.[180]

Enabling and supporting large research teams that encompass not only multiple disciplines but also consider civic, cultural, and other types of community participation is critical to understanding the complexity of values, needs, and perspectives that should inform technological developments. To meet the ongoing and multifaceted challenges of responsibly developing nanotechnology, educational approaches and requirements may need to shift accordingly. Ongoing attention to providing students, postdoctoral fellows, faculty, and other members of the research community with relevant ELSI resources and training is a key step. Responsible and ethical conduct of research (RECR) education should be central to such efforts; RECR includes a broad range of topics, from how to behave professionally and with integrity in research environments to what a researcher's and the research community's ethical obligations are to the public. In addition to building the nanotechnology

[178] 2021 NNI Strategic Plan (https://www.nano.gov/2021strategicplan)

[179] For example, the 160-member Pontifical Academy for Life aims to address "emerging and converging technologies (nanotechnology, biotechnology, information technology, and cognitive science…), focusing on their interrelation and integration and their impact on the environment, health, and society as a whole" (https://www.exaudi.org/the-pope-wrote-it-is-necessary-to-reflect-on-the-new-emerging-and-converging-technologies/).

[180] https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3814422#

community's capacity and proficiency with ELSI issues, researchers need the skills to work across disciplines and sectors to identify and address societal challenges associated with nanotechnology.

Closing Statements of Progress and Evaluation of Unmet and New Needs

Significant progress has been made over the past decade in fulfilling key elements of the 2011 NNI EHS Research Strategy. This progress includes advances in the measurement and characterization of ENMs, improvements in understanding nanomaterial transport and transformations, development of human exposure assessment models, characterization of biological responses and health impacts, evaluation of environmental effects, integration of risk assessment methods, and effects improvements to nanoEHS data reproducibility and interoperability.

Nevertheless, critical scientific and societal challenges that warrant increased focus remain and inform this refreshed NNI EHS research strategy. Fundamental questions persist regarding nanoscale-specific hazards. The vast diversity of emerging nanomaterial types creates difficulties for characterization and toxicity evaluation using conventional techniques.

Looking forward, the NNI EHS Research Strategy: 2024 Update is framed by successes and advancements in the practice of nanomaterial safety. However, gaps remain, which offer opportunities to improve nanomaterial EHS practice over the coming decade. In Part B, these and other advancements to the EHS strategy are framed, including (a) unmet needs from the 2011 strategy, and (b) emerging, novel challenges that have arisen since then.

PART B: FUTURE DIRECTIONS

Introduction

The EHS Research Strategy: 2024 Update lays out an extensive catalogue of research needs and gaps, honing these into a suite of strategic actions. The NNI recognizes it is crucial that this comprehensive vision leads to prioritizing research needs that are achievable with existing resources and the NNI's nanoEHS research infrastructure.

Since 2011, this research infrastructure—the tools, methodologies, approaches, datasets, and supported talent—has been foundational to the scientific discoveries on nanoEHS. This EHS infrastructure will continue to support research to tackle the remaining unmet needs from 2011 while also addressing new questions that have arisen over the past decade. These unmet needs and new questions encompass both scientific developments and broader societal considerations. Identified by interested and affected parties both within and outside the government, these new questions reveal the potential of the nanoEHS infrastructure to help address new areas of concern beyond ENMs.

Amplified by stakeholder input, the scope of the NNI's EHS research strategy has been expanded to leverage the lessons learned from evaluating and managing the potential environmental and human health risk of exposure to engineered nanomaterials to assist in addressing global environmental and sustainability challenges. Additionally, nanotechnology has transitioned from an emerging technology to a foundational aspect of many emerging fields. The nanoEHS community must expand efforts beyond ENMs to support the responsible conduct of scientific research and product development in all sectors (academia, industry, and government institutions) with embedded and enabled nanotechnology (see call-out box on nanomedicine in Part A).

In addition to expanding the scope of interest and taking an integrated approach to needs and goals, this refreshed strategy also reflects the addition of new elements to the NNI's definition of responsible development.[181] In 2021, NNI stakeholders acknowledged the need to consider inclusion, diversity, equity, and access, as well as responsible conduct, in its definition of responsible development. Since the publication of the 2011 strategy, issues of environmental justice are now connected with responsible development as well and have led to the development of new questions regarding ethical, legal, and social implications. It is also vital to capture the significant progress in training scientists to conduct interdisciplinary research—an essential component of the nanoEHS research infrastructure—funded by agencies such as NSF and NIH.

The 2011 NNI EHS Research Strategy presented the needs for the core research areas as separate areas for the community to address. The first part of this refreshed strategy organized examples of the accomplishments in those research categories for comparative purposes. However, participants in the NEHI Working Group recognize that the core research areas identified in the 2011 strategy and discussed in Part A are "strongly interrelated and synergistic," as illustrated in Figure 1.4 of the 2011 strategy.[182] Therefore, it is important to address the future directions as themes that cut across the core research areas, emphasizing cross-disciplinary and integrative approaches to tackle 21st century risk

[181] 2021 NNI Strategic Plan, https://www.nano.gov/2021strategicplan; https://doi.org/10.1021/acssuschemeng.9b06635; https://doi.org/10.1016/j.scitotenv.2021.152460

[182] 2011 NNI EHS Research Strategy, https://www.nano.gov/2011EHSStrategy

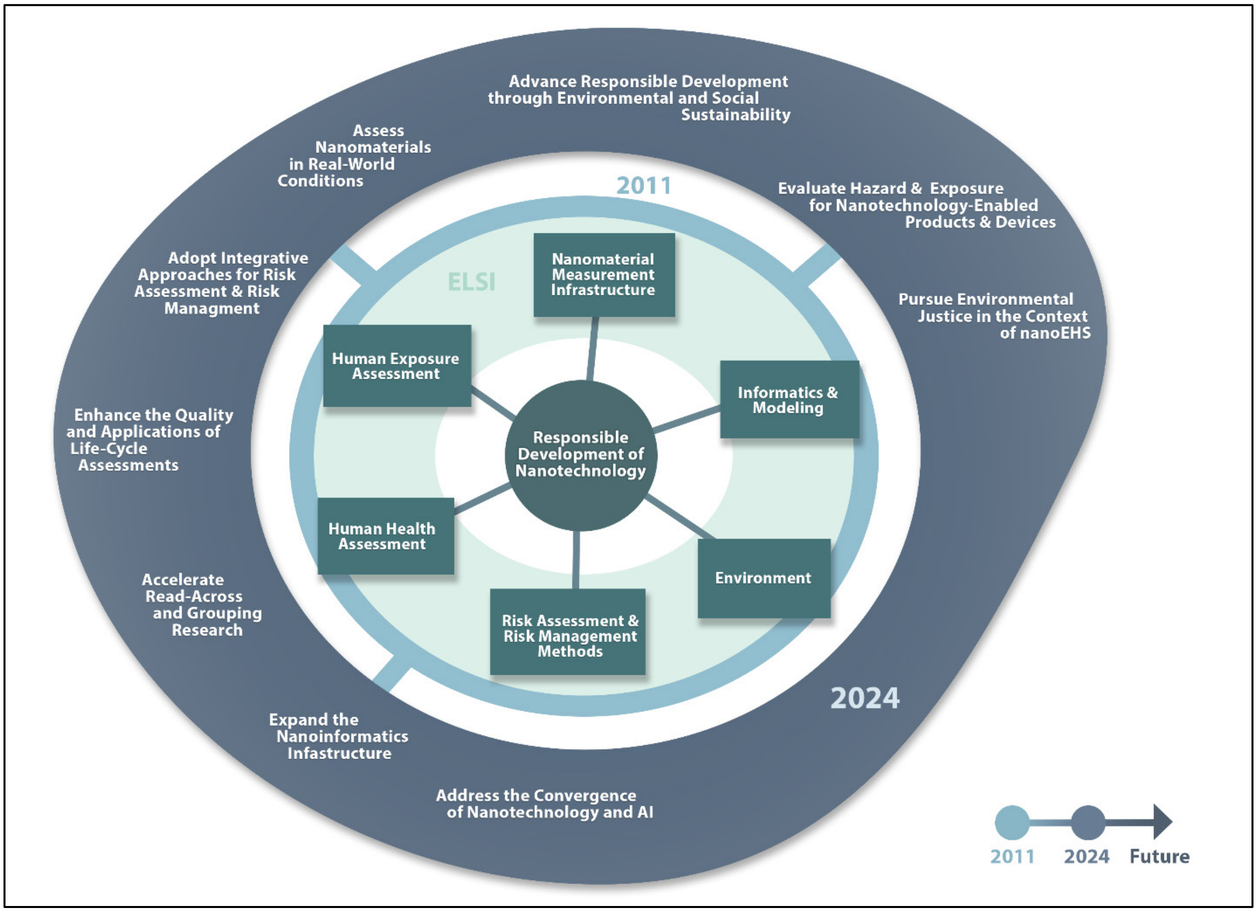

Figure 3: The 2024 update to the 2011 NNI EHS Research Strategy reflects an evolution in approach from the 2011 strategy. Building on the six core research areas and ELSI concepts identified in 2011 (inner pale blue ring), the cross-cutting themes identified in this strategy (outer dark blue ring) emphasize the need for an integrated approach as the NNI continues to support the responsible development of nanotechnology. Graphics by G. Siharulidze (Contractor, USACE-ERDC).

assessment and risk management challenges (Figure 3). This integrated and thematic approach was also adopted by NEHI participants to describe critical issues in nanoEHS from the perspective of members of the federal nanosafety community.[183]

This updated EHS research strategy delineates the trajectory, needs, and emergent challenges within the nanoEHS domain, stemming from extensive discussions across federal working groups and interactions with stakeholders, including industry and academia. The analysis of safety challenges and opportunities acknowledges the dynamic evolution of nanotechnology and its consequential implications for EHS considerations. Part B of the strategy underscores the necessity of advancing the understanding of engineered nanomaterial hazards and risk assessments, alongside the imperative to integrate ELSI principles within the framework of nanotechnology's responsible development.

The document includes an exploration of cross-cutting research themes, evaluating future opportunities as identified by various participants. Next, it examines sustainability within the nanoEHS context, articulating the dual objectives of addressing global environmental challenges and ensuring the sustainable development of nanotechnologies. Building off these themes, environmental justice

183 https://doi.org/10.1039/D3EN00062A

practices are discussed in the context of an expanded responsible development framework, as called for by the NNI nanoEHS community. The strategy then touches on the potential for AI to aid in the responsible development of nanotechnology, with appropriate training and guidance. The document culminates in proposing strategic actions for the EHS domain, aimed at navigating the outlined challenges and capitalizing on the identified opportunities. It proposes a forward-looking strategy that leverages existing research infrastructures, facilitated by NNI participating agencies, to address both enduring and emerging nanoEHS needs.

Crosscutting Themes to Address Real-World NanoEHS Needs

Assessing the safety of chemicals and materials to humans and the environment requires a comprehensive understanding of their fate and transport in ecosystems across the life cycle. Two decades of research in nanomaterials has revealed many features and processes. Advancements in toxicological research, specifically in developing more representative *in vitro* models, are crucial and may reduce the reliance on laboratory animals for safety testing. These models should mimic complex biological interactions at the cellular and molecular levels, providing insights into the potential hazards posed by nanomaterials. Additionally, there is a need to understand the long-term effects of sub-lethal and chronic exposure to nanomaterials, which remains a largely unexplored area.

Environmental risk assessment must evolve to address the unique challenges posed by nanomaterials. This type of assessment involves not only understanding the immediate impact of nanomaterials on ecosystems but also studying their long-term fate and transport in the environment.

Modern approaches (AOPs, assessment strategies, integrated approaches to testing and assessment, safe-by-design, or safe- and sustainable-by-design) are often data-intensive. There is a growing need to develop robust databases and computational models that can predict the behavior and hazards associated with nanomaterials. These tools should integrate data from diverse sources, including experimental studies and real-world monitoring, to provide a holistic view of the risks across the life cycle. Machine learning and AI have the potential to revolutionize risk assessment by identifying patterns, enhancing data visualization, and predicting outcomes from complex datasets, thereby supporting more informed decision-making.

Finally, addressing future safety assessment needs continued proactive and preventive approaches. Doing so includes the incorporation of safer-by-design principles in the development of nanomaterials, in which potential risks are considered and mitigated from the earliest stages of design and synthesis. Continued collaborative efforts among scientists, industry, and regulatory bodies are essential to establish guidelines and best practices for the safe development and use of nanotechnology, ensuring protection of human health and the environment.

Assess Nanomaterials in Real-World Conditions

There is a continued need to evaluate the potential human and environmental exposure and hazards to real-world forms of ENMs and nanotechnology-enabled materials, products, and devices. This includes (1) the capacity to quantify ENMs in real-world samples; (2) improved measurements relevant for dose metrics such as the particle number concentration (PNC) of nanoparticles; (3) improved analytical methods for ENMs including carbon nanotubes and graphene, especially at lower concentrations, as well as incidental particles of global concern, such as nanoplastics; and (4) improved measurements of cellular or tissue exposure. Many exposure scenarios involve nanomaterials that are fully or partially encapsulated by a product matrix, such as plastics. Risk assessments must account for these matrix effects, rather than evaluating exposure to only pristine ENMs.

Incidental Nanomaterials of Concern

The scale of plastic pollution and its impact on humans and the environment has emerged as a global crisis.[184] *Nanoplastic particles are anticipated to be formed from the breakdown of larger microplastic particles in the environment. However, identifying and characterizing them in real-world samples—such as from bodies of water, food, seafood, and animal feed—and conducting accurate hazard, exposure, and risk assessment, remains a significant challenge. There is a need to fully address the impacts of nanoplastics on human health and the environment. There is an exciting potential to apply the methods developed for testing manufactured ENMs to evaluate incidental nanoplastics. Recent research has begun to provide data to understand generation rates of microplastic particles and nanoparticles from consumer plastic products and macroplastic debris.*[185] *These activities will enable additional insights, and potentially facilitate the application of prior ENM knowledge to relevant incidential nanomaterial risk assessment (Figure 4).*

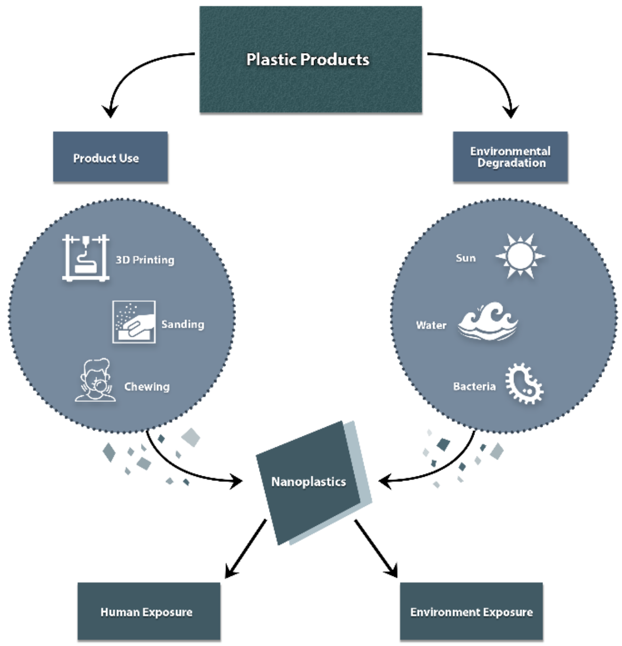

Figure 4: The nanoEHS infrastructure is being leveraged to understand the potential impact of nanoplastics formation. Graphics by G. Siharulidze (Contractor, USACE-ERDC).

Advanced manufacturing methods, e.g., additive manufacturing (AM) and 3D printing, are democratizing production while also extending exposure beyond traditional facilities. AM/3D printing is now widely used by manufacturers and consumers to produce a vast array of products such as children's toys, dental crowns, and automotive parts. Raw materials that are printed into consumer products may include nanomaterials such as graphene, carbon nanotubes, nanosilver, and metal oxides. The technical advances made in AM/3D printing are resulting in a range of devices that are becoming more affordable, particularly for small manufacturers, many of whom develop production sites within their homes or other non-traditional manufacturing sites. Small business manufacturers may be unaware of health and safety concerns involved in storage, handling, and disposal of raw materials used in the AM/3D printing process. It is important to evaluate the uptake and impact of recent guidance for makerspaces, schools, and libraries on personal protective equipment and engineering controls.[186]

ENMs may undergo various physical, chemical, and biologically mediated transformations, as well as interactions with molecules in biological systems. Transformations such as chemical oxidation, reduction, and physical dissolution can alter surface chemistry and reactivity, and ultimately potential toxicity. Changes in agglomeration state may impact transport and exposure potential. Protein corona formation in biological media also modifies the biological identity and environmental downstream impacts. Additional research related to these transformations and the release of ENMs during their life cycles is needed. While progress has been made on select materials such as carbon nanotubes and

184 https://doi.org/10.1073/pnas.1502108112
185 https://doi.org/10.1016/j.scitotenv.2021.152460
186 https://www.cdc.gov/niosh/docs/2024-103/default.html

metal nanoparticles, emerging 2D and 3D nanomaterials require characterization in environmental matrices and biological systems. Performing this type of nanomaterials characterization requires continued development of metrology standards and protocols for emerging nanomaterial classes, including 2D nanosheets, 3D nanoclusters, hybrid organic-inorganic nanoparticles, and incidental nanomaterials such as nanoplastics. Priority measurements include PNC, effective surface area, and dissolution rate.

While dissolution standards are being developed by OECD for water samples,[187] standardized methods could be valuable for other media such as cell culture media, blood and tissues, soil, sediment, and air. In addition, more broadly available methods for assessing changes to particle speciation such as silver nanoparticles to silver chloride nanoparticles could be helpful. Improved measurement capacities of colloidal ENMs are still needed in more complex test media. For example, agglomeration and protein binding can impact measurements in cell culture media with plasma or serum. Measurements in higher-ionic-strength media are also needed.

Comparative analysis of pristine versus transformed ENMs is still warranted because exposures depend on the life cycle stage. More complex exposure scenarios of *in vitro* and *in vivo* toxicology studies are vital to improving real-world relevance. These exposure scenarios include environmentally aged nanomaterials, mixture effects with other contaminants, doses that are consistent with realistic exposures and timeframes, and incorporation of ENMs into product matrices to assess release potential. Integrating exposure science and toxicology is critical for robust risk assessment.

Leveraging the current efforts to further develop and validate exposure assessment methods could spur significant progress in risk evaluation.[188] Sought-after improvements include better characterization of exposure scenarios, refinement of measurement techniques, and the exploration of novel strategies for monitoring ENMs in various environments. Ecotoxicity research should prioritize understudied materials such as 2D ENMs, identifying mechanisms that could mitigate exposure concerns to humans or the environment.[189] Recovery studies tracking ecosystem responses are also needed to fully evaluate ecological resilience. Greater emphasis on whole-ecosystem studies would boost the evaluation of community impacts and recovery after ENM exposures. Nanomaterials exposure research has advanced from individual biotic elements up to mesocosm-level investigations. Further development of the protocols and methodologies to make robust *in situ* assessments of ecosystem- and population-level effects is key to understanding large-scale environmental impacts.

In environmental media for either toxicity testing or epidemiological measurements of real-world samples, the presence of background particles, which may have the same chemical composition as the ENM being detected, can challenge measurements or limit their accuracy. One approach that could help in this area is to develop standard protocols for adding reference or representative test materials to model environmental matrices. These model matrices could then be used to improve analytical methods and better understand their specific limitations, which can then support performing measurements on samples for which the shape and size of the ENMs is unknown, such as for a field sample from the environment or in a biological tissue. Although surface area and particle number concentration measurements are valuable for assessing nanomaterial toxicity, standardized methodologies for these measurements—even for known particles in simple matrices—have not yet

[187] https://one.oecd.org/document/env/jm/mono(2020)9/en/pdf
[188] https://doi.org/10.1038/s41565-020-0742-1
[189] https://doi.org/10.1016/j.impact.2020.100226

been developed. In a Versailles Project on Advanced Materials and Standards (VAMAS) inter-laboratory study, even measurement of the PNC of a relatively simple sample of monodispersed gold nanoparticles showed significant variability among laboratories for spICP-MS and nanoparticle tracking analysis.[190] These measurements will be even more challenging for polydisperse particles.

For human health toxicity testing of ENMs, improved methods for dose measurements are also key. Many ENMs may agglomerate in cell media, which can hinder determination of their size distribution during *in vitro* testing. Standard methods for measuring other relevant attributes of the nanoparticles, such as their effective density, could help advance the use of dosimetry modeling for some *in vitro* test methods. (See the section on adopting integrative approaches for risk assessment and risk management for additional discussion on dosimetry.)

There is also a need for improved standardization of the measurement of the release of ENMs from NEPs, including food contact materials and a broad array of consumer products that could be nanotechnology-enabled. While a pilot inter-laboratory study was conducted in NanoRelease,[191] a full inter-laboratory study could be a key future step toward standardization. One significant challenge, though, is determining whether changes in a measured nanoparticle are either from incorporation, and potentially also release, from another matrix, or from biases in the analytical methods. Orthogonal measurements, when available, could provide clarity on the measured parameters. There is still the need to evaluate real-world exposures from consumer products and occupational settings using environmentally relevant ENMs that undergo transformations. More testing of commercial products and manufacturing releases is also critical.

There is also a measurement need for standard methods to characterize the surface of ENMs extending beyond surface charge (zeta potential), such as coating material quantitation, density, heterogeneity, hydrophobicity, and hydrophilicity, that can have significant impacts on how these materials interact and behave in the biological system. The protein corona has been investigated extensively, but it is a complex parameter that depends on the heterogeneity of nanomaterials and their surfaces. In addition, for human exposure, the formation of the protein corona is complicated by the inter-individual and temporal variability in the plasma proteome among humans; the same person has a different blood plasma protein profile on different days. Further development of methods to quantify carbon nanomaterials such as carbon nanotubes at lower concentrations is another key research need. Such methods would be used during occupational exposure, for testing the released effluent from manufacturing facilities, and for measurements at lower concentrations in environmental and biological matrices, which also often contain other forms of carbon at orders of magnitude higher concentrations than the carbonaceous ENMs. Some efforts are underway to develop such methods for carbon nanotube releases in occupational exposure settings.[192]

For environmental toxicity testing of ENMs, valuable guidance on aquatic and sediment toxicity testing has been published in OECD GD 317.[193] However, several issues were highlighted, such as the need to develop additional methods to improve the measurement of ENMs in environmental hazard testing methods like those developed by OECD. One such example is the development of more reliable

[190] https://doi.org/10.1039/D1NR07775A
[191] https://doi.org/10.1016/j.carbon.2016.11.011
[192] https://doi.org/10.3390/nano14010120
[193] https://one.oecd.org/document/env/jm/mono(2020)8/en/pdf

methods for measuring dose metrics in addition to the mass concentration (e.g., number concentration, particle surface area, etc.).

Evaluate Hazard and Exposure for Nanotechnology-Enabled Products and Devices

A critical goal of the NNI is to "promote commercialization of nanotechnology R&D."[194] An important factor in supporting this goal is the development of robust data needed to adequately assess potential exposures to workers and consumers, including vulnerable populations such as children and the elderly, and mitigate any potential risks identified. The general population's exposure to nanomaterials may occur in homes and private spaces, where conducting epidemiological studies may be more challenging. However, advances in sensor technology will facilitate the collection of exposure data in addition to biometric data that will link exposures to a possible adverse health outcome in non-traditional work environments.

However, the critical question of whether people working with ENMs have or will develop adverse health effects requires longitudinal epidemiological studies. Prospective epidemiological studies are quite effective in determining medium-term and long-term health impacts.[195] Conducting exposure studies in the workplace may provide ample opportunities to characterize worker exposures and acute and chronic health outcomes. Workers may be exposed to a range of materials in a variety of use scenarios across the life cycle, including the production of raw nanomaterials and their incorporation into consumer products. Generally, workers are not part of vulnerable population subgroups (e.g., young children) of people who may use or be exposed to nanomaterials.

To enable epidemiological studies, longitudinal data on occupational settings are needed, along with strategies to enable cohort formation, biomarker usage, and exposure registries. Communicating the state of knowledge, including negative results (i.e., toxicological effects that are not observed) is critical. Ultimately, a multifaceted approach addressing key knowledge gaps will support innovation while safeguarding human health. For example, the emergence of nanotechnology-enabled fertilizers and pesticides warrants a focus on agricultural workers exposed to these products. Conducting epidemiological studies on such small, exposed populations can be difficult. Therefore, innovative strategies drawing from nanomedicine and research on ultrafine particles could provide insights into predicting the biological impacts of nanotechnology-enabled pesticides. Developing exposure registries to build predictive epidemiological models would also be beneficial, aiding understanding of disparate community and population impacts and addressing potential environmental justice concerns.

It is important to know where nanotechnology-enabled products, ranging from clothing to 3D printers, are used within a household and the factors such as home ventilation that may mitigate these exposures. Major exposure routes—inhalation, dermal contact, and ingestion—warrant ongoing investigation. For human health, new questions arise regarding potential neurological, cardiovascular, immune, carcinogenic, and reproductive/developmental impacts of ENM exposures, including from repeated exposures that warrant investigation through *in vitro, in vivo,* and epidemiological studies. Sensitive populations, for example, pregnant women, children, and the elderly, also require specific focus. The extent of transgenerational effects is an open question. Studying exposure to complex, low-dose mixtures mimicking real-world scenarios is also important to better understand risks to humans and ecological receptors. Identifying relevant biomarkers and potential biological pathways would

[194] 2021 NNI Strategic Plan, https://www.nano.gov/2021strategicplan
[195] http://dx.doi.org/10.1136/jech-2016-208668

strengthen epidemiological studies. Applying tools from exposure science, predictive toxicology, complex mixture assessment, and computational modeling could aid risk analysis.

The nanoEHS community can also leverage the rapidly developing sensors that enable traditional scientists and consumers to quantify human exposures in real time. These nanotechnology-enabled and more traditional sensors may provide new tools to meet some of the aforementioned data needs. Wearable devices may be used to monitor the time-activity patterns of test subjects, characterize and quantify their exposure to a range of airborne nanomaterials, and assess the biometric changes that may occur in heart rate, breathing rate, and other factors. To study health impacts, researchers are working with possible at-risk populations (e.g., low-income groups) who are using wearable devices. Taken together, these devices may provide much-needed data regarding exposures in a population and their health impacts. Research into the robustness of the data is needed to allow citizen scientists to properly use and calibrate these new tools. Questions regarding the accuracy and longevity of these devices, privacy, and the use of personal data should also be addressed.

Understanding mechanistic pathways forms the bedrock of exposure assessment. The nanoEHS community should prioritize the characterization of mechanistic determinants of exposure, applied and internal dose, and the response of cells, organs, or tissues. Enhancing the understanding of the relationship between physicochemical properties of nanomaterials and susceptibility factors across their life cycles is of particular interest. The generation of these data will enhance researchers' ability to predict exposure outcomes, refine risk assessment strategies, and guide the development of safer nanotechnology-enabled products.

Despite tremendous progress over the past 20 years of research, challenges in exposure characterization and incorporation into robust epidemiological studies remain. Advancements in computer technology such as AI and machine learning and wearable technology can be used by scientists to meet new and existing data gaps. Additionally, these tools may provide innovative approaches to analyzing data and developing robust models to provide useful information on the relationship between the incorporation of nanomaterials into products, their fate across the life cycles of NEPs, and any potential impacts on exposed populations. More importantly, these tools may assist and proactively identify potentially vulnerable populations and mitigation strategies, which would facilitate the responsible use of the technology.

Accelerate Read-Across and Grouping Research

Accelerating the generation of hazard data through high-throughput screening is required to efficiently evaluate potential health and environmental impacts for legacy materials and the expanding suite of novel ENMs. Since ENMs have diverse physicochemical properties, grouping based on property-activity relationships (size, morphology, charge, etc.) and adverse outcome pathways should be further explored and documented.

However, reconciling results across different assay types and tying non-traditional assays to regulatory endpoints remains difficult, challenging the development of fit-for-purpose exposure and hazard assessments. Grouping approaches based on functional assays and AOPs shows promise to bridge data gaps. Knowledge from other research areas, such as informatics, metrology, exposure assessment, and environmental transport, should be integrated.

One key future need is the ability to group carbon-based nanomaterials such as CNTs and graphene with similar ecotoxicological hazard properties. For ecotoxicity testing, this grouping could only be performed by first generating test data using acute and chronic OECD TGs for the traditional aqueous/sediment base set of test species (algae, fish [*in vivo*], aquatic invertebrates [Daphnids and chironomids]) using guidance provided in OECD GD 317.[196] The limits and boundaries of data could also be evaluated using a case-study approach. One key factor is determining which properties are important to measure in order to assess sufficient similarity. Frameworks have been proposed that include factors such as reactivity and the potential for release of toxic ions after dissolution, for example, silver ions from silver nanoparticles or toxic ions released from CNT catalysts.[197] These frameworks would be especially helpful for carbonaceous nanomaterials such as CNTs with the same shape but some differing properties including catalytic activity, length, diameter, and rigidity. Evaluating studies using similar methods but different CNTs could help determine the extent to which differing CNT characteristics impact the results. It would also be beneficial to assess grouping strategies that extend from the pristine ENMs to those that have been aged in the environment or released from consumer products through different stresses like combinations of combustion, mechanical stresses such as abrasion, and photodegradation. For human health testing, *in vivo* subchronic pulmonary toxicity studies of carbon nanotubes to assess inhalation risks using OECD methods could be beneficial to support grouping strategies. Evaluating graphene materials could also be valuable for grouping strategies. This human health and ecotoxicity *in vivo* test data could also support the validation of new approach methods, for example, a fish embryo acute toxicity test. The European Union, through its Framework Funding Programmes such as FP7, Horizon 2020, and Horizon Europe,[198] has made advancements in this area. Notable projects like Gracious, HARMLESS, and SUNSHINE have developed innovative approaches to read-across and grouping for nanomaterials that could significantly inform and enhance the NNI's strategy. The NNI should prioritize research that not only develops new methods but also rigorously evaluates and refines existing ones to ensure their robustness across the diverse spectrum of nanomaterials.

Furthermore, there is a push to establish and report minimum standards for nanotechnology research that ensures consistent data translation and exposure alignment across various studies. This is particularly important as non-traditional workplaces and distributed manufacturing, like 3D printing, gain traction because guidance has lagged or is just being developed for non-traditional workspaces. Integrating the proposals for minimum reporting criteria into a common framework or frameworks may boost transparency and reproducibility of research findings.

Expand the Nanoinformatics Infrastructure

The rapidly evolving landscape of nanoEHS research underscores the pressing need to prioritize and refine the informatics and modeling aspects of research. The journey toward establishing common ontologies or frameworks for nanoEHS data within the United States, as guided by DIIG, is a testament to this need. Drawing from successful international models like eNanomapper,[199] there is a requirement to innovate and implement a robust semantic structure for domestic nanoEHS datasets, which would ensure interoperability and consistency.

Overcoming the logistical hurdles around data storage, accessibility, and maintenance across the federal government to ensure efficient sharing of information for decision-making is an essential goal for this nanoEHS strategy. As nanoEHS data undergo refinements through semantic mapping, this strategy supports the delineation of the storage architecture, be it on a centralized platform or in

[196] https://one.oecd.org/document/env/jm/mono(2020)8/en/pdf
[197] https://doi.org/10.1016/j.yrtph.2015.11.020
[198] https://www.nanosafetycluster.eu/nsc-overview/nsc-structure/ongoing-projects/
[199] https://doi.org/10.3762/bjnano.6.165

distributed repositories. This decision will inherently shape the data's reach and impact. Moreover, in the spirit of transparency and collaboration, the strategy should actively consider how open this data should be to the public and collaborators, while protecting confidential business information.

Boost informatics and data infrastructure for robust risk assessment and decision-making

The integration of informatics tools enables the systematic collection, management, and analysis of large datasets related to nanomaterials properties, environmental interactions, and biological effects. By leveraging advanced data analytics, machine learning, and AI, informatics facilitates the identification of patterns and correlations that are not readily discernible through traditional analysis methods. As a result, informatics enhances an understanding of nanomaterials risks and supports more informed decision-making.

The use of informatics in risk assessment relies on the development of comprehensive curated databases that catalog the physiochemical properties of nanomaterials and their associated biological and environmental interactions. These databases serve as valuable repositories for researchers and policymakers, providing accessible and up-to-date information. For effective risk assessment, these databases need to be regularly updated and standardized to ensure consistency and reliability of data. Interoperability between different databases is also essential to enable seamless sharing and integration of data across various platforms and institutions.

Ensure alignment with FAIR and TRUST principles

Ensuring consistent alignment in nanotechnology research and data management is essential for enhancing accessibility and adherence to FAIR and TRUST principles.[200] The adherence to these principles requires the development of standardized protocols for data reporting and sharing, ensuring that data generated from nanotechnology research is easily findable and accessible to a broad range of stakeholders. Such standardization should include reporting of any adjustments of exposures to internal doses, so that inferences across various experimental platforms utilize the same metric for response analyses.[201] Reference to policy procedures or modeling assumptions and parameters used prior to reporting exposure measurements or outcomes would be an essential component.

Standardization includes the use of common terminologies and metadata standards that facilitate data discovery, translation, interpretation, and integration across various platforms and disciplines. Aligning with the FAIR principles also involves ensuring that data are interoperable, allowing seamless integration and reuse in different research contexts, thereby fostering collaboration and innovation in the field. An important objective going forward will be to facilitate opportunities for training students and researchers on the importance of these principles. Nanotechnology researchers should have best practices and standards on how to incorporate the FAIR principles into their research plans.

With every advancement in material and product development, there is a consistent need for more and improved data across the diversity of materials and product classes. Addressing critical interagency questions about safety and usage requires a strategy for data acquisition, application of any adjustments for translation, and its subsequent integration or aggregation into a central, transparent, and accessible hub. The application of TRUST principles in nanotechnology research emphasizes the need for transparency and responsibility in data management, both of which include clear documentation of data provenance, ensuring that the origins, context, and methodologies used in data collection are transparently reported. The TRUST principles also involve a user-focused approach to

200 https://www.nature.com/articles/s41597-020-0486-7
201 https://doi.org/10.17226/24635

data management, where the needs and expectations of different user groups, including researchers, policymakers, and the public, are considered. The NNI should consider community-wide engagement to frame these concepts in the context of the responsible development of nanotechnology.

Critical needs in moving forward with understanding the environmental and health effects of the numerous ENMs include more standardized and accessible quantitative data on the toxicity and physicochemical properties of ENMs.[202] Moreover, as technology and data science advance, the issue of data formats remains at the forefront. The dynamic nature of data science and technology further prompts the nanoinformatics community to continuously evaluate and adapt data formatting standards. While the FAIR principles currently stand as the gold standard, this research strategy aims to remain agile, anticipating potential shifts toward newer, more tailored standards that cater specifically to the intricacies of nanoEHS data. It is essential to be proactive, assessing potential formats or standards that could further enhance data accessibility and utility in the future.

Broader adoption of high-throughput screening, *in vitro* assays, and computational modeling enables more efficient nanomaterial evaluation but must address the challenges of IVIVE for exposure alignment across experimental *in vitro, in vivo,* and epidemiological platforms. Consistent translation and robust IVIVE is necessary to ensure that inferences can be integrated and can demonstrate their reliability and utility for regulatory use. Establishing the confidence per specific regulatory contexts, linkage to apical endpoints, and clear communication of the benefits of ENMs are essential. Access to high-quality open data to develop robust models and groupings remains limited.

Enhance the Quality and Applications of Life Cycle Assessments

Life cycle assessment is a "systematic method for assessing the potential environmental impacts of products, services, and processes across their entire life cycles."[203] LCA as a tool for understanding nanotechnology's impacts has been well studied. However, many challenges remain to adequately model nanotechnology in the LCA framework. These include accounting for releases and lack of inventory for the production of nanomaterials that are in commerce.

In discussing life cycle considerations for nanomaterials, it is essential to recognize the broader environmental, economic, and social sustainability impacts across a nanomaterial's life cycle. These impacts encompass the entire spectrum from cradle to grave (or preferably, cradle to cradle): raw material extraction, laboratory and industrial production, consumer use, and disposal or recycling. Each stage presents unique challenges and opportunities for minimizing environmental footprints and enhancing social sustainability.

How and where raw materials are extracted and processed influence social and environmental sustainability. The extraction of raw materials and associated processing often involve energy-intensive procedures with potentially toxic inputs and byproducts on landscapes with people who suffer from histories of environmental and social injustice. Responsible development thus necessitates the adoption of more efficient and less polluting extraction and processing technologies, the pursuit of alternatives to conflict-sourced critical minerals, and the inclusion of relevant local communities to reduce environmental harms and social disruption and maximize local economic, social, and ecological benefits.

During the production phase, a sustainability focus combines attention to worker safety with considerations of resource efficiency and waste minimization. The implementation of green chemistry

[202] https://doi.org/10.1016/j.yrtph.2018.03.018
[203] https://doi.org/10.1016/j.impact.2017.12.003

principles, such as reducing hazardous substance use and optimizing production processes to minimize waste, plays a crucial role. Nanotechnologies can require less energy, use less material resources, and be more efficient than other technologies. Addressing these issues calls for the development of even more sustainable and efficient manufacturing processes, which could include the use of renewable energy sources, the implementation of energy-saving technologies, the exploration of waste-minimization approaches, and water recycling and treatment methods.

The use phase of the life cycle of nanomaterials has enormous consequences for environmental and social sustainability. Here, the emphasis is on maximizing the functional lifespans of nanomaterials and assessing the potential for unintended environmental or health impacts during their use. This phase requires continual monitoring and research to understand long-term exposure risks and to develop strategies for safe and sustainable use. Moreover, it is important to consider the societal implications of nanotechnology applications, ensuring equitable access and addressing any potential social disparities that may arise in beneficial and adverse impacts.

Finally, the end-of-life management of nanomaterials is critical in the life cycle perspective. It involves assessing the recyclability and biodegradability of nanomaterials, as well as developing safe disposal methods. The challenge lies in effectively retrieving and repurposing nanomaterials, alternatively, ensuring that their disposal does not lead to environmental contamination or disproportionate environmental health burdens. Developing standardized protocols for the disposal and recycling of nanomaterials is essential to mitigating their long-term environmental impacts, completing the life cycle loop with sustainable practices. Additional discussion of leveraging nanotechnology for sustainability occurs in the section on "Advancing Responsible Development through Environmental and Social Sustainability."

Adopt Integrative Approaches for Risk Assessment and Risk Management

The 21st century presents unique challenges in risk assessment due to the increasing complexity and interconnectivity of nanotechnology applications. Traditional risk assessment models, primarily based on linear causality and single-factor analysis, are increasingly insufficient.[204] To address these limitations, there is a growing emphasis on developing more holistic, interdisciplinary, and integrative risk assessment frameworks. These new models incorporate a wider array of variables, including environmental, biological, and socio-economic factors. Such an approach acknowledges the dynamic and often unpredictable nature of nanomaterials' interactions within biological and ecological systems. These frameworks aim to provide a more comprehensive understanding of potential hazards for all compounds.

In this context, the role of interdisciplinary research becomes paramount in 21st-century risk assessment and risk management.[205] Bridging disciplines—for example, biology, chemistry, toxicology, materials science, data science, engineering, environmental health, epidemiology, medicine, and social sciences—is essential for a comprehensive risk assessment. This integration allows for a multifaceted understanding of the material under investigation and is especially critical for nanomaterials, considering not only their physical and chemical properties but also their biological interactions, environmental fate and transport, and socio-economic impacts. For instance, reducing

204 https://doi.org/10.1016/j.nantod.2020.100989
205 https://doi.org/10.17226/24635

barriers to collaborations between hazard assessors, computational biologists, and materials scientists can lead to the development of safer nanomaterials by design.

Risk assessment is values-driven, for example, in setting acceptable risk levels.[206] This creates enormous opportunities for the integration of social science expertise and methods facilitated by the development of multidisciplinary collaborations between natural scientists and social scientists. Such interdisciplinary partnerships may also increase the likelihood for risk communication that is effective and culturally sensitive. Further developing multidisciplinary cadres of researchers would be a potential mechanism to address this risk communication need.

Moreover, advances in computational modeling and data analytics have opened new avenues for risk assessment. Big data approaches, employing machine learning and AI, are increasingly being utilized to analyze vast datasets, predict nanomaterial behaviors, and assess potential risks more efficiently. These technologies enable the identification of patterns and correlations that might be missed in traditional assessments, thus offering a more nuanced understanding of nanomaterials risks. However, careful consideration of data quality, representativeness, and ethical implications surrounding the generation and use of these data is critical.

Nanotechnology-specific risk assessment approaches will need significant enhancement to address emerging challenges. One critical area is the development of more robust *in vitro* models that support hazard assessment by more accurate simulations of exposure to nanomaterials. Current models often fail to replicate the complexity of human and biological systems, leading to gaps in understanding nanomaterials' interactions and effects. Improving these models will require interdisciplinary collaboration, integrating insights from biology, chemistry, computational science, and social sciences. Another example is the enhancement of environmental monitoring techniques to track the life cycles and dispersion of nanomaterials. Current monitoring systems are often limited in detecting and quantifying nanomaterials in diverse environments. Advancements in sensor technology and analytical methods are vital to provide more accurate and comprehensive environmental assessments.

Also, there is a need for more dynamic regulatory frameworks that can adapt to the rapid pace of nanotechnology development. Creating dynamic regulatory frameworks consists of not only refining existing regulations but also developing new guidelines that can swiftly incorporate the latest scientific findings and address novel risks posed by emerging nanomaterials. Innovative policy analysis may help identify pathways to tie the iterative advancement of evolving nanoEHS knowledge with various ENM guidance, making sure that future regulatory activities and codes of conduct keep pace with ongoing advances in ENM research and commodification.

Align hazard and exposure for fit-for-purpose risk assessment

Understanding mixture toxicology, handling suspended materials in mixtures, and assessing the risk of these mixtures are pressing needs. It is also necessary to continue developing new approach methods to support *in vitro* to *in vivo* extrapolation and AOP analysis. These methods should aim for comprehensive coverage of potential endpoints, high-throughput toxicology screening/assays that can collectively predict outcomes, and assessment of their relevance to nanomaterials exposure. New approach methodologies should continue to focus on lab and organ-on-a-chip technologies, alongside initiatives like Tox21 and the National Toxicology Program's Interagency Center for the Evaluation of

[206] https://onepetro.org/PS/article-abstract/55/05/30/33254/Acceptable-Risk-Time-for-SH-amp-E-Professionals-to

Alternative Toxicological Methods (NICEATM) alternative methods.[207] These advances will aid in better prediction and management of the potential risks associated with exposure to nanomaterials.

Human toxicology practitioners emphasize vulnerable populations and transgenerational effects as areas requiring specific focus. Leveraging knowledge from particulate matter, fiber toxicology, and nanomedicine studies could help inform epidemiological modeling approaches and AOPs for ENMs based on shared modes of action, according to population clusters sharing similar health traits. Also, elucidating underlying toxicity mechanisms for ENMs is essential to predict potential health impacts.

Overall, integration of exposure, hazard, and fate data through modeling and informatics tools is required to realize the vision of predictive toxicology to design inherently safer nanomaterials. Predictive models for ENM behavior and effects are also needed, with an emphasis on advancing *in vitro* and *in silico* tools and methods. By integrating these tools with experimental data, the aim is to better support risk assessment and management efforts.

Life cycle assessment is key to understanding potential exposure, evaluating risk, and developing risk management options. These approaches are being expanded to consider a broader range of ENMs and their potential combined effects. Strengthening collaborations with global organizations like OECD, the UN Global Harmonized System of Classification and Labelling of Chemicals (GHS), ASTM International, and ISO offers opportunities for consistent risk management decision-making.[208] Engaging with stakeholders and tailoring risk communication strategies remain priorities, ensuring that the public, industry, and policymakers are well informed about potential nanotechnology risks. Lastly, integrating ELSI into risk management can offer a holistic approach, aligning technological advancement with societal values and expectations.

Improve dosimetry modeling as a critical link between exposure and key events

Dosimetry modeling plays a pivotal role in bridging the gap between exposure to nanomaterials and biological responses. Current methods often fall short in their ability to accurately translate exposure scenarios into internal doses in target tissues. The development of advanced IVIVE models is needed to address this gap. Further development of IVIVE will enable comparability of responses in different test approaches with similar doses, paving the way for more robust and reliable risk assessments, ultimately improving the protection of populations from potential health risks associated with exposure to nanomaterials. There is also potential to move some of the innovative *in vitro* test methods toward standardization. In inhalation testing, for example, standard methods could be developed for biological test systems at the air-liquid interface, thereby allowing direct exposure of cells to aerosolized ENMs. In addition, there are organ-on-a-chip models for the lung (i.e., lung-on-a-chip) and some *ex vivo* organ test methods (i.e., precision-cut lung slices) that could be further developed and standardized. These topics will support the broader acceptance of new approach methods for evaluating inhalation exposure scenarios for ENMs.

Dosimetry models are essential for quantifying the dose of nanomaterials delivered to biological targets—a critical factor in determining the nature and magnitude of the response. Traditional models have primarily focused on dissolved materials, but the advent of nanotechnology created a pressing need to further develop dosimetry models that can accurately account for the unique behaviors of nanoparticles in quantifying actual doses. These dosimetry models consider particle size, shape,

[207] https://ntp.niehs.nih.gov/whatwestudy/niceatm

[208] https://doi.org/10.1002/ieam.4590

surface properties, and aggregation behavior, which can significantly influence biodistribution and bioavailability.

One of the major challenges in dosimetry modeling for nanomaterials is the dynamic nature of their interactions with biological systems. Nanoparticles can undergo transformations in size, aggregation state, and surface chemistry upon exposure to biological fluids, which can alter their dosimetry profiles.[209] Therefore, advanced models must incorporate these dynamic processes to predict more accurately the dose reaching the target sites within the body. *In vivo* and *in vitro* studies provide essential data for these models, aiding in the understanding of how nanomaterials interact with cellular and subcellular structures and how these interactions trigger various biological pathways leading to adverse effects.

In addition to physical and chemical transformations in indoor and outdoor environments, the biological fate of nanomaterials, including absorption, distribution, metabolism, and excretion (ADME) must be considered in dosimetry modeling. Current models are being refined to better simulate these processes, integrating pharmacokinetic and pharmacodynamic aspects.[210] This integration is crucial for predicting the concentration of nanomaterials at specific sites and understanding the dose-response relationships. Improving these models is a current research need and necessitates interdisciplinary collaborations, leveraging advancements in computational biology, nanotechnology, and toxicology to create more sophisticated and predictive models.

Future directions in dosimetry modeling for nanomaterials should focus on the development of multiscale models that can link molecular-level interactions with systemic responses. This type of dosimetry modeling involves coupling detailed mechanistic models at the nano-bio interface with whole-organism pharmacokinetic models. Such an approach would enable a more comprehensive assessment of the risks associated with exposure to nanomaterials, ultimately informing safer design and utilization of these materials. Additionally, the integration of AI and machine learning techniques with traditional modeling approaches holds promise for enhancing the predictive power of dosimetry models, enabling the handling of complex datasets and identification of novel patterns in nanomaterials behaviors and biological responses.[211]

Establish consistent exposure metrics across all systems

The need for consistent exposure metrics across all systems is crucial for advancing risk-related evaluations in nanotechnology.[212] Consistency in these metrics allows for comparability of data across different studies and contexts, enabling a more comprehensive understanding of exposures to nanomaterials and their effects. This necessitates standardized methodologies for sampling, measuring, and reporting in scientific publications of nanomaterial characteristics, such as size, shape, surface chemistry, composition, and concentration, which are vital in determining their interactions with biological systems.

Current exposure metrics often vary significantly across studies, leading to challenges in interpreting and comparing results. This inconsistency can be attributed to the diverse nature of nanomaterials and the varying experimental conditions under which they are assessed. To address this inconsistency, there is a pressing need for the continued development of universally accepted guidelines and protocols for nanomaterial characterization and exposure measurements. Furthermore, applying

[209] https://doi.org/10.1186/s12989-018-0243-7; https://doi.org/10.1186/s12989-018-0283-z
[210] https://doi.org/10.1016/j.xphs.2018.10.037
[211] https://www.tandfonline.com/doi/full/10.2147/IJN.S344208
[212] https://doi.org/10.17226/24635

advanced analytical techniques and tools is imperative for achieving consistent exposure metrics. Such advanced analytical techniques and tools include spectroscopic, microscopic, and other nanoscale measurement techniques that can provide accurate and repeatable data on nanomaterials properties. Additionally, the integration of computational modeling and simulation can play a pivotal role in predicting and standardizing exposure metrics, especially in complex environmental or biological systems where direct measurement may be challenging.

Advance Responsible Development through Environmental and Social Sustainability

This updated NNI EHS research strategy considers additional elements in its "responsible development" paradigm that were not explicitly a part of the 2011 EHS research strategy. The National Environmental Policy Act calls for federal policy "to create and maintain conditions under which humans and nature can exist in productive harmony, that permit fulfilling the social, economic, and other requirements of present and future generations."[213] Inherent in the idea that sustainability requires addressing each of the three pillars—environmental, economic, and social—is the interdependence and need for an integrated framework.[214] Environmental sustainability principles include commitments to future generations to maintain ecological integrity and biodiversity, minimize environmental footprints of human activities, conserve natural resources, and address environmental threats at many scales. Social sustainability principles include commitments to ethical business and scientific practices, equity and justice in the distribution of harms and benefits from human action, protection of human rights and Indigenous sovereignty, adherence to laws and regulations, and respect for democratic norms and freedoms.[215]

As nanotechnology continues to advance, it is crucial to expand research on its ethical and scientific implications in addressing global challenges. This includes investigating the potential benefits and risks of nanomaterials and nanotechnology-enabled solutions for renewable energy, carbon capture, and resilient infrastructure. Additionally, there is a growing need to examine the international landscape of nanotechnology development and use. This encompasses research on implications of intellectual property concerns for both developed and developing nations, and the varying approaches to EHS assessments across different countries. In the absence of international consensus on ethical and research standards, it is essential to study the potential for inadvertent or intentional misuse of nanotechnologies and explore opportunities for building global consensus on responsible development practices.

Experience shows that environmental and social sustainability complement one another and create important opportunities for convergent action. For example, nanotechnology's potential in addressing environmental challenges like potable water purification and sustainable energy solutions highlights the convergence of technology and environmental ethics.[216] The 2011 EHS research strategy reinforced the need to ensure that nanotechnology innovations solve environmental challenges. The alignment of nanoEHS efforts with a global sense of environmental and social sustainability emphasizes the importance of using nanotechnology in ways that respect and preserve the integrity of natural ecosystems and social fabrics.

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213 https://ceq.doe.gov/
214 https://doi.org/10.1021/acs.est.6b00298
215 https://unglobalcompact.org/what-is-gc/our-work/social
216 https://doi.org/10.1021/acsnano.1c10919

NNI community members support broad sustainability considerations in the updated strategy, including safe- and sustainable-by-design approaches and circularity. Importantly, "safe" and "sustainable" should not be traded against each other but considered equally. Accordingly, explicit examination of the safe- and sustainable-by-design concepts are important for efforts to address the responsible development of nanotechnology more fully.[217]

In addition, nanotechnology can be used in spaces and matrices that are not available for conventional technologies. For example, traditional drug delivery methods often are not specific, potentially causing side effects by affecting healthy tissues. In contrast, nanotechnology enables the creation of drug delivery mechanisms that can navigate the body's complex environments to deliver therapeutic agents directly to diseased cells.[218] The lens of social sustainability further encourages attention to how such treatments might reduce health inequities by addressing historically unjust environmental health burdens and also to how existing health inequities create challenges for producing treatments that are available and affordable to historically marginalized groups.

Pursue Environmental Justice in the Context of nanoEHS

The NNI community has called for the responsible development framework of nanotechnology to more fully align with the understandings of and visions for environmental justice. Nanotechnology research and development continues to work towards solutions that improve air quality, water quality, the safety and health of food, and climate resiliency. At the same time, the NNI community has strived to mitigate and reduce harmful pollution and chemical exposures across the life cycles of these nanotechnology-enabled solutions. However, based on the 2023 Executive Order 14096 definition of environmental justice, there are greater opportunities for NNI agencies to integrate environmental justice practices into nanoEHS efforts.[219] The EO states that environmental justice is "the just treatment and meaningful involvement of all people, regardless of income, race, color, national origin, Tribal affiliation, or disability, in agency decision-making and other Federal activities that affect human health and the environment so that people: (i) are fully protected from disproportionate and adverse human health and environmental effects (including risks) and hazards, including those related to climate change, the cumulative impacts of environmental and other burdens, and the legacy of racism or other structural or systemic barriers; and (ii) have equitable access to a healthy, sustainable, and resilient environment in which to live, play, work, learn, grow, worship, and engage in cultural and subsistence practices."[220] Possible areas in which environmental justice could guide activities include the following:

- Acknowledging that the 2011 strategy lacked any explicit attention to environmental justice, future NNI EHS efforts would benefit from the inclusion of methods to identify, acknowledge, and address legacy exposures to ENMs and incidental NMs of concern, cumulative impacts of chemical pollution, and the compounding effects of social injustices. Such efforts help fill the gaps in environmental and human health data that conceal harms from public view. By recognizing the remnants and present manifestations of discrimination, such activities can also reduce future environmental burdens and equip communities facing pollution and environmental degradation with knowledge and tools to increase opportunities for accountability.

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217 https://echa.europa.eu/hot-topics/chemicals-strategy-for-sustainability

218 https://doi.org/10.3389/fonc.2022.867655

219 https://www.federalregister.gov/documents/2023/04/26/2023-08955/revitalizing-our-nations-commitment-to-environmental-justice-for-all

220 https://www.federalregister.gov/documents/2023/04/26/2023-08955/revitalizing-our-nations-commitment-to-environmental-justice-for-all

How might environmental justice inform the changing landscape of nanotechnology use and commercialization?

The emissions from 3D printing technologies may cause exposure to incidental nanoparticles with potential adverse health effects. Moreover, this technology is increasingly being used in homes, makerspaces, schools, libraries, small businesses, and other non-traditional workplace settings not covered by existing occupational exposure standards and regulations (Figure 5).

Figure 5: Non-traditional workspaces for 3D printing activity are rising. Image credit: V. Loring (Pexel.com).

To address this concern, NIOSH began evaluating emissions from different printer and filament combinations in both chamber studies and workplace environments and has produced a guide that recommends approaches to safe 3D printing.[221] To further risk mitigation approaches, nanotechnology-enabled sensors could be developed to measure and analyze such emissions,[222] providing real-time information about potential exposures near 3D printers. This seems like a straightforward technical problem to solve, but how does the lens of environmental justice (EJ) impact the way to approach innovation in this space?

Embracing the principle of engaging communities, scientists and engineers may partner with affected populations, such as people who work with 3D printers in schools, makerspaces, and small businesses, recognizing that they are co-producers of knowledge in order to understand how communities' priorities and concerns align (or not) with this problem and proposed solutions. Discussions would be needed to establish whether prospective users want to know the details of air quality at every moment, or if running averages are more helpful. Are users equally concerned about the full range of incidental nanoparticles, or only those with proven health effects?

Remembering that there are historically marginalized populations or those who have suffered higher burdens of environmental toxic exposure, what are the profiles of the different kinds of users in 3D printing environments? Will young children in schools require sensors with lower detection thresholds? Do technicians in makerspaces or small businesses come into their jobs with histories of toxic exposures that make them more vulnerable to additional exposure to incidental nanoparticles? Will schools with more resources be more likely to design 3D printer makerspaces in large rooms with enhanced ventilation in comparison to less well-resourced schools? Will the cost of sensors make them inaccessible to all but the most privileged users?

This is not an exhaustive list of questions inspired by EJ lenses and does not touch on other areas such as data management, or if developing sensor technologies to address this issue is the best use of resources. However, this case illustrates how NNI agencies may better integrate environmental justice practices into their efforts.

- NNI agencies are encouraged to contribute to forward-looking initiatives to prevent future environmental injustices by pursuing meaningful engagement with communities historically underserved by advances in science and technology and overburdened by environmental pollution. Such collaborations can inform (1) directions of research and development through

221 https://www.cdc.gov/niosh/docs/2024-103/pdfs/2024-103.pdf

222 https://www.sciencedirect.com/science/article/pii/S0166526X21000970?via%3Dihub

community-driven problem framings that identify barriers to equitable, inclusive, and sustainable economies; (2) metrics of success that account for community priorities and needs; (3) risk assessment procedures that honor environmental justice concerns; (4) decisions about deployment that remain sensitive to issues of access, control, and ownership; and (5) the monitoring of processes that ensure ongoing accountability.

- NNI agencies are encouraged to promote and explore processes that further engage people on nanoEHS issues. These can take many forms but should be viewed as both a means to more just outcomes, as well as satisfying the goals of procedural justice that include recognizing groups and communities that have faced disproportionate burdens of environmental pollution and degradation, creating avenues for participation, and listening with humility and respect.

Address the Convergence of Nanotechnology and AI

The convergence of AI and nanotechnology is a notable development in science and technology, offering substantial advancements while posing unique challenges. AI, as an umbrella term, refers to the development of computer systems capable of performing tasks that typically require human intelligence.[223] These tasks include learning, reasoning, problem-solving, and understanding natural language. The dominant research paradigm in modern AI is machine learning, in which AI systems are "trained" on large quantities of data, from which they determine patterns that can be used to make predictions about new, previously unseen data.[224] This powerful technology plays a crucial role in driving the advancements of nanotechnology.

In the coming years, it is likely that many promising avenues will be found for the application of AI in nanoscale science and technology. Possible applications include the following:

- Acceleration of atomic-scale simulation and structure prediction, similar to the recent success of DeepMind's AlphaFold system for predicting the structures of proteins based on their amino acid sequences. AI will be key to understanding complex systems such as the dynamics of protein coronas and ecocoronas.
- New possibilities for nanomaterials synthesis, based on large datasets of synthetic conditions and materials characterization.
- Rapid analysis of large experimental datasets to aid in nanomaterials characterization.
- Simulation and prediction of the biological effects of nanomaterials at the tissue, organism, or ecosystem scales. Accurate predictions of biological effects could be useful in drug development, personalized medicine, and environmental impact assessment.
- As in other areas of science, large language models are likely to improve knowledge management and accelerate research by making research outputs more searchable and discoverable.

Recent advances in AI have given rise to a large and robust literature on risk mitigation, including the AI Risk Management Framework (RMF) published by NIST.[225] The RMF identifies seven key characteristics of trustworthy AI systems: safe, secure and resilient, explainable and interpretable, privacy-enhanced, fair, valid and reliable, and accountable and transparent (Figure 6).

[223] https://www.whitehouse.gov/briefing-room/presidential-actions/2023/10/30/executive-order-on-the-safe-secure-and-trustworthy-development-and-use-of-artificial-intelligence/
[224] https://doi.org/10.1007%2Fs12178-020-09600-8
[225] https://www.nist.gov/itl/ai-risk-management-framework

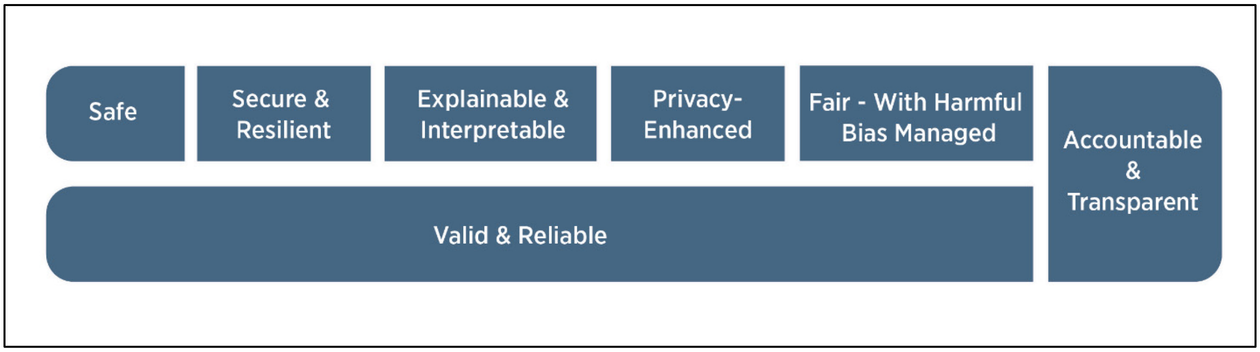

Figure 6: Characteristics of trustworthy AI systems. The NIST AI Risk Management Framework.[226]

In nanoscience applications, many of the most serious risk concerns outlined in the RMF will be less acute than with AI applications that focus on data or decisions related to individual people. At the same time, there are categories of risks that may result in EHS concerns:

- Poor or uneven performance: AI systems can make errors, particularly when attempting to make predictions about situations in which training data are inadequate. Performance concerns can be mitigated by tightly coupling predictions (about nanomaterials structures, properties, and their synthesis) with experimental validation. When properly identified, discrepancies between model predictions and experimental outcomes can be vital to improving the next generation of AI models.
- Overreliance and overconfidence: AI-based predictions of the biological and ecological effects of nanomaterials can be invaluable in accelerating EHS efforts. At the same time, EHS professionals may face the temptation to rely too heavily on *in silico* predictions in preference to *in vivo* and *in vitro* work that is needed to ground-truth AI predictions. While AI models may be a welcome adjunct to EHS work, there may be danger in turning to AI as a measure for cutting costs.
- Systemic bias: In many cases, AI systems have been shown to exhibit racial, gender, and other biases informed by the sociopolitical context from which data come. While this may seem far removed from nanotechnology, these types of systemic biases may still appear, for example in geographic data about the environmental risks faced by communities with a history of environmental under-monitoring.
- As indicated in the discussion on life cycle assessment, effects of emerging AI infrastructure and server operating requirements on energy generation, water and electricity demand, and emissions must be accounted for when considering benefits derived from AI-nanotechnology convergence.

The integration of AI tools into nanotechnology fields offers unprecedented capabilities to analyze complex nanoscale interactions, which can facilitate the development of predictive models for nanomaterials' behaviors. AI-driven predictive modeling expedites the identification of promising materials, reducing resource and time requirements for experimental testing. This is crucial for addressing future challenges and ensuring a proactive approach to risk mitigation. Furthermore, AI's ability to analyze large, complex datasets may play a pivotal role in personalized medicine. AI can tailor nanomaterial-based therapies to individual patient needs, thus optimizing treatment efficacy while minimizing side effects. This AI property empowers researchers to design nanomaterials with specific

[226] https://www.nist.gov/itl/ai-risk-management-framework

properties and functions, potentially revolutionizing various fields such as risk assessment, drug delivery, and environmental impact studies.

However, this advancement also brings significant EHS concerns. AI-based predictive models may be limited or biased by limitations or biases of the training data. Therefore, it is important to avoid over-reliance on predictions from AI models without separate empirical validation. Moreover, the rapid pace of AI-driven nanomaterials development could outstrip regulatory frameworks, resulting in gaps in safety evaluations, particularly for long-term effects. Although the democratization of nanomaterials synthesis through AI promises to accelerate developments in materials science research, it also raises concerns about the safety, potential misuse, and need for robust risk assessment practices. To address these challenges, proactive engagement among stakeholders is essential. Incorporating EHS considerations into AI algorithms from the outset, alongside the development of reliable algorithms and better large language models, can help ensure the accuracy and validity of outputs. Anticipating and overcoming challenges in AI, such as training data errors or biases, is critical for fostering responsible innovations in nanotechnology.

NNI EHS Research Strategic Actions

This section of the EHS research strategy outlines the main elements of a strategic action plan. The outline was created by extracting and synthesizing the main research needs identified in Parts A and B. These high-level topics will need further elaboration on the specific approaches and responses necessary to achieve their objectives. Thus, the NNI encourages the nanotechnology community to continue to develop the nanoEHS infrastructure to address these needs. The National Nanotechnology Coordination Office (NNCO), on behalf of the NNI, will coordinate NEHI's efforts to engage stakeholders in organizing a dynamic and agile response to the challenges outlined here.

Address Remaining EHS Knowledge Gaps for Engineered Nanomaterials in Commerce

Improving the understanding of the environmental and health implications of the main ENMs currently in production should continue, with a targeted focus on elevating the use and robustness of life cycle analyses and other areas previously mentioned. Activities in support of these objectives include the following:

- Continue to align hazard and exposure research and to improve dosimetry models.
- Encourage the conduct of longitudinal epidemiological studies on occupational exposure.
- Promote the development of portable and robust approaches such as personal breathing zone and on-site monitors for characterizing and assessing worker exposure.
- Explore more broadly potential organ and system toxicity; continue research on inhalation effects in non-pulmonary organ systems (cardiovascular, immunological, reproductive, neural, and gastrointestinal).
- Encourage additional investigation of transgenerational effects, including maternal-to-offspring impacts.
- Validate and standardize *in vitro* test methods, computational models, and *in vitro*-to-*in vivo* extrapolation tools.
- Encourage the integration and alignment of responsible research conduct training and ELSI in nanotechnology workforce development programs and initiatives.

Monitor and Evaluate Emerging Nanotechnology Applications

The NNI anticipates and supports continued growth in the application of nanoscale science and engineering in the development and commercialization of new materials, processes, and devices. Areas with significant nanotechnology-enabled applications and/or implications include food, agriculture, water and energy sustainability, electronics, semiconductors, batteries, 3D printing/advanced manufacturing, and biomedical applications. These directions will involve the creation of novel and hybrid materials and new tools, platforms, and methods, including machine learning and AI. Maintaining a proactive stance is vital to the NNI's responsible development goal. The NNI should:

- Convene collaborations (U.S. government, private sector, and international organizations) to explore informal mechanisms to regularly evaluate the fitness of risk frameworks to evaluate ongoing technological innovations.
- Foster dialogue and connections with the information technology community to improve transparency and robustness and reduce bias in EHS attributes that are used in machine learning and AI algorithms in understanding exposure, hazard, fate, and transport of nanomaterials.
- Apply, as appropriate, the advances in categorizing and grouping well-studied ENMs and associated products to new nanotechnology-enabled applications.
- Continue research on how the release of nanomaterials from composite materials impacts workers, makerspace users, consumers, and those closest to production sites that encompass manufacturing facilities and, increasingly, non-traditional work environments.
- Assess the sufficiency of current occupational health and safety technology, equipment, guidelines, and regulatory frameworks for emerging and critical work environments, including agricultural, electronic, and home environments. Assessments should aim to:
    - Discover any disparate exposure and risk associated with demography or socioeconomic backgrounds and prioritize protecting sensitive population segments and traditionally underserved groups and populations. "Underserved," in this context, refers to individuals or groups who have not had equitable access to, or benefited from, nanotechnology or may have been disproportionately exposed to risks from the technology.
    - Further develop risk management and risk communication strategies for distributed manufacturing environments such as home manufacturing and makerspaces that may not have access to trained EHS and industrial hygiene personnel.
    - Promote and/or develop tools to incorporate ELSI and environmental justice considerations early on and to the forefront of the design of epidemiological studies of worker exposure and long-term effects. Consent, privacy, community inputs, diversity of study populations, and of the researchers conducting these assessments, are some of the issues to be addressed.

Investigate Emerging Nanoscale Contaminants of Concern

The federal nanosafety community is committed to leveraging the nanoEHS infrastructure to assess environmental and health effects of emerging incidental nanomaterials of concern such as nanoplastics and 3D printer emissions. Federal agencies will maintain strong connections across the nanoEHS community to accelerate the coordination of activities around future challenges. Strategic actions to address this issue would:

- Facilitate collaboration, including sharing of samples, data, and tools between researchers within and outside of the federal government. Key research areas include the determination,

characterization, and quantification of nanoplastics in animal populations, the food supply chain, and potential human health risks from exposure to nanoplastics.
- Forge greater connections to state governments, academia, the private sector, and community interests in designing and conducting a research agenda to fulfill these goals.
- Support U.S. scientific engagement and cooperation in inter-laboratory studies, guidelines and standard materials development, and the exchange of nanoplastics research data.
- Continue to conduct research to integrate exposure and toxicity data into risk assessment of 3D printer emissions, and the impact of these emissions on indoor air quality.
- Increase the amount and quality of available data for life cycle assessment of 3D-printed products and devices.

Strengthen the Collaborative Informatics Infrastructure

Strengthening the integrative, interdisciplinary data and informatics infrastructure is vital to reducing disciplinary silos and accelerating the availability, use, and reuse of federally supported nanoEHS data. Here are key actions toward this objective:

- Continued participation and support of interagency activities such as DIIG's efforts to develop robust, interoperable nanoinformatics platforms for federal nanoEHS databases and identify mechanisms to reduce barriers to cross-agency collaboration.
- Leverage the nanoEHS data to integrate information across the life cycles of nanomaterials from synthesis to disposal, in support of risk assessment and risk management decisions.
- Build connections between the nanoinformatics community and other informatics communities in multistakeholder community forums, developing mutually beneficial use-case histories, solutions, and best practices.

Increase Engagement with the International Nanosafety Community

The EHS strategy should align with the 2021 NNI Strategic Plan, which states that "NNI agencies and NNCO leadership will strengthen engagement with international counterparts and nanotechnology-focused organizations to share information, learn from each other, and monitor emerging trends." The NNI's international engagement, particularly through the U.S.-EU NanoEHS CORs, has been effective in building a cooperative research agenda. To leverage and strengthen the U.S. role in bridging nanoEHS concerns and focus across regions, the federal community can provide leadership with actions that include:

- Expansion of the NanoEHS CORs outreach and engagement with emerging/early-career nanoEHS experts.
- Growth of international nanoEHS research collaborations to regions beyond Europe.
- Facilitation of information sharing regarding U.S. government and foreign programs that support international nanotechnology engagements.
- Fostering international collaboration and knowledge sharing on nanoEHS research, including cooperation on standards for ethics in research. These activities should aim to align international engagement with NNI strategic goals and identify potential areas of concern. This global perspective will help ensure that U.S. efforts to address responsible development of nanotechnology consider and address domestic and international challenges and opportunities.

Expand Public Engagement in the Responsible Development of Nanotechnology

The NNI should continue to enhance societal understanding of progress in determining the EHS implications and potential risks of nanotechnology. Additionally, agencies are encouraged to create opportunities for the meaningful involvement of all people in developing forward-looking initiatives around nanoEHS. The NNI agencies should:

- Foster dialogue among scientists, the general public, policymakers, and industry on strategies to increase the information available to consumers and civil groups. Particular attention should be paid to including communities overburdened by pollution and environmental degradation in these discussions. (See the section above, "Pursue Environmental Justice in the Context of nanoEHS" for further discussion.)
- Work with international collaborators to exchange information on fostering inclusive, diverse, and multistakeholder dialogues to share information regarding benefits and risks of nanotechnology.
- Update methods and approaches to effectively tailor communication of the risks and benefits of nanotechnology to diverse audiences and evaluate the results of these activities to inform future efforts.
- Connect demographic, environmental, and social vulnerability data to nanotechnology infrastructure to identify communities that historically have not received equitable access to the benefits of nanotechnology or have been disproportionately exposed to its potential harms.
- Foster the development of a community of expertise on ELSI issues related to nanotechnology, as called for since 2011. The capacity of federal agencies to do so rests on creating and connecting a resource base of ELSI, environmental justice, RECR, and RRI experts to identify and address nanotechnology-specific features in these areas.