

2016 U.S.–EU: Bridging NanoEHS Research Efforts Workshop Synopsis

In the 16 years since the establishment of the U.S. National Nanotechnology Initiative (NNI) and the 15 years since the European Commission (EC) began funding research on the potential environmental, health, and safety implications of nanotechnology (nanoEHS), researchers around the world have developed a wealth of knowledge about the potential risks and benefits of nanotechnology. Yet, some questions about nanoEHS—such as the potential for exposure to engineered nanomaterials from consumer products—are incompletely answered. To address these questions with the best available science, the NNI and the EC have an ongoing collaboration to exchange information, target future research needs, and leverage limited resources.

As part of this cooperation, the NNI and the EC jointly hosted a workshop, *U.S.–EU: Bridging NanoEHS Research Efforts*, on June 6–7, 2016, in Arlington, Virginia. This was the fifth joint workshop in an annual series that began in 2011. Over the years, the joint U.S.–EU workshops have led to the proposal, establishment, and refinement of the U.S.–EU Communities of Research¹ (CORs) as a mechanism to strengthen communication and collaboration among American and European nanoEHS scientists. The CORs were the central focus of the 2016 workshop, and the first day of the workshop was devoted to an interactive nanoEHS scrimmage² in which the groups collectively responded to a spill of a hypothetical nanotechnology-enabled product. This activity was planned and executed by the CORs representatives, and the highlights and findings from the nanoEHS scrimmage are expected to be reported in the scientific literature.

The rest of the workshop included plenary presentations and discussions, as well as breakout sessions in which each of the seven CORs met to discuss accomplishments and set priorities and plans for the coming year. The final plenary session was an open discussion where the need to assess the current state of nanoEHS knowledge emerged as a significant priority for the entire community. Several participants noted that this is a substantial and complex task to undertake, but that the CORs are uniquely positioned to contribute to such an activity.

The COR breakout sessions were each organized by their respective co-chairs, and discussions covered topics ranging from reproducibility to technical foci to lessons learned from the nanoEHS scrimmage activity. The conversations during the breakout sessions highlighted that the CORs' activities vary widely depending on each group's research interests and on the participating members. For example, in 2016 the Risk Assessment COR was the primary driver for organizing the nanoEHS scrimmage, while Ecotoxicity Testing COR members collaborated to publish a perspective article on nanomaterials in the aquatic environment.³ The CORs' plans for the coming year are equally diverse. For example, the Exposure through Product Life COR discussed possible projects looking into chronic exposures to nanomaterials and into the release of nanomaterials from consumer products, while members of the Databases and Computational Modeling for NanoEHS COR will work with BILAT USA 4.0⁴ to organize a workshop on *Enabling a Sustainable Harmonised Knowledge Infrastructure Supporting Nano Environmental, Health, and*

¹ us-eu.org/communities-of-research/

² nanoehs.enanomapper.net/

³ Selck, H., *et al.*, Nanomaterials in the aquatic environment: A European Union–United States perspective on the status of ecotoxicity testing, research priorities, and challenges ahead. *Environ. Toxicol. Chem.*, **35**, 1055–1067 (2016).

⁴ www.euussciencetechnology.eu/

Safety Assessment. More information about the CORs and their activities can be found at us-eu.org and in the annex to this document, which includes a brief summary of each breakout session.

There was a renewed sense of vigor and enthusiasm among the COR members at this meeting, and participants repeatedly mentioned ideas for future nanoEHS scrimmages and for future COR activities. Building on the strong foundation and history of collaboration, the NNI and the EC will continue to work together and share information on key nanoEHS issues and to facilitate the collaboration among the scientists in the CORs. These communities serve as a valuable platform for researchers to collectively discuss issues and develop plans to address priority nanoEHS research areas. These activities will continue to support the responsible development of nanotechnology-enabled products for the benefit of society.

Annex: COR Breakout Session Summaries

Characterization COR

Discussions during the Characterization COR breakout session highlighted how issues of poor data quality and reproducibility can negatively impact research and translation in areas as diverse as nanoEHS and biomedicine. For example, some preclinical studies have shown that multifunctional nanomaterials with targeting, imaging, and drug delivery capabilities are beneficial. Yet, the translation of these technologies for human use is limited with very few getting into clinical trials for multiple reasons. Several meeting and workshops have dealt with the need for more thorough nanomaterial characterization to combat issues of poor data reproducibility and quality, and one such activity is the Minimum Information for Nanomaterial Characterization (MINChar) Initiative.⁵ Participants emphasized that it is important to consider ways to improve the quality and reproducibility of data, particularly with the introduction of new biological and ecotoxicology approaches and techniques. It was further noted that lessons learned from previous mistakes should be taken into consideration to avoid pitfalls and to enable the production of robust and reproducible results. Toward this end, members of the Characterization COR are helping plan the 2016 Global Summit on Regulatory Science,⁶ which is scheduled for September 7-9 in Bethesda, Maryland. The theme of the summit is “Nanotechnology Standards and Applications,” and it will have presentations to stimulate this discussion. The plan is to collaboratively identify standards needs, and to co-develop appropriate standards in response to these needs.

Databases and Computational Modeling for NanoEHS COR

The conversations in the Databases and Computational Modeling for NanoEHS COR breakout session touched on key findings from the nanoEHS scrimmage, as well as future COR plans. Much of the discussion on the nanoEHS scrimmage centered on the utility of the mock safety data sheets (SDSs). The SDSs were generally regarded as helpful, particularly given the time constraints during the scrimmage. Notably, the scrimmage participants assumed that the SDSs were valid, and the data supporting the SDS were not examined.

The subsequent discussion addressed themes of database management, ontology development and use, data curation, and data completeness. Attendees suggested leveraging ongoing activities—such as the recently generated data templates in Europe and the U.S. Nanotechnology Working Group’s series of papers on curation, database workflows, annotation, and zeta potential⁷—to reinforce the concept of building in quality at the beginning of an effort to avoid retrospective fixes. A case study was suggested to examine a subset of the European JRC templates as they are applied to the test results from the OECD Working Party on Manufactured Nanomaterials test program. This effort would broaden awareness of data completeness while fostering best practices within the U.S.–EU community. The group will poll the other CORs for suggestions on which OECD test products to emphasize, as well as to communicate with the communities that are examining the OECD dossiers for their coherence and utility in selecting benchmark materials. Finally, members of this COR will work with BILAT USA 4.0 to organize a workshop on *Enabling a Sustainable Harmonised Knowledge Infrastructure Supporting Nano Environmental, Health, and Safety*

⁵ characterizationmatters.wordpress.com/about/

⁶ www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/WhatWeDo/ucm488022.htm

⁷ nciphub.org/groups/nanowg

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Assessment. This workshop is scheduled for October 2016 in Europe and will serve as a venue for an in-person COR meeting.

Human Toxicity COR

Human Toxicity COR breakout session attendees came from a variety of backgrounds, but all participants shared an interest in the applications of human toxicological knowledge. Reflections on the nanoEHS scrimmage were positive overall. The following improvements for future scrimmages were suggested: documenting the wide range of opinions in response to the scrimmage scenario; giving each COR different starting information; and focusing more on the nanotechnology-specific aspects of the materials. As an idea for the next scrimmage, participants suggested looking at common consumer products (e.g., sunscreen, antimicrobial textiles, carbon nanotubes in electronics) to determine if there is agreement among the CORs on exposure implications, as well as on potential impacts on human health or the environment.

The COR co-chairs, Gabriele Windgasse and Albert Duschl, proposed a few options for future COR activities, and the group focused on two topics in particular. The first topic was determining the three most important engineered nanomaterials under study in a number of divergent areas of nanomaterial investigations. It will be informative to see if commonalities emerge across the topic areas. The second topic was determining if COR members can agree on a list of “benchmark” materials that can represent an entire class of engineered nanomaterials. For example, could carbon nanotubes serve as a benchmark for fibers? The group is interested in tying into the current activities at NIOSH and CPSC and in working together with other CORs on future activities.

Ecotoxicity COR

The two main topics discussed during the Ecotoxicity COR breakout session were quantification of nanomaterials in organism tissues after ecotoxicology testing and more environmentally relevant ecotoxicity testing. The group learned that a review paper had recently been published on quantifying metal and metal oxide nanoparticles within organisms and cells,⁸ and discussed another review paper on quantification of carbon nanotubes in various matrices.⁹ There was also extensive discussion regarding how to conduct more environmentally relevant toxicity testing. It was noted that some papers had been recently published on this topic by various groups,^{10,11} but there were many topics that were not yet well understood. For example, the idea of testing “aged” samples is widespread in the literature, but this term is used in different ways by researchers in the nanoparticle and metal ion toxicity literature. There are some key differences between aging of metal ions in environmental matrices (where aging usually refers to binding of the ions to more chemically stable sites on the soil with time thus decreasing bioavailability) as compared to aging of metal or metal oxide nanoparticles where transformations (e.g., dissolving into ions or transforming to a different compound such as silver nanoparticles to sulfidized silver nanoparticles) often occur in environmental matrices across time. There was an agreement to study both topics further during the upcoming year and to explore possibilities for writing joint papers

⁸ Schultz, C., *et al.*, Analytical approaches to support current understanding of exposure, uptake and distributions of engineered nanoparticles by aquatic and terrestrial organisms. *Ecotoxicology*, **24**(2), 239–261 (2015).

⁹ Petersen, E.J., *et al.*, Quantification of carbon nanotubes in environmental matrices: Current capabilities, case studies, and future prospects. *Environ. Sci. Technol.*, **50**(9), 4587–4605 (2016).

¹⁰ Holden, P.A., *et al.*, Considerations of environmentally relevant test conditions for improved evaluation of ecological hazards of engineered nanomaterials. *Environ. Sci. Technol.*, **50**(12), 6124–6145 (2016).

¹¹ Nowack, B., *et al.*, Meeting the needs for released nanomaterials required for further testing—The SUN approach. *Environ. Sci. Technol.*, **50**(6), 2747–2753 (2016).

similar to the paper published by COR members earlier in 2016.¹² Participants proposed developing a workshop or paper on the quantification of carbon nanoparticles in environmentally relevant matrices in the short term and initiating longer-term planning of a workshop on environmentally relevant ecotoxicity testing.

Exposure through Product Life COR

Paul Westerhoff, the U.S. co-chair for the Exposure through Product Life COR, opened breakout session by describing a COR-led workshop that was held in France in April 2016. The discussions at the workshop led to a manuscript on exposure-informed hazard assessment that is currently under development. Breakout session attendees then brainstormed possible focus areas for the COR to address, with the following high-level needs emerging: (1) data on chronic exposures to engineered nanomaterials; (2) information on scenarios in which engineered nanomaterials may be released from consumer products; and (3) methods to rapidly detect and quantify engineered nanomaterials in products at levels of potential exposure concern. Participants discussed how exposure tools could help prioritize toxicity testing, in conjunction with properties of concern (e.g., aspect ratio). The Exposure COR proposed arranging a cross-COR teleconference or a half-day workshop with the Human Toxicity COR to further pursue this concept. Finally, participants emphasized the need to engage epidemiologists to consider retrospective exposure scenarios for engineered nanomaterials or to engage in developing new cohorts.

Risk Assessment COR

Participants in the Risk Assessment COR breakout session discussed the lessons learned from the nanoEHS scrimmage, with the primary conclusions that (1) differences exist between risk assessment reference documents, governance, and communication across the United States and Europe and (2) differences exist between the scientific assessment of risk carried out within this research community and the short-term evaluation and management processes required for successful management and communication of emergency situations. Participants developed a plan to hold a series of four teleconferences showcasing and analyzing key differences on these topics over the next year. Each teleconference will be co-lead by representatives from the United States and Europe. The topics of the teleconferences will be (1) human health risk assessment, (2) ecological/environmental risk assessment, (3) risk communication, and (4) risk assessment in relation to regulation and governance. Preparation for this series has already begun with Christine Hendren and Janeck Scott-Fordsmand, the COR co-chairs, hosting a call with the teleconference leaders, and all other CORs are invited to attend as interested. The outcomes of this series will include material that can be shared at the next U.S.-EU meeting, as well as a potential publication on behalf of the COR.

Risk Management and Control COR

The breakout session began with a Risk Management and Control COR status report from the EU co-chair, Ulla Vogel. Dr. Vogel described the potential routes of worker exposure as inhalation, ingestion, and dermal and noted that inhalation is considered the major route of occupational concern for nanomaterials. She argued that it is useful to group nanoparticles by physicochemical properties that impact bioactivity, for example, size, shape, surface area, solubility, durability, functionalization, and surface reactivity. The most pressing challenges were described as

¹² Selck, H., *et al.*, Nanomaterials in the aquatic environment: A European Union–United States perspective on the status of ecotoxicity testing, research priorities, and challenges ahead. *Environ. Toxicol. Chem.*, **35**, 1055–1067 (2016).

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standardization of exposure and hazard assessment methods, mapping sites and processes of engineered nanomaterial exposure, and developing and implementing control methods and exposure limits. The U.S. co-chair, Vince Castranova, then gave a presentation on “Proposed Amendments to OECD Subacute and Subchronic Inhalation Test Guidelines.” Over the past 4 years, U.S. EPA has lead an effort by scientists in the United States, Europe, and Asia to implement updates to Organization for Economic Cooperation and Development Test Guidelines 412 and 413. Dr Castranova observed that two changes appear likely: (1) the current limit for mass median aerodynamic diameter (MMAD) may change from the current 1-4 μm limit to $<2 \mu\text{m}$ and (2) the current biological analysis of pulmonary response may change from histopathology alone to histopathology plus analysis of damage and inflammatory markers in bronchoalveolar lavage samples. Further, it appears that measurement of lung burden and clearance of pulmonary nanoparticles will be recommended as optional.

A discussion of future directions for the COR followed. Participants suggested engaging with emergency responders to share relevant information. Noting the need for safe handling practices for the workplace and university labs, the attendees further recommended reaching out to universities to share information on the safe handling of engineered nanomaterials.¹³

¹³ Note: The U.S. National Nanotechnology Coordination Office hosted a webinar on and created a webportal of resources for nanotechnology laboratory safety in 2016. The webinar archive and portal are available at www.nano.gov/LabSafety.