Progress and Plans for NNI Agencies' Environmental, Health, and Safety (EHS) Investments, Taken from the National Nanotechnology Initiative (NNI) Annual Supplements to the President's Budget[1]

Background

The annual NNI supplements to the President's Budget are submitted to Congress and serve as the Annual Report for the NNI, as called for under the provisions of the 21st Century Nanotechnology Research and Development Act (15 USC §7501). The information below describes (1) agency plans for EHS investments for Program Component Area (PCA) 5, and (2) examples of progress toward the NNI's Responsible Development goal. The published material has been edited to streamline multiple references to the same projects. The extract has been prepared as a resource document for the 2023 review of the 2011 NNI EHS Research Strategy.

2019 Agency Progress and Plans

FY 2019 Plans (PCA 5. EHS)

NSF sponsors two ongoing university-based Centers for Environmental Implications of Nanotechnology. NIOSH will continue to conduct toxicology studies to evaluate biomarkers of exposure; cardiovascular, pulmonary, and dermal effects of exposure; and immune response to a wide variety of nanomaterials and nanotechnology-enabled products. DOD will continue to work with industry to develop "organ-on-a-chip" technology for next-generation toxicity testing of advanced nanomaterials used in aerospace applications, for portable, low-cost toxicology testing methods to influence material formulation, material down-select, and risk mitigation.

NanoEHS research at NIH is led by the National Institute of Environmental Health Sciences (NIEHS). These research efforts are designed to gain a fundamental understanding of the molecular and pathological pathways involved in mediating responses to engineered nanomaterials (ENMs). To continue the success achieved with a small library of ENMs, ongoing centers for nanotechnology health implications research are funded through two NIEHS funding opportunity announcements through 2021. The NIEHS National Toxicology Program will also continue to conduct research in collaboration with FDA to understand the potential health hazards of nanomaterials and to develop novel methods and approaches for detection of nanomaterials in FDA-regulated products. In addition, the Nanotechnology Health Implications Research (NHIR) Consortium research efforts will be expanded to include an additional 20 ENMs, including graphene, graphene oxide, nanocellulose, and other anisotropic ENMs. Work on these ongoing projects will continue into 2019.

NNI agencies develop and share a diverse collection of resources for stakeholders—from academic researchers to product developers. NIOSH plans to develop, test, and evaluate direct-reading instruments capable of detecting and measuring airborne nanoparticles. Additional plans include continuing field tests of the portable aerosol multielement spectrometer developed by NIOSH at nanomaterial producer and user facilities, as well as efforts in detection of airborne nanoparticles, including in biological systems, to evaluate and predict biological behavior and translocation between organ systems. NIOSH will also explore the feasibility of applying advanced sensing technology to biomarkers as a means of evaluating nanomaterial exposure and possible early response. CPSC and NIST will collaboratively work on the development of a bioassay validation program, including a protocol and validation procedures for analysis of nanomaterials in various matrices, evaluating the sensitivity of *in vitro* assays such as the NIOSH electrophilic allergen screening assay. CPSC and NIST will also assess the presence of nanomaterials in house dust, including the

[1] https://www.nano.gov/NNIBudgetSupplementsandStrategicPlans

development of a protocol for analyzing dust samples collected from the Department of Housing and Urban Development Healthy Homes Survey.

The continued creation and deployment of computational tools to inform nanosafety researchers and guide responsible development remains an active area for several NNI agencies. For instance, DOD will integrate the Army Engineer Research and Development Center-developed Nano Guidance for Risk Informed Deployment (NanoGRID) framework[2] for collection and assessment of chemical, physical, and toxicology data to support systems acquisition decision-making. Based on a previously funded state-of-the-science literature review on the toxicity of commercially relevant forms of nanoscale silver, carbon nanotubes, and titanium dioxide, CPSC will assemble a database that identifies and evaluates the strengths and weaknesses of analytical methods that detect the presence and measure release of nanomaterials. An additional database will include a summary of hazard and characteristics/properties data on 10 nanomaterials.

NNI agency activities will continue to contribute to the suite of adaptable, transparent, and robust tools and frameworks that support the safety assessment of nanotechnology. DOD will support work towards demonstrating the utility of multi-criteria decision analysis approaches to risk assessment, and transitioning from traditional risk assessment towards risk-based decision-making and alternatives-based governance for nanotechnology and other emerging technologies. Ongoing DOD work with industry and academia will support the life-cycle assessment of nanotechnology-enabled products, and will disseminate standard operating procedures for assessment of characterization, release fate, and hazard. DOD will also work with NIOSH to finalize a framework for conceptualizing the sustainability of advanced materials (including nanomaterials), including a new point source nanomaterial fate and transport model (NanoTRAK).

The development and adoption of standards for consistent and globally recognized terminology, nomenclature, specifications, and tests are indispensable to evaluating nanoEHS research. Representatives from NNI agencies, including the NNI Coordinator for Standards Development, continue to be actively engaged with standards developing organizations. For example, NIST—in collaboration with other agencies, academic institutions, and the private sector—is leading efforts in the International Organization for Standardization's Technical Committee 229: Nanotechnologies (ISO TC 229) to develop methods for assessing the release of manufactured nanomaterials from commercial, manufactured nanomaterial-containing polymer composites. This work will help improve understanding of how ENMs may be released from commercial products.

NNI agencies will continue to share information and best practices with the research and development community through a variety of mechanisms, including guidance documents and other publications. FDA's Center for Biologics Evaluation and Research and Center for Drug Evaluation and Research will assess public comments received on their December 2017 joint draft guidance document, *Drug Products, Including Biological Products, that Contain Nanomaterials, Guidance for Industry*.[3] DOD will work with EPA, NIST, and industry to develop internationally recognized guidance documents and methods to assess potential EHS impacts of nanomaterials and nanotechnology-enabled products. NIOSH plans to finalize the Current Intelligence Bulletin (CIB) on *Occupational Exposure to Silver Nanomaterials* and release a draft CIB, *Approaches to Developing Occupational Exposure Limits or Bands for Engineered Nanomaterials*. NIOSH recently published four new documents, including three workplace design solutions and one poster, to provide options to companies for controlling possible exposure of their workers to nanomaterials on the job.[4]

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[2] https://www.youtube.com/watch?v=SM92WzHA87w

[3] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588857.pdf

[4] https://www.cdc.gov/niosh/topics/nanotech/pubs.html

As nanotechnology-enabled innovations and products increasingly make their way into the marketplace, NNI agencies are targeting their activities to address nanoEHS considerations that are specific to the use of nanomaterials in manufacturing and consumer products, as well as in food and agriculture. DOD will continue to work with academia and industry to organize a series of workshops on the EHS decision process for implementing nanomaterials, other advanced materials, and additive manufacturing. NIOSH and CPSC will collaborate to study the release of engineered nanomaterials from laser printer toner and from 3D printers. NIOSH plans to work with industry to develop practical, "real world" evaluation of hazard and risk represented by nanomaterials through their life cycles and collaborate with industry to assess the toxicology of carbon-based, metal-based, and nanoclay-enabled materials.

Work on evaluating the use of nanomaterials in consumer products spans several agencies. CPSC and NIST will participate in an ISO project, "Nano-screening Program on Nanomaterial Release from Consumer Products," to review and evaluate the utility of available methods to assess material released from commercial polymer composites containing added nanomaterials, in support of product use and safety decisions. CPSC and DOD will develop models for the risk of exposure to nanomaterials released from consumer products. NIST's 2019 request includes research to understand and measure the reduced flammability of upholstered materials incorporating nanomaterials, and the analysis of nanomaterials in complex matrices. NIOSH plans to continue collaborations to evaluate zinc and titanium-enabled sprays and treated surfaces.

NIFA's nanotechnology programs will continue to support EHS research relevant to agricultural production and food applications, including characterization of hazards, exposure levels, and transport and fate of engineered nanoparticles or nanomaterials in crops, soils (and soil biota), livestock, and production environments. These assessments may also include animal feed formulations and processes that utilize novel nanomaterials or the development of new nanostructured materials or nanoparticles that are bio-persistent in digestive pathways.

FY 2019 Progress towards the NNI Goal (Responsible Development

Detecting and understanding the effects of nanomaterials in the environment and the human body. The ability to detect nanomaterials in products and understand their interactions within the human body is central to understanding the potential EHS impacts of nanomaterials. FDA and NIEHS have collaborated to develop novel methods and approaches for detection of nanomaterials in FDA-regulated products, including physicochemical characterization and standards development. Knowledge gained from this research has enabled FDA to better assess the safety and efficacy of medical products with this novel technology, for premarket review, postmarket assessment, and guidance development.[5]

Examples of programs supporting research on material-specific effects include the NHIR Consortium, funded by NIH.[6] NHIR has developed a system to prioritize the selection criteria for sets of engineered nanomaterials to be investigated using a wide range of test systems to reflect diverse routes of exposure (inhalation, ingestion, and ocular). Efforts are focused on developing biological response profiles for 15 engineered nanomaterials. The NIEHS National Toxicology Program has completed an evaluation of the immune system impact of inhalation of multiwalled CNTs in rodent models to better understand the potential health effects

[5] https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm

[6] https://www.niehs.nih.gov/research/supported/exposure/nanohealth/index.cfm

from low-dose exposure in workers.[7] This work complements the exposure assessment of nanomaterial manufacturing facilities conducted in collaboration with NIOSH.[8]

Understanding and mitigating potential impacts in the workplace. NIOSH researchers develop hazard and safety assessments using key classes of engineered nanomaterials, including carbon nanotubes; metal oxides; silver; the nanowire forms of silver, silica, and titania; graphene and graphene oxide; and cellulose nanocrystals and nanofibers. "Real-world" evaluations of hazard and risk represented by various nanomaterials through their life cycles have been performed by NIOSH, including the characterization of 22 commercially available spray products that advertised the use of nanoscale silver or colloidal silver as the active ingredient. NIOSH also has collaborated with over 20 national and international universities in the characterization of toxicological effects of pulmonary and dermal exposure to a wide range of industrially relevant nanoparticles and nanotechnology-enabled materials.[9]

DOD researchers have developed and released the NanoGRID v1.0 tool.[10] NanoGRID is a software program that implements a tiered-based approach for EHS testing and assessment. DOD also has published a methodology and website supporting the life-cycle assessment of nanotechnology-enabled products developed by small businesses in collaboration with industry and academia.[11]

Developing and disseminating information. In response to a critical need expressed by the nanomanufacturing community, NIOSH has published a new chapter in the *NIOSH Manual of Analytical Methods*: Analysis of Carbon Nanotubes and Nanofibers on Mixed Cellulose Ester Filters by Transmission Electron Microscopy.[12] FDA has released draft guidance on *Drug Products, Including Biological Products, that Contain Nanomaterials* for public comment.[13] The draft guidance provides recommendations to industry engaged in developing human drug products in which nanomaterials are present in the finished dosage form, including recommendations regarding investigational, premarket, and postmarket submissions for these products.

2020 Agency Progress and Plans

FY 2020 Plans (PCA 5. EHS)

NSF continues to sponsor a Center for Environmental Implications of Nanotechnology. NIOSH will continue to conduct toxicology studies to evaluate biomarkers of exposure and disease using proteomic, metabolomic, and bioinformatic approaches. NIOSH will also continue developing innovative *in vitro* methodology to better predict *in vivo* outcomes, and evaluating pulmonary and dermal exposure and toxicity, and systemic toxicity that results from occupational exposures.

FDA's investments span several FDA centers. Select highlights include Center for Drug Evaluation and Research (CDER) research on quality considerations for complex drug products, bioequivalence of drug products containing nanomaterials, and advanced and emerging characterization methods; Center for

[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5215911/

[8] https://ntp.niehs.nih.gov/annualreport/2015/partners/niosh/index.html

[9] https://www.cdc.gov/niosh/topics/nanotech/default.html

[10] https://nano.el.erdc.dren.mil/tools.html

[11] https://nano.el.erdc.dren.mil/index.html

[12] https://www.cdc.gov/niosh/nmam/pdf/chapter-cn.pdf

[13] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588857.pdf

Devices and Radiological Health (CDRH) efforts to better understand the complex interactions that occur between the body's physiological processes and various types of nanoengineered surfaces; and National Center for Toxicological Research and Office of Regulatory Affairs investments in advanced tools, safety assessments, staff training, standard methods, and methodology development.

EPA's nanoEHS research is focused on developing and applying information on engineered nanomaterials to inform both exposure and hazard assessments and support risk-based decisions related to the agency's implementation of the Toxics Substances Control Act and the Federal Insecticide, Fungicide, and Rodenticide Act. For example, the agency is conducting research to characterize the transport, transformation, fate, and environmental impacts of nanotechnology-enabled pesticides.

NIH nanoEHS research efforts are designed to gain a fundamental understanding of the molecular and pathological pathways involved in mediating biological responses to engineered nanomaterials (ENMs). To continue the success achieved with a small library of ENMs, the Nanotechnology Health Implications Research (NHIR) consortium centers will continue to be funded through 2021. The centers will continue their efforts to gain understanding on ENM-biological interactions using diverse *in vitro*, tissue-on-chip, and *in vivo* models, and will expand their efforts to include additional emerging anisotropic ENMs. This research complements exposure assessment of nanomaterial manufacturing facilities conducted in collaboration with NIOSH.

NIST researchers are working with CPSC under an interagency agreement to develop protocols to screen, collect, and detect ENMs in house dust. NIST and the European Commission Joint Research Centre intend to continue a collaborative effort to address the need for proven methods, standards, and reference materials to expedite the testing and regulatory approval of nanotechnology-enabled medical products. Two pilot programs focused on liposomal drug formulations are under development.

As the use of 3D printers and additive manufacturing expands, agencies are working to ensure the responsible development of these technologies. CPSC and NIOSH will continue to investigate potential emissions, human exposures, and health implications of human exposure to ultrafine particles and bioactive compounds from 3D printers. EPA is planning complementary research to characterize the filaments, emissions, and products of 3D printing processes, and the resulting human exposures. DOD is characterizing emissions of nanoparticle additives and volatile organic compounds from fused deposition modeling 3D printers and stereolithography 3D printers, respectively; a future collaboration with NIOSH is anticipated.

NIFA support for EHS research relevant to agricultural production and food applications includes EHS assessments of engineered nanoparticles applied in food and agricultural systems; characterization of hazards, exposure levels, and transport and fate of engineered nanoparticles or nanomaterials in crops, soils (and soil biota), livestock, and production environments; as well as research on transport and fate of engineered nanoparticles in digestive pathways.

NIOSH plans to continue its work with trade unions and industrial partners to evaluate nanotechnology-enabled spray coatings, composites, and other nanotechnology-enabled materials in construction and manufacturing.

FY 2020 Progress towards the NNI Goal (Responsible Development)

Understanding and mitigating potential impacts in the workplace. Recently NIOSH provided a second draft of its *Current Intelligence Bulletin on Occupational Exposure to Silver Nanomaterials*[14] for public review and held an open public meeting to solicit comment. It published three workplace design solutions to

[14] https://www.cdc.gov/niosh/docket/review/docket260a/pdfs/260-A-Draft-Silver-NM-CIB_8-24-18_1.pdf

provide options to companies for controlling possible nanomaterial exposure of their workers. NIOSH also released *Continuing to Protect the Nanotechnology Workforce: Nanotechnology Research Plan for 2018–2025* in January 2019.[15]

The National Institute of Justice administers the Compliance Testing Program (CTP), a voluntary conformity assessment program for the testing and certification of body armor used by law enforcement. In 2018, the NIJ CTP published program requirements for ballistic-resistant and stab-resistant body armor submitted to the program for testing that contain carbon nanotubes or other nanomaterials. These requirements focus on protecting the health of workers involved in the manufacturing, testing, handling, and wearing of body armor submitted to NIJ's program who may be exposed to nanomaterials.

Developing methodologies and standards to support nanoEHS research. Over the past three years, NHIR consortium researchers funded by NIH have studied 26 ENMs of diverse physicochemical properties. The focus has been to generate biological response profiles for the emerging 2D and 3D ENMs (graphene, graphene oxide, nanocellulose, and other anisotropic materials). The NIH National Toxicology Program has been collaborating with FDA to understand the health hazards of nanomaterials and to develop novel methods and approaches for detection of nanomaterials in FDA-regulated products. This includes physicochemical characterization and standards development processes.

NIST researchers working in conjunction with FDA have studied the effect of cutting, washing, and scratching nanosilver-containing materials to determine if these common consumer practices initiate or impact nanoparticle release into the environment or into food. The studies showed that while bits of matrix polymer were released by the various methods of abrading the surface, no free silver nanoparticles were observed.[16] NIST and CPSC are collaborating to develop testing and measurement protocols to evaluate the quantities and properties of engineered nanoparticles released from floor coatings and paints by abrasion and/or weathering. Knowledge gained from these efforts contributed to the ongoing development of ISO Technical Report 22293, "Evaluation of methods for assessing the release of nanomaterials from commercial, nanomaterial-containing polymer composites."

Developing and disseminating information. As knowledge is created to support the responsible development of nanotechnology, the NNI agencies employ a variety of means to disseminate and incorporate this information into practice. Examples of resources include the NIOSH documents referenced above, FDA guidance documents, and a joint DOD-CPSC knowledge document on a risk prioritization framework and tool to group different nanomaterials in consumer products.[17]

2021 Agency Progress and Plans

FY 2021 Plans (PCA 5. EHS)

Agencies continue to build on the rich body of nanoEHS knowledge and to collaboratively protect researchers, workers, consumers, and the environment. NIOSH plans to develop, test, and evaluate direct-reading instruments capable of detecting and measuring airborne nanoparticles. The portable aerosol multi-element spectrometer developed by NIOSH will be field tested at nanomaterial producer and user facilities. NIOSH will work with industry to develop practical, "real-world" evaluations of hazard and risk represented by nanomaterials through their life cycles, and will assess the toxicology of carbon and metal-based nanomaterials, nanocellulose, and nanoclay-enabled materials. NIOSH will also work with trade unions and

[15] https://www.cdc.gov/niosh/docs/2019-116/default.html

[16] www.nist.gov/news-events/news/2018/11/do-kitchen-items-shed-antimicrobial-nanoparticles-after-use

[17] https://pubs.rsc.org/en/content/articlelanding/2018/en/c8en00848e/unauth#!divAbstract

industrial partners to evaluate nanotechnology-enabled spray coatings, composites, and other nanomaterials in construction and manufacturing. NIOSH and CPSC will collaborate to study the release of engineered nanomaterials from three-dimensional (3D) printers.

NIST will establish a research effort on nanofluidic measurement devices and optical microscopy methods to characterize nanoplastics. NIST is also developing nanoparticle Standard Reference Materials (SRMs) of different materials and sizes including polystyrene, gold, and silica to enable accurate calibration of instruments used to characterize nanoparticles. NIST is studying the performance of vinyl siding made of polyvinyl chloride and particulate additives on the micrometer and nanometer scales. Performance measures include appearance, impact performance, and flammability before and after UV exposure. NIST continues to refine computational tools to evaluate consumer exposure to airborne engineered nanoparticles by incorporating enhancements associated with transport phenomena, usability, and input data into its models. NSF supports the Center for Sustainable Nanotechnology.[18]

The nanoEHS efforts of NIH's National Institute of Environmental Health Sciences (NIEHS) are designed to gain a fundamental understanding of the molecular and pathological pathways involved in mediating biological responses to engineered nanomaterials. The Nanotechnology Health Implications Research (NHIR) Consortium[19] will continue through 2021 with efforts to evaluate engineered nanomaterial (ENM)-biological interactions using diverse *in vitro*, tissue-on-chip, and *in vivo* models. NIEHS will continue studies to better understand the immune system response to the inhalation of CNTs in rodent models, as well as CNT chronic cancer bioassays. The NIEHS Superfund Research Program[20] plans to emphasize research that includes nanotechnology-enabled structures to enhance sustainable remediation. Collaborative efforts with FDA under the National Toxicology Program[21] and active participation in the interagency discussion of nanoplastics will continue to be a priority. FDA's National Center for Toxicological Research (NCTR) and Office of Regulatory Affairs (ORA) will invest in advanced tools, safety assessment, staff training, standards methods, and methodology development to better understand emerging issues with nanomaterials in FDA-regulated products.

NIFA supports EHS research relevant to agricultural production and food applications. Risk assessments of nanotechnology uses in food and agricultural systems include characterization of hazards, exposure levels, and transport and fate of engineered nanomaterials in crops, soils (and soil biota), livestock, and production environments. The program also supports research on transport and fate of engineered nanoparticles or nanomaterials associated with food production, processing, and interactions with microbiota in the human gastrointestinal tract.

FY 2021 Progress towards the NNI Goal (Responsible Development)

Developing and disseminating information. The NIH/NIEHS National Toxicology Program recently completed an evaluation of the immune system impact of inhalation of multiwalled carbon nanotubes in rodent models to better understand the potential health effects from low-dose exposures in workers. This research complements exposure assessment of nanomaterial manufacturing facilities conducted in collaboration with NIOSH. NIST developed two computational tools to evaluate consumer exposure to airborne engineered nanoparticles. The first is an online tool that provides estimates of indoor occupant exposure to airborne particles. The second tool, referred to as the size-resolved tool, includes additional

[18] https://susnano.wisc.edu/

[19] https://www.niehs.nih.gov/research/supported/exposure/nanohealth/grantees/index.cfm

[20] https://www.niehs.nih.gov/research/supported/centers/srp/index.cfm

[21] https://ntp.niehs.nih.gov/

physical models that account for the properties of nanoparticles that may impact their transport within the built environment.[22]

Examples of documents published in the last year include an FDA document entitled *Nanotechnology—Over a Decade of Progress and Innovation*[23] and two workplace posters from NIOSH to share information on 3D printing.[24]

Developing protocols and methods. NIST and CPSC collaboratively developed protocols and methodologies for characterizing size, morphology, and composition of ENMs released from floor coatings and paints by abrasion and/or weathering. NHIR consortium investigators developed the Scatter Enhanced Phase Contrast method, which provides a generalized label-free approach for monitoring nanoparticle transport in living cells. The technique works for a variety of metal and metal oxide nanoparticles and is expected to contribute to the design of next-generation drug delivery systems.

FDA continues to develop analytical methods for the characterization of nanomaterials in FDA-regulated products. Such methods will enable FDA to identify potential risks associated with products that contain nanomaterials and will provide guidance to sponsors/reviewers for the future approval of products. FDA also continues research to addresses fundamental data gaps and challenges associated with safety assessment of medical devices containing nanomaterials. Research efforts have been focused on evaluating and refining biological test methods, as well as investigating the interaction of pulsed lasers with plasmonic nanoparticles used in emerging optical diagnostic and therapeutic products.

Understanding and mitigating potential impacts in the workforce. NNI agencies support efforts to understand potential impacts in the workplace and protect workers as the introduction of nanomaterials and nanotechnology-enabled products accelerates into commerce. For example, NIOSH performs real-world evaluations of hazard and risk represented by various nanomaterials through their life cycles, including the characterization of aerosols generated in spray coating of paints, sealants, and disinfectants. Environmental chambers are used to evaluate a variety of nanotechnology-enabled construction materials in a controlled environment. NIOSH also has collaborated with national and international universities and numerous industrial partners in the characterization of toxicological effects of pulmonary and dermal exposure to a wide range of industrially relevant nanoparticles and nanotechnology-enabled materials. NIOSH is also evaluating workplaces such as schools that are using 3D printers and is working with a printer manufacturer that is developing a local exhaust ventilation system for its newest model of fused filament fabrication printer.

Leveraging efforts to address emerging concerns. Through the years, the NNI agencies have worked together to develop a broad body of knowledge and supporting tools related to the nanoEHS implications of ENMs. This collaborative ecosystem is poised to apply the lessons learned from research on engineered nanomaterials to emerging incidental materials, including nanoscale plastic particles arising from the degradation of plastic waste in the environment.

Many agency activities related to nanoplastics are focused on understanding the EHS implications of these materials. For example, agencies such as FDA, ATSDR, NCEH, USGS, and NIST are interested in the development of sampling and measurement protocols. NIST developed a measurement system that enables dimensional and optical metrology of single nanoparticles with record precision, accuracy, and efficiency,

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[22] https://pages.nist.gov/CONTAM-apps/

[23] https://www.fda.gov/media/140395/download

[24] https://www.cdc.gov/niosh/docs/2020-115/pdfs/2020-115.pdf?id=10.26616/NIOSHPUB2020115, https://www.cdc.gov/niosh/docs/2020-114/pdfs/2020-114.pdf?id=10.26616/NIOSHPUB2020114

and that can inform the characterization of environmental nanoplastics. NIST also developed a method to characterize the concentration of metal, oxide, and plastic nanoparticles in water involving microdeposition of aqueous suspensions by inkjet printing. The measurement achieves a relative uncertainty that is an order of magnitude better than the benchmark method of microdroplet gravimetry.

2022 Agency Progress and Plans

FY 2022 Plans (PCA 5. EHS)

Agencies continue to build on the rich body of nanoEHS knowledge and to collaboratively protect researchers, workers, consumers, and the environment. NSF's ENG Directorate will begin a program that supports quantum biology proposals in 2022 to better understand nano/bio quantum phenomena and control interfacial nanoEHS interactions. The Center for Sustainable Nanotechnology will continue its activities through 2025 with support from the MPS Directorate.

FDA invests in nanotechnology research to help address questions related to the safety, effectiveness, quality, and/or regulatory status of products that contain engineered nanomaterials or otherwise involve the use of nanotechnology. FDA also invests in research to develop models for safety and efficacy assessment and to study the behavior of nanomaterials in biological systems and their effects on both human and animal health. NIEHS efforts under the National Toxicology Program (NTP) will continue studies to better understand the impacts of inhalation of multiwalled CNTs on immune system function.

NIOSH will continue to develop occupational safety and health guidance that can be incorporated into business plans to both protect worker safety and promote safe application development and commercialization. NIOSH is evaluating biomarkers of exposure and disease using proteomic, metabolomic, and bioinformatic approaches; developing innovative *in vitro* methodology to better predict *in vivo* outcomes; and evaluating pulmonary and dermal exposure and toxicity, and systemic toxicity that may result from occupational exposures to wide variety of nanomaterials and nanotechnology-enabled products along the life cycle of the materials. NIOSH plans to develop, test, and evaluate direct-reading instruments capable of detecting and measuring airborne nanoparticles. Additional plans include continuing field tests of the portable aerosol multielement spectrometer developed by NIOSH, and efforts in detection of airborne nanoparticles to evaluate and predict biological behavior and translocation between organ systems. NIOSH will also explore the feasibility of applying advanced sensing technology and data analytics to biomarkers as a means of evaluating nanomaterial exposure and possible early response. NIOSH plans to work with industry to develop practical, "real world" evaluations of hazard and risk represented by nanomaterials through their life cycles and collaborate with industry to assess the toxicology of carbon-based, metal-based, nanocellulose, and nanoclay-enabled materials. NIOSH plans to continue collaborations with non-profit organizations, trade unions, and industry to evaluate nanotechnology-enabled spray coatings, composites, and other nanotechnology-enabled materials in construction and manufacturing.

The NIST nanoEHS research portfolio includes projects focused on understanding and measuring incidental nanoplastics, development of reference materials, establishment of new measurement techniques for consumer products, and evaluations in real-world environments. For example, NIST researchers working in conjunction with FDA and academic scientists are investigating the degradation of polymers containing nanomaterials that exhibit barrier properties useful in many diverse applications, including outdoor coatings for corrosion-resistant infrastructure and food packaging for extended ingredient freshness. Efforts continue to develop metrics to assess changes in nanocomposite performance—including mechanical strength, gas permeability, corrosion resistance, and antimicrobial properties. Recently, NIST researchers have begun to investigate how different formulations of polyvinyl chloride (PVC, a key component of vinyl home siding) regulate the appearance, impact performance, and flammability of the resultant composite siding material before and after UV exposure. Chemical characterization and impact test analyses to simulate vehicle collision, hail, and debris during windstorms are ongoing.

EPA's engineered nanomaterials research is focused on developing, collating, mining, and applying information on engineered nanomaterials to inform both exposure and hazard assessments and to support risk-based decisions related to the agency's implementation of the Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). EPA's research activities have two objectives. The first objective is to evaluate the environmental release and assess human and ecological exposures to engineered nanomaterials. For example, EPA is conducting research to characterize the weathering, release, and transformation of nanomaterials from nanotechnology-enabled consumer products, and to characterize the transport, transformation, fate, and environmental impacts of nanotechnology-enabled pesticides.[25] The second objective of EPA's research activities is focused on integrating information and developing a user interface for the existing nanomaterials database, NaKnowBase.

NIFA supports nanoEHS research relevant to agricultural production and food applications. Risk assessments of the use of engineered nanoparticles in food and agricultural systems include characterization of hazards, exposure levels, and transport and fate of engineered nanoparticles or nanomaterials in crops, soils (and soil biota), livestock, and production environments. The program also supports research on transport and fate of engineered nanoparticles or nanomaterials and nanostructures for nutrient delivery in food production, processing, and interactions with microbiota in the human gastrointestinal tract.

CPSC engages with Federal partners in projects intended to characterize and quantify exposures to engineered nanomaterials released from products. For example, CPSC and NIST continue to work on the optimization of *in vitro* test methods used to determine the toxic endpoints of nanomaterials. CPSC and ERDC continue their collaboration, along with the Center for the Environmental Implications of NanoTechnology, to develop a model to predict the health effects of matrix-bound nanomaterials. The findings of this project, which uses novel and advanced techniques to capture toxicity and exposure data for a range of nanomaterials, and its resultant database will be released to the public.

Collaborative research efforts between NIEHS, FDA, and other Federal agencies on incidental nanoplastics are planned. The National Center for Environmental Health is supporting a research fellowship focused on understanding the environmental and health effects of micro- and nanoplastics. The Fellow is developing a scoping literature review and a plan to host a science symposium on microplastics.

CPSC, EPA, NIOSH, and NIST collaborative work is evaluating emissions, factors influencing emissions, and the potential toxicity from exposure to emissions from fused deposition modeling 3D printers. This interagency work is expanding to other types of 3D printers that are becoming more affordable to small businesses and the public. NIOSH and CPSC will continue collaborations to study the release of ultrafine particulate and engineered nanomaterials from polymer-based 3D printers. A study of metal-powder-based additive manufacturing will commence in 2022.

Consensus standards activities play an important role in developing confidence in the safety and efficacy of nanomaterials. Several Federal agencies contribute to efforts in the International Organization for Standardization (ISO) TC 229 Working Group 3: Health, Safety and Environmental Aspects of Nanotechnologies. NIOSH plans to continue collaborations with ISO 23151—Nanotechnologies—Particle Size Distributions for Cellulose Nanocrystals, and the Organisation for Economic Co-operation and

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[25] More information is available at https://www.epa.gov/chemical-research/research-nanomaterials.

Development (OECD) Test Guideline 110—Particle Size Distribution/Fibre Length and Diameter Distributions. CPSC staff are engaged in voluntary standards activities to create validated methods for quantifying and characterizing exposures from products, including an ISO project evaluating the release of nanomaterials from treated wood.

FY 2022 Progress towards the NNI Goal (Responsible Development)

Leveraging interagency nanoEHS expertise. CPSC has collaborated with other Federal agencies to address the critical need for focused research on consumer product applications of nanomaterials and their potential risks to consumers. CPSC's collaborative activities have produced more than 72 reports and publications, in addition to voluntary standards that address nanomaterial hazards in consumer products. In 2020 and 2021 CPSC produced 12 publications on topics including toxicology of 3D printer emissions and method development.

Developing analytical methods for regulatory science. FDA collaborates with other organizations to develop analytical methods and conduct regulatory science research. New analytical methods enable FDA to identify potential risks through pre- and post-market oversite and will provide guidance to sponsors/reviews for future products. FDA's regulatory science research on the advanced characterization, safety, and biodistribution of nanomaterials includes, for example, biochemical, genetic, and neurotoxicology effects and liposomal drug products. Results from this research help ensure the safety of FDA-regulated products containing nanomaterials and are used in capacity building and standards development. FDA scientists also are researching potential release of engineered nanomaterials from nanotechnology-enabled food contact materials. Data on nanoparticle migration and transformation within food systems will improve FDA's ability to make recommendations to manufacturers and will help regulatory scientists make informed decisions when reviewing future submissions.

Understanding and mitigating potential impacts in the workplace. NIOSH works with a variety of groups to understand the potential health and safety impacts of nanotechnology in occupational settings. NIOSH researchers develop hazard and safety assessments using key classes of engineered nanomaterials, including carbon-based nanomaterials, metals, metal oxides, and 2D materials. NIOSH researchers have performed "real-world" evaluations of hazard and risk represented by nanomaterials through their life cycles, including characterization of aerosols generated in spray coating of paints, sealants, and disinfectants. NIOSH is working with industry to develop a registry of workers who have worked with carbon nanotubes and nanofibers. This registry will form the basis of a longitudinal study that will evaluate the early health effects of exposure to carbon nanotubes or nanofibers.

In May 2021, after extensive review and public comment, NIOSH published the Current Intelligence Bulletin 70: Health Effects of Occupational Exposure to Silver Nanomaterials. Nanoscale silver is among the mostly widely used nanomaterials, and workers may be exposed during production or use of silver nanoparticles. The Bulletin reviewed 100 studies and made use of robust risk-assessment techniques built on more than a decade of research. These efforts supported advanced characterization tools and elucidated the role of factors such as dose metrics, particle size, and dissolution in observed responses. NIOSH concluded that it is prudent and reasonable to derive a recommended exposure limit (REL) for nanoscale silver. The CIB also sets out exposure control recommendations, identifies safe work procedures, training and education, and recommends the use of established medical surveillance approaches to protect workers.

Understanding the implications of incidental nanoplastics. NNI agencies are collaborating to address emerging issues associated with micro- and nanoplastics in the environment. Although these materials are not intentionally engineered nanomaterials, techniques developed and lessons learned from studying engineered nanomaterials can be used to investigate this emerging area of concern. The interagency nanoplastics interest group is helping to coordinate this work across the Federal Government and internationally. For example, an APEC workshop on nanoplastics in marine debris[26] is scheduled for December 2021, and NIST and the European Commission's Joint Research Centre are leading an effort to develop methods to collect nanoplastics from ocean water.[27] ATSDR and NCEH have been conducting research on incidental nanoplastics, presenting at national conferences, identifying and addressing data needs to evaluate human exposures to microplastics, and quantifying human exposure and risks.[28] NIST researchers developed measurement protocols that assess polymer nanocomposite degradation following accelerated moisture, heat, and UV exposure to simulate degradation of products. This work addresses challenges in distinguishing nanomaterials from polymer matrices during polymer nanocomposite degradation. It also evaluates how changes to the polymer nanocomposite morphology, including release of the nanomaterials, affects the potential exposure pathways of nanomaterials to their surroundings during use and disposal.

Investigating potential hazards of 3D printer emissions and aerosols. EPA in collaboration with CPSC and NIST investigated the potential risks from 3D printer emission.[29] These projects[30] demonstrated that exposure concerns may vary based on whether or not an additive is included in the 3D printing filament. Understanding the printing parameters that have the greatest influence on VOC emissions in a variety of filaments can lead to printer designs and/or containment measures that better limit exposure concerns. NIST researchers built the online Fate and Transport of Indoor Microbiological Aerosols (FaTIMA) tool that considers ventilation, filtration, and aerosol properties to estimate the concentration of aerosols in a room.[31] The tool can be used to evaluate options for reducing occupant exposure to SARS-CoV-2.

2023 Agency Progress and Plans

FY 2019 Plans (PCA 5. EHS)

FDA invests in nanotechnology research to help address questions related to the safety, effectiveness, quality, and/or regulatory status of products that contain engineered nanomaterials or otherwise involve the use of nanotechnology. FDA also invests in research to develop models for safety and efficacy assessment, as well as to study the behavior of nanomaterials in biological systems and their effects on both human and animal health. These investments support FDA's mission to protect and promote public health and helps to foster the responsible development of nanotechnology.

The nanoEHS efforts of NIH's National Institute of Environmental Health Sciences (NIEHS) are designed to gain a fundamental understanding of the molecular and pathological pathways involved in mediating biological responses to engineered nanomaterials. Building on the previous efforts of the Nanotechnology Health Implications Research Consortium, current NIEHS-funded nanoEHS efforts include investigator-initiated research projects such as work focused on understanding how nanoparticle exposure modulates

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[26] APEC Workshop on Nanoplastics in Marine Debris, http://www.nanoplasticworkshop.org; accessed 18 March 2022

[27] https://www.nist.gov/news-events/news/2021/05/nist-collaborators-develop-new-method-better-study-microscopic-plastics

[28] https://doi.org/10.1016/j.scitotenv.2020.144010

[29] https://www.epa.gov/sciencematters/keeping-3d-printing-epa-researchers-build-new-plastic-emissions-study

[30] https://doi.org/10.1021/acs.est.9b00765

[31] https://www.nist.gov/news-events/news/2020/06/nist-airflow-model-could-help-reduce-indoor-exposure-aerosols-carrying

allergic lung disease using animal models. Planned activities in the NIH/NIEHS Division of Translational Toxicology include completion of analysis and reporting of studies evaluating immunotoxicity and chronic carcinogenicity of multiwalled nanotubes. The NIEHS Superfund Research Program plans to emphasize research that includes nanotechnology-enabled structures to enhance sustainable remediation and to enable rapid, accurate environmental monitoring. The NIEHS Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program also supports research efforts for developing tools for nanomaterials exposure monitoring, including characterization of toxicity of airborne engineered nanomaterials (ENMs) using a direct *in vitro* exposure method and development of a third-party verification process for characterizing exposures to products containing ENMs.

NIOSH conducts toxicology studies that advance the understanding of potential human health implications of exposure to nanomaterials. NIOSH will evaluate biomarkers of exposure and disease using proteomic, metabolomic, and bioinformatic approaches; develop innovative *in vitro* methodologies to better predict *in vivo* outcomes; and evaluate pulmonary and dermal exposure and toxicity, and systemic toxicity that may result from occupational exposures, including effects in the cardiovascular, reproductive, neurological, and immune systems in response to wide variety of nanomaterials and nanotechnology-enabled products along the life cycle of the materials.

To enable detection and measurement of airborne nanoparticles, NIOSH plans to develop, test, and evaluate direct-reading instruments. Additional plans include continuing field tests of the portable aerosol multielement spectrometer developed by NIOSH at nanomaterial producer and user facilities, as well as efforts in detection of airborne nanoparticles, including in biological systems, to evaluate and predict biological behavior and translocation between organ systems. NIOSH will also explore the feasibility of applying advanced sensing technology and data analytics to biomarkers as a means of evaluating nanomaterial exposure and possible early response.

NIOSH and CPSC are collaborating to study the release of ultrafine particulate and engineered nanomaterials from laser printer toner and from polymer-based 3D printers. An extensive study of metal-powder-based additive manufacturing is planned for 2023. NIOSH will collaborate with university partners and collaborators in private industry to promote safe practices in nanotechnology and advanced manufacturing. NIOSH plans to collaborate with industry to assess the toxicology of carbon-based, metal-based, nanocellulose, and nanoclay-enabled materials.

In collaboration with a private industry trade organization, trade unions, and industrial partners, NIOSH plans to evaluate nanotechnology-enabled spray coatings, composites, and other nanomaterials in construction and manufacturing. It is also participating in the development of nanoEHS-related standards, e.g., ISO 23151—Nanotechnologies—Particle Size Distributions for Cellulose Nanocrystals, and OECD's Test Guideline 110—Particle Size Distribution/Fibre Length and Diameter Distributions.

The NIST nanomaterial EHS research portfolio includes projects ranging from nanoplastics and reference materials to new measurements on consumer products and real-world environments. For example, NIST researchers are working with FDA and academia to investigate degradation of model polymers containing nanomaterials that exhibit barrier properties and that could have potential applications in the construction industry (e.g., outdoor coatings for corrosion-resistant infrastructure) and the food packaging industry (e.g., to extend ingredient freshness). This work addresses challenges in distinguishing nanomaterials from polymer matrices during polymer nanocomposite degradation, and evaluates how changes to the polymer nanocomposite morphology, including release of the nanomaterials, affects the potential exposure pathways of nanomaterials to their surroundings during use and disposal. NIST researchers are also investigating how different formulations of polyvinyl chloride (PVC) regulate the appearance, impact performance, and flammability of composite vinyl siding materials (which include micro- and nanoscale particles added to improve UV stability and impact performance) before and after UV exposure. NIST has completed UV exposure experiments on PVC with different composition/formulations at high temperature and high humidity. Chemical characterization and impact test analyses to simulate vehicle collision, hail, and debris during windstorms are ongoing.

EPA conducts research on emerging materials as part of the Chemical Safety for Sustainability National Research Program within the Office of Research and Development (ORD). This research is focused on developing, collating, mining, and applying information on engineered nanomaterials (including nanopesticides) and incidental nanomaterials (including micro-/nanoplastics) to inform both exposure and hazard assessments and support risk-based decisions related to the agency's implementation of the Toxics Substances Control Act (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). These efforts are coordinated with the Office of Chemical Safety and Pollution Prevention (OCSPP), which is responsible for implementation of these statutes. However, the information is important for other EPA program offices and external stakeholders.

Support for implementation of an improved evaluation framework for nanomaterials under TSCA and FIFRA is an ongoing need. Research activities include evaluating environmental release and assessing human and ecological exposures to engineered nanomaterials, including research to characterize the weathering, release, and transformation of nanomaterials from nanotechnology-enabled consumer products, such as emissions from 3D printers, as well as research to characterize the transport, transformation, fate, and environmental and health effects of nanotechnology-enabled pesticides and engineered nanomaterials. EPA supports ORD's nanomaterials database (known as NaKnowBase), which captures the chemical and physical parameters of materials tested by EPA, the assays in which they were tested, and measured results. EPA is working in coordination with other Federal agencies to promote interoperability of NaKnowBase between NNI participating agencies. Furthermore, OCSPP is actively engaged in international co-operation efforts with OECD to develop new and/or improved test approaches and methods leading to better understanding of the human health and environmental hazards, exposure, and risks of nanomaterials.

NIFA supports nanoEHS research relevant to agricultural production and food applications. AFRI's Nanotechnology for Agricultural and Food Systems program supports projects on EHS assessments of engineered nanoparticles used in food and agricultural systems. This research includes detection and quantification of engineered nanoparticles; characterization of hazards and exposure levels; transport and fate of the engineered nanoparticles or nanomaterials in foods, crops, soils (and soil biota), water, and livestock (including aquaculture species); or exposures to agricultural and allied industry workers. The program also supports research on transport and fate of engineered nanoparticles or nanomaterials and nanostructures for nutrient delivery in food production, processing, and interactions with microbiota in the human gastrointestinal tract.

CPSC engages with Federal partners in a number of projects that are intended to characterize and quantify exposures to engineered nanomaterials released from products across the product life cycle. CPSC, EPA, NIOSH, and NIST collaborative work evaluates emissions, factors influencing emissions, and the potential toxicity from exposure to emissions from 3D printers, including the release and accumulation of nanoplastics. This interagency work is expanding to other types of 3D printers that are becoming more affordable to small businesses and the public, with an emphasis in 2023 on potential exposures to children. Information collected from these efforts will be used in the development of best practices for product use. This includes work with a university to develop a best practices white paper that will assist CPSC staff in applying current thinking regarding nanotoxicology when assessing the safety of products. The report will provide a risk management framework that includes evaluations unique to nanoscale properties of materials.

CPSC and NIST are working on the optimization of *in vitro* test methods used to determine the toxic endpoints of nanomaterials. CPSC staff and partners are engaged in voluntary standards activities to create validated methods for quantifying and characterizing exposures from products, including an ISO project evaluating the release of nanomaterials from treated wood.

NCEH and ATSDR are conducting research on incidental micro- and nanoplastics, presenting at national and international professional events, identifying and addressing data needs to evaluate human exposures to micro- and nanoplastics, and reviewing the available scientific literature to quantify human exposures and risks. In 2021, they completed a scoping review to identify trends and gaps in the literature of micro- and nanoplastics in the environment that may threaten human health. Currently they are conducting a systematic review to understand potential human exposures to micro- and nanoplastics in water and health effects. Completion of a paper on this review is expected during calendar year 2023.

The Forest Service is developing research plans for technical and economic assessments of cellulose nanomaterials, life cycle assessments of cellulose nanomaterials, and EHS tools for chemically modified cellulose nanocrystals.

Consensus standards activities play an important role in developing confidence in the safety and efficacy of nanomaterials. For example, Federal agencies contribute to efforts in ISO TC 229's Working Group 3: Health, Safety and Environmental Aspects of Nanotechnologies, chaired by a U.S. industry representative.

FY 2023 Progress towards the NNI Goal (Responsible Development)

Developing novel approaches to detecting and understanding biological interactions of engineered nanomaterials. An NSF-funded university researcher developed a multi-element inductively coupled plasma mass spectrometry approach for detecting engineered titanium nanoparticles in the environment. The low contribution of sunscreen Ti nanoparticles and their rapid dilution upon release suggested minimal ecotoxicological impacts to surface waters during recreational activities such as tubing and swimming.[32] In another NSF-funded project, a Faculty Early Career Development (CAREER) program awardee developed a multispectral imaging approach to investigate how single human cells interact with and process engineered nanomaterials. Single-walled carbon nanotube sensors with unique physical, optical, and electronic properties were actively internalized by cells and localized to specific organelles that function to "eat" and digest extracellular biomolecules. From there, the nanosensors simultaneously reported their progression through the intracellular environment and the resulting changes to their physical condition.[33]

EPA scientists recently reviewed the major types and applications of quantum dots (QDs) and their potential environmental exposures, fates, and adverse effects on organisms. Potential effects were analyzed in relation to QD structure, function, synthesis methods, and exposures. They identified data gaps in QD exposure and ecological effects to inform future research.[34] EPA also teamed with university researchers to demonstrate a novel method for quantitative detection of engineered nanomaterials in contaminated soil by extracting $Ce0_2$ nanoparticles using tetrasodium pyrophosphate aqueous solution and then characterizing the extracts via single-particle inductively coupled plasma mass spectroscopy.[35]

Leveraging interagency nanoEHS expertise. The NIH/NIEHS Division of Translational Toxicology is collaborating with NIOSH to allow for the evaluation of industry-wide exposure assessment of worker exposure

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[32] https://nsf.gov/awardsearch/showAward?AWD_ID=1512695

[33] https://nsf.gov/awardsearch/showAward?AWD_ID=1844536

[34] https://doi.org/10.1039/D1EN00712B

[35] https://doi.org/10.1021/acs.jafc.0c06343

to graphene and other two-dimensional nanomaterials, and with FDA/NCTR to support development of standards and analytical approaches for characterization and quantitation of nanomaterials, including characterization of real-world samples containing nanoplastics. These studies will facilitate appropriate planning for studies to assess the potential human health impact of exposure to nanoplastics.

Given CPSC's size and budget, partnering has been a key element in achieving mission success. It has collaborated with NIST, NIOSH, EPA, DOD, and other NNI participating agencies to address various potential EHS implications of nanomaterials and nanotechnologies in consumer products. Since 2003, these collaborative activities have produced more than 70 reports and publications, in addition to voluntary standards resulting from CPSC-funded research that addresses nanomaterial hazards in consumer products. In 2021, five publications evaluated the influence of polymer additives on gas-phase emissions from 3D printer filaments, characterized the influence of carbon nanotube content on abraded products and microplastic particle production, and evaluated the safer use of 3D printers in educational settings. In addition, CPSC supported the U.S. participant in an international research collaboration, completed in 2021, to understand how silver nanowire properties (e.g., dimensions) influence human and environmental toxicity and to develop mechanisms to minimize potential hazards. Three publications highlight the collaboration on silver nanowire synthesis and characterization, human and environmental toxicity testing, and silver nanowire release from products and recycling.[36] Results of this work could help emerging nanowire-enabled products to be safer and more sustainable for people and the environment.

Ensuring the safety and efficacy of nanotechnology-enabled vaccines. Over the last several years, FDA's Center for Biologics Evaluation and Research (CBER) has been reviewing a new class of vaccines against viral infectious diseases that uses lipid nanoparticles, based on a novel technology to produce the viral protein against which immune responses are mounted, encapsulating messenger RNA to synthesize the viral protein antigen inside the cells of the vaccine recipient. An advance that made this vaccine approach possible was the development of suitable LNPs that not only protect the mRNA from degradation, but also allow the release of the mRNA from the LNP once inside cells. The body then raises immune responses against the viral protein. Because CBER had reviewed earlier versions of mRNA vaccines that were directed against other infectious diseases (e.g., Zika), there was considerable experience evaluating the safety and manufacturing of this class of vaccine, which facilitated the safe and expeditious introduction of LNP mRNA vaccines against COVID-19. Based on the demonstrated safety and effectiveness of these vaccines, FDA authorized for emergency use the first two mRNA COVID-19 vaccines in December 2020. The first mRNA vaccine was licensed in August 2021 and the second in January 2022. From the success of these COVID-19 vaccines, it is clear that LNP-encapsulated mRNA will continue to be explored as a vaccine platform against many infectious diseases, including new COVID variants and other pandemic and seasonal influenza viruses, Nipah and Hendra viruses, Lassa virus, and other coronaviruses. In addition to vaccines, FDA is evaluating and facilitating the development of other uses of mRNA technology.

Assuring and improving food safety, sustainability, and security. FDA's Center for Food Safety and Applied Nutrition has been conducting research on the use of nanotechnology in food ingredients and food contact substances, e.g., exploring the potential for consumers to be exposed to engineered nanomaterials from nanotechnology-enabled food contact materials. Information about nanoparticle migration and transformation within food systems improves the center's ability to make recommendations to manufacturers about this emerging technology and will help its regulatory scientists make informed decisions when reviewing future submissions to its food contact notification program. In addition, CFSAN is

[36] https://doi.org/10.1073/pnas.1820041116, https://doi.org/10.1039/C8EN00890F, https://doi.org/10.1016/j.impact.2020.100217

also actively conducting research on certain regulated food additives that may have incidental presence of nanoparticles. This type of work ensures that current data are available for the safety assessment of food additives that may contain nanoparticles. Furthermore, CFSAN is involved in research and development of nanotechnology-enabled sensors for contaminants, biological toxins, and pathogens in food products, which help improve FDA's ability to respond rapidly to foodborne disease outbreaks and other emerging threats to human and animal health.

Complementing CFSAN's work, a multistate research committee supported by NIFA conducted a literature survey on micro-/nanoplastics in agricultural production and food. The published article[37] provides a broad overview of recent literature on the presence and impact of microplastic (1 μm to 5 mm in size) and nanoplastic (1 to 1000 nm in size) particles across the agricultural and food supply chain and discusses methods and technologies for the detection and characterization of these particles. It also makes recommendations for future research and infrastructure needs, including novel analytical methods and sensors, high-precision lab analysis combined with rapid onsite screening, and data hosting and curation.

A team of EPA, university, and State government scientists, with partial support from NIFA, conducted a review of nanotechnology-enabled pesticides (e.g., nanomaterial-encapsulated pesticidal active ingredients that can be used for controlled and targeted delivery) to assess their potential for supporting sustainable agriculture and improving global food security. The researchers analyzed the properties of nanopesticides in controlling agricultural pests for crop enhancement compared them with conventional pesticides. The preliminary conclusions showed higher efficacy of nanopesticides against target organisms and lower toxicity to non-target organisms. The study assessed other potential benefits, including enhanced adhesion to foliage, improved crop yield and quality, and the ability to mitigate stresses such as heat, drought, and salinity. The team also noted some remaining uncertainties and recommended further research.[38]

Complementary efforts by ARS and the Forest Service are assessing the use of nanocellulose and other nanomaterials and nanotechnologies to improve food safety, quality, and shelf life.

Understanding and mitigating potential impacts of nanotechnology in the workplace. As nanomaterials and nanotechnology-enabled products make their way into commerce, NNI agencies work with a variety of partners to fully understand the potential health and safety impacts. NIOSH plays a key role in addressing the impacts of nanotechnology in occupational settings. NIOSH researchers develop hazard and safety assessments of key classes of engineered nanomaterials that are, or are likely to be, entering into commerce. NIOSH has performed "real-world" evaluations of hazard and risk represented by various nanomaterials through their life cycles, including the characterization of aerosols generated in spray coating of paints, sealants, and disinfectants. Environmental chambers are being used to evaluate sanding, sawing, and cutting of nanotechnology-enabled polymer composites and construction materials, as well as sanding of coated surfaces, in a controlled environment. NIOSH also has collaborated with over 20 national and international universities and numerous industrial partners in the characterization of toxicological effects of pulmonary and dermal exposure to a wide range of industrially relevant nanoparticles and nanotechnology-enabled materials.

Agencies participating in the NNI are also actively engaging with industry to share nanoEHS knowledge and best practices. NIOSH has published an extensive library of documents offering guidance and best practices in the safe

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[37] https://doi.org/10.1007/s00216-022-04069-5

[38] https://doi.org/10.1038/s41565-022-01082-8

use of nanotechnology in the workplace.[39] NIOSH is also working with industry to develop an exposure registry that currently consists of ~585 workers across the United States who have been exposed to carbon nanotubes and nanofibers in the workplace. This registry will form the base of a longitudinal study that will evaluate the early health effects of exposure to carbon nanotubes or nanofibers among workers exposed to these engineered nanomaterials.

Understanding and addressing the implications of incidental nanoplastics. In 2021, NIST and the EU Joint Research Centre held an internal workshop to coordinate efforts in measurement and metrology for identifying and characterizing micro- and nanoplastics. The group also played a key role in proposing and helping to organize the December 2021 APEC Workshop on Nanoplastics in Marine Debris.[40] Examples of recent research include work by an EPA team to demonstrate the use of molecular tools such as metabarcoding to assess the types of organisms present in marine sediment by using genetic material extracted from the sediment. The team studied changes in the composition of organisms as a result of nanoplastics contamination to understand how plastic particles can adversely affect marine ecosystems and what types of organisms are most sensitive to nanoplastics.[41] NCEH and ATSDR have reviewed data in the literature for quantifying human exposures to micro- and nanoplastics and potential health risks, and presented the results at two 2021 national conferences.[42] ARS scientists have published a review of micro- and nanoplastic-induced cellular toxicity in mammals, assessing cytotoxicity of micro-/nanoplastics as a function of cell type; the effects of particle size, dose, charge, exposure time, and additives; and the implications of oxidative stress and membrane damage for cell viability.[43] NIST and Army/ERDC scientists collaborated with European university researchers to review standardized methods for assessing potential environmental hazards of engineered nanomaterials and how those methods might be applied to assessment of micro- and nanoplastics. They outlined a strategy for leveraging OECD guidance documents developed for ENMs to improve the quality of the data generated for micro- and nanoplastics.[44] Another NIST team developed a technique for isolating, measuring, and identifying sub-100 nm plastic particles in water, using ultra-high purity water solutions exposed to plastic samples. The resulting suspensions were atomized and injected into a flowing air stream and rapidly dried to isolate the plastic particles. A variety of particle counting and characterization methods were then used to enable sample identification, quantification, and comparability for a range of nanomaterials suspended in water.[45]

Investigating potential hazards of 3D printer emissions. EPA, NIOSH, CPSC, NIST, and other NNI participating agencies are collaborating in this area, including on research to characterize the release and transformation of nanomaterials from 3D printer emissions.[46] In December 2021, the agencies convened an internal coordination meeting to discuss research results so far and potential future collaborations. Many studies have focused on fused filament fabrication (FFF) 3D printers and other technologies utilizing polymer feedstocks. Future research will likely investigate metal additive manufacturing technologies and materials,

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[39] See https://www.cdc.gov/niosh/topics/nanotech/default.html. See also the NNI Supplement to the President's 2022 Budget, p. 51: https://www.nano.gov/sites/default/files/pub_resource/NNI-FY22-Budget-Supplement.pdf.

[40] http://nanoplasticworkshop.org/

[41] https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=354774&Lab=ORM

[42] https://doi.org/10.1016/j.scitotenv.2020.144010

[43] https://doi.org/10.1016/j.scitotenv.2020.142518

[44] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9029759/

[45] https://doi.org/10.1021/acs.est.1c06768

[46] See the NNI Supplement to the President's 2022 Budget, p. 52, for details: https://www.nano.gov/sites/default/files/pub_resource/NNI-FY22-Budget-Supplement.pdf.

as well as potential hazards of the use of 3D printers by consumers and small businesses. For example, an EPA research team recently investigated human exposure to metals in FFF printers aimed at consumer markets.[47]

Developing and curating databases of nanoEHS research findings. EPA has published a peer-reviewed journal article documenting its efforts on the NaKnowBase project,[48] and has posted an initial publicly available version of the database on the EPA website.[49] EPA is working in coordination with other Federal agencies to promote interoperability of NaKnowBase between NNI participating agencies. This complements long-standing efforts by NIH/NCI's caNanoLab to facilitate data sharing in the cancer nanotechnology research community to expedite and validate the safety and efficacy of nanomaterials used in biomedicine. CaNanoLab supports the annotation of nanomaterials with composition information, and physico-chemical, *in vitro*, and *in vivo* characterizations, providing access to samples, protocols, and publications from NCI/NCL, the NCI Alliance for Nanotechnology in Cancer, and the broader biomedical nanotechnology community.[50] In 2021, caNanoLab compiled and curated 83 samples, 36 publications, and 1 new protocol to its database. OSHA, NIOSH, NIEHS, and NSF have also been supporting nanoEHS database efforts. These and other NNI nanoEHS informatics activities are coordinated through an informal interagency interest group.

Addressing science and technology challenges to a sustainable plastics economy. NNI agencies are pursuing a variety of basic and applied nanotechnology research in pursuit of the goal of making plastics more sustainable. For example, a DOE-wide effort, the Plastics Innovation Challenge, is exploring approaches to encourage increased recycling, develop methods for "upcycling" plastic waste into useful products, and develop new plastics that are recyclable by design.[51] One project has developed a method for upcycling polystyrene plastic into a reusable adhesive with a rare combination of strength and ductility, using boronic esters to couple the polystyrene with silica nanoparticles. This opens pathways for a new class of tough adhesives that can bear heavy loads, tolerate extreme stress and heat, and reversibly bond to surfaces such as glass and metals.[52]

NIST's Circular Economy Program supports a model in which the atoms and molecules that are the building blocks of products repeatedly cycle within the economy and retain their value.[53] The initial focus of this program is on innovative technologies for recycling/upcycling plastics and polymers

The NSF Emerging Frontiers in Research and Innovation (EFRI) program, partnering with DOE's Bioenergy Technologies Office and NIST, supported 17 projects under the Engineering the Elimination of End-of-Life Plastic Waste EFRI topic.[54] Research themes, many of which leverage nanotechnology, range from synthetic biology for mixed plastic degradation and reutilization, to plasma-assisted hydrogenolysis of waste plastics, and rationally designed enzyme-containing plastics. Additional projects are supported under NSF's Critical

[47] https://doi.org/10.1016/j.scitotenv.2021.152622

[48] https://doi.org/10.1038/s41597-021-01098-0

[49] https://gaftp.epa.gov/EPADataCommons/ORD/NaKnowBase/

[50] https://cananolab.nci.nih.gov/caNanoLab/

[51] https://www.energy.gov/plastics-innovation-challenge/plastics-innovation-challenge

[52] https://doi.org/10.1126/sciadv.abk2451

[53] https://www.nist.gov/circular-economy

[54] https://www.nsf.gov/news/news_summ.jsp?cntn_id=303230

Aspects of Sustainability[55] and Environmental Convergence Opportunities in Chemical, Bioengineering, Environmental, and Transport Systems[56] programs.

[55] https://beta.nsf.gov/funding/opportunities/critical-aspects-sustainability-cas

[56] https://beta.nsf.gov/funding/opportunities/environmental-convergence-opportunities-chemical-bioengineering-environmental