

Workshop Proceedings

U.S.-EU: Bridging NanoEHS Research Efforts Joint Workshop December 2-3, 2013

February 2015

This document is the report of the United States–European Union Joint Workshop on Bridging Nanotechnology Environmental, Health, and Safety (“nanoEHS”) Research Efforts, held December 2–3, 2013, in Arlington, VA. The workshop was sponsored by the U.S. National Nanotechnology Initiative and the European Commission. The workshop brought together U.S. and EU scientists engaged in nanotechnology environmental, health, and safety research to identify areas of shared nanoEHS interest and mechanisms for collaboration to advance the science.

This report is not a consensus document but rather is intended to reflect the diverse views, expertise, and deliberations of the workshop participants.

The report was designed, assembled, and edited by staff of the U.S. National Nanotechnology Coordination Office (NNCO).

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1. Introduction and Background

The 2013 *U.S.–EU: Bridging NanoEHS Research Efforts* joint workshop was held on December 2–3, 2013, at the National Science Foundation in Arlington, Virginia. The workshop was organized by the U.S. National Nanotechnology Initiative (NNI) and the European Commission. Approximately 115 participants attended the meeting in person, and over a third of the attendees travelled from Europe. An additional 15 participants joined by phone. Attendees included scientists, policy makers, regulators, administrators, and authorities from the European Union and the United States.¹

This was the third in an annual series of U.S.–EU nanoEHS workshops. The purpose of this third joint workshop was to further deepen and promote EU-U.S. collaboration on nanotechnology-related environment, health, and safety (nanoEHS) research. Additionally, the aim was to publicize progress toward Community of Research (COR) goals and objectives, clarify and communicate future plans, share best practices, and identify areas of cross-Community collaboration.

The CORs, which provide a platform for scientists to develop a shared repertoire of protocols and methods, were proposed at the first *U.S.–EU: Bridging NanoEHS Research Efforts* workshop in Washington, DC, in March 2011. The following six Communities of Research were announced at scientific meetings in the United States and Europe in early 2012:

- Databases and Ontologies
- Exposure through Product Life
- Predictive Modeling for Human Health
- Ecotoxicity Testing and Predictive Models
- Risk Assessment
- Risk Management and Control

The CORs defined their scope and goals at the second *EU-U.S.: Bridging NanoEHS Research Efforts* joint workshop in Helsinki, Finland, in October 2012. More information about the CORs, including a list of upcoming events, is available at www.us-eu.org/communities-of-research/.

¹ A full list of workshop participants is included in Appendix B. Presentation slides are available at www.us-eu.org.

2. Welcoming Remarks

Words of Welcome

Mihail C. Roco, U.S. National Science Foundation

Robert Pohanka, U.S. National Nanotechnology Coordination Office

Mihail Roco opened the workshop by welcoming the participants on behalf of the U.S. National Science Foundation, which hosted the event. He noted that nanotechnology-based innovations continue to grow at a rapid pace, with the number of nanotechnology patents doubling roughly every three years since 2000.² Timely consideration of nanoEHS issues is essential for the continued progress of nanotechnology and to protect human health and the environment.

Dr. Roco encouraged workshop attendees to incorporate two key principles into their discussions over the course of the meeting: (1) long-term thinking and (2) taking opportunities to support convergence. He urged participants to take the long-term view of what types of nanotechnology-enabled systems and devices are likely to be developed in the future, moving beyond an emphasis on simple particles. On the topic of convergence, Dr. Roco mentioned a recent report on the convergence of nanotechnology, biotechnology, cognitive science, and information technology.³ He stated that cross-disciplinary thinking is critical for nanoEHS, noting several interdependent areas for consideration, including sustainability and applications, as well as ethical, legal, and societal implications.

Robert Pohanka welcomed attendees to the event, adding that the responsible development of nanotechnology is one of four primary goals of the U.S. National Nanotechnology Initiative. Dr. Pohanka mentioned that the *2014 NNI Strategic Plan* was scheduled for release in early 2014 and that a strong emphasis on nanoEHS knowledge generation, incorporation, and dissemination is maintained in the plan.⁴ He further detailed the potential for collaboration between the CORs and the NNI's Nanotechnology Signature Initiatives (NSIs),⁵ which are intended to enable the rapid advancement of science and technology in the service of national economic, security, and environmental goals by focusing resources on critical challenges and R&D gaps. All five of the NSIs have environmental, health, and safety (EHS) components to them, but the "Nanotechnology Knowledge Infrastructure (NKI)" and "Nanotechnology for Sensors and Sensors for Nanotechnology" NSIs are particularly relevant to the COR activity.

² M. C. Roco. Nanotechnology: From discovery to innovation and socioeconomic projects, *CEP Magazine, An AIChE Publication*: May 2011, 21–27 (2011).

³ M. C. Roco, W. Bainbridge, B. Tonn, G. Whitesides, Eds., *Convergence of Knowledge, Technology and Society: Beyond Convergence of Nano-Bio-Info-Cognitive Technologies* (Springer, Boston, Massachusetts, 2013).

⁴ Nanoscale Science, Engineering, and Technology Subcommittee of the Committee on Technology, *The National Nanotechnology Initiative Strategic Plan* (National Science and Technology Council, Washington, District of Columbia, 2014; www.nano.gov/2014StrategicPlan).

⁵ Please see www.nano.gov/signatureinitiatives for more information on the NSIs.

2. Welcoming Remarks

Welcome on Behalf of the European Commission

Elke Anklam, Joint Research Centre, European Commission

Elke Anklam welcomed all of the participants on behalf of the European Commission. She mentioned that nanotechnology and nanoEHS are important topics to the Commission, as evidenced by its activities on labeling and definitions. Dr. Anklam introduced Horizon 2020,⁶ the European Union's new research Framework Programme. Nanotechnology is included as a Key Enabling Technology under Horizon 2020 because it is expected to play an important role in addressing societal challenges and in recovering from the economic downturn.

Dr. Anklam emphasized that, as with any emerging technology, nanotechnology development should be accompanied by concurrent advances in EHS efforts. For example, a safe-by-design approach could be used to meet consumer needs and to minimize risks. She maintained that it is important for scientists to communicate and collaborate frequently in the development of a robust risk assessment framework and that such a framework would benefit all countries. Thus, it is critical that scientists cooperate internationally through mechanisms such as this workshop.

Purpose and Goals of the 2013 Workshop

Chris Cannizzaro, U.S. Department of State

Chris Cannizzaro gave a summary of previous U.S.–EU nanoEHS events (as described in Chapter 1). He outlined five goals for the 2013 workshop: (1) review priorities for nanoEHS research in the United States and the European Union; (2) identify mechanisms to bridge these efforts; (3) communicate progress toward the COR objectives; (4) discuss potential linkages between the CORs and other efforts; and (5) gather information on how to improve the COR platform. Dr. Cannizzaro described the strong correlation between the core nanoEHS research categories outlined in the 2011 NNI EHS Research Strategy⁷ and the common nanosafety research themes in the research strategy⁸ of the EU NanoSafety Cluster.⁹ He concluded by noting the diverse makeup of the audience, with approximately a third of the participants from the European Union, representing 12 countries and the European Commission, and the remainder from the United States. Attendees also represented government, academia, industry, and nongovernmental organizations.

⁶ ec.europa.eu/programmes/horizon2020/

⁷ Nanoscale Science, Engineering, and Technology Subcommittee of the Committee on Technology, *National Nanotechnology Initiative Environmental, Health, and Safety Research Strategy* (National Science and Technology Council, Washington, District of Columbia, 2011; www.nano.gov/2011EHSStrategy/).

⁸ K. Savolainen *et al.*, Eds., *Nanosafety in Europe 2015-2025: Towards Safe and Sustainable Nanomaterials and Nanotechnology Innovations* (Finnish Institute of Occupational Health, Helsinki, Finland, 2013; www.ttl.fi/en/publications/Electronic_publications/Nanosafety_in_europe_2015-2025/Documents/nanosafety_2015-2025.pdf).

⁹ www.nanosafetycluster.eu

3. NanoEHS Research Priorities

Overview of Nanosafety in Europe 2015–2025

Kai Savolainen, Finnish Institute of Occupational Health

Kai Savolainen contended that appropriate, risk-based regulation of engineered nanomaterials (ENMs) will ensure public safety and facilitate innovation by building and maintaining trust in nanotechnology-enabled products. He emphasized that a robust knowledge base is required for reliable risk assessment and that there is currently too little systematic research supporting risk assessment. Most of the papers in the literature focus on toxicity mechanisms for a small number of ENMs and are not generalizable.

In 2013, European NanoSafety Cluster participants published a nanoEHS research strategy: *Nanosafety in Europe: 2015-2025: Towards Safe and Sustainable Nanomaterials and Nanotechnology Innovations*.¹⁰ The goal of the strategy is to support a transition from mechanistic research to research driven by risk assessment needs. Dr. Savolainen noted that this document emphasizes research on exposure and toxicity mechanisms, as well as the development of tests that eventually will inform regulatory decisions.

The research strategy details how basic research in four key areas will lay the foundation for research testing and regulations that will enable the development of new technologies:

- *Material Identity*—This area includes the interactions of ENMs with molecules, such as proteins, that can form a corona around an ENM.
- *Transformation and Exposure*—Life cycle analysis should include predictions of release mechanisms, transport and transformation, and routes of exposure.
- *Hazard Mechanisms*—It is important to understand the interactions of ENMs with living organisms, as well as the consequences of these interactions.
- *Risk Prediction and Management Tools*—This area includes the development of predictive models and nano-specific exposure indicators.

Frameworks for categorizing nanomaterials were discussed at length following Dr. Savolainen's presentation. He noted that, despite extensive research on the topic, there is still insufficient data to group classes of nanomaterials. One participant mentioned the U.S. Environmental Protection Agency's ToxCast™ program,¹¹ which uses high-throughput screening to prioritize certain classes of chemicals and nanomaterials. Another attendee recommended a pilot project in which a full risk assessment would be conducted for a specific ENM. Such a project could be used to assess potential gaps in the data and in the risk assessment process.

¹⁰ K. Savolainen et al., Eds., *Nanosafety in Europe 2015-2025: Towards Safe and Sustainable Nanomaterials and Nanotechnology Innovations* (Finnish Institute of Occupational Health, Helsinki, Finland, 2013; www.ttl.fi/en/publications/Electronic_publications/Nanosafety_in_europe_2015-2025/Documents/nanosafety_2015-2025.pdf).

¹¹ www.epa.gov/ncct/toxcast/

3. NanoEHS Research Priorities

Overview of the 2011 NNI EHS Research Strategy

Treye Thomas, U.S. Consumer Product Safety Commission

Treye Thomas described the U.S. National Nanotechnology Initiative and how the member agencies collaborate, leverage resources, and share data. The Nanotechnology Environmental and Health Implications (NEHI) Working Group of the National Science and Technology Council, Committee on Technology, Subcommittee on Nanoscale Science, Engineering, and Technology addresses nanoEHS issues and produced the *2011 NNI Environmental, Health, and Safety Research Strategy*.¹² This document is a critical component of a cohesive and comprehensive nanoEHS research program because the NNI agencies can use it to guide their individual and collective activities.

The 2011 NNI EHS Research Strategy builds on and replaces the 2008 strategy, with a new emphasis on taking a life cycle perspective and on informatics and modeling. Dr. Thomas outlined how the life cycle approach encompasses a product from raw material production through use and disposal. The various transformations that ENMs can undergo throughout the life cycle further complicate analysis of fate and transport in living organisms and the environment. Dr. Thomas stressed the importance of developing robust measurement methods to estimate, for example, ENMs released from coatings throughout the life cycle.

The EHS research strategy outlines a conceptual framework that incorporates risk assessment, risk management, and life cycle analysis to inform specific research principles. Dr. Thomas further described how six core research areas support this framework, and he gave one example of progress toward implementing the strategy for each topic:

- *Nanomaterial Measurement Infrastructure*—Participation in international standardization activities
- *Human Exposure Assessment*—Participation in and support for the ILSI NanoRelease Consumer Products project,¹³ which is working to understand releases of nanomaterials from a variety of matrices
- *Human Health*—Development of toxicity assays by the Nanotechnology Characterization Laboratory¹⁴
- *Environment*—Support for large-scale centers that are developing approaches for understanding risks in the environment and the impacts on ecosystems
- *Risk Assessment and Risk Management Methods*—Collaboration with the United Kingdom to investigate releases and potential risks from consumer products
- *Informatics and Modeling*—Development of Data Readiness Levels¹⁵ by the Nanotechnology Knowledge Infrastructure Signature Initiative to rank data quality and maturity

¹² Nanoscale Science, Engineering, and Technology Subcommittee of the Committee on Technology, *National Nanotechnology Initiative Environmental, Health, and Safety Research Strategy* (National Science and Technology Council, Washington, District of Columbia, 2011; www.nano.gov/2011EHSSStrategy/).

¹³ www.ilsi.org/ResearchFoundation/RSIA/Pages/NanoRelease1.aspx

¹⁴ ncl.cancer.gov/

¹⁵ www.nano.gov/node/1015

3. NanoEHS Research Priorities

In the ensuing discussion, one participant emphasized the need for standardized material characterization and risk assessment methodologies. Another attendee asked about specific case studies that have been used to gather information and focus research efforts. Dr. Thomas agreed with the identified needs and described work that the U.S. Environmental Protection Agency has done on nanosilver¹⁶ and carbon nanotubes.^{17,18} Finally, the observation was made that there is generally much more data on the hazards of ENMs than on exposure and that new approaches are needed to further engage exposure scientists.

¹⁶ cfpub.epa.gov/ncea/nano/recordisplay.cfm?deid=241665

¹⁷ cfpub.epa.gov/ncea/nano/recordisplay.cfm?deid=253010

¹⁸ U.S. EPA has also complete a case study on TiO₂: cfpub.epa.gov/ncea/nano/recordisplay.cfm?deid=230972

4. Bridging NanoEHS Research Efforts

International Dimensions of NSF Projects

Alan Tessier, U.S. National Science Foundation

Alan Tessier described several mechanisms that the U.S. National Science Foundation (NSF) uses to promote international collaborations, noting that the NSF's goal of ensuring the vitality of science in the United States is best achieved when U.S. scientists and engineers are globally engaged. NSF's Office of International and Integrative Activities funds international workshops to build collaborations, as well as direct collaborations. Two specific programs from this office have funded nanotechnology-related projects in the past: Partnerships for International Research and Education (PIRE)¹⁹ and International Research Experience for Students (IRES).²⁰ PIRE supports collaborations between U.S. and foreign institutes on specific research topics. The most recent solicitation was on the theme of sustainability, and two awards involved nanotechnology. The next PIRE solicitation was scheduled for summer 2014. The IRES program sends undergraduate students to international labs to promote cultural exchange and to build research experience. Three IRES awards have had nanotechnology components.

In addition to the activities above, nanoEHS research funded by NSF also has a very strong international component. NSF and the U.S. Environmental Protection Agency jointly support two large-scale centers: the Center for the Environmental Implications of NanoTechnology (CEINT), which is directed by Duke University, and the Center for Environmental Implications of Nanotechnology (UC CEIN), which is directed by the University of California, Los Angeles. Support for each of these centers was renewed for another five years in 2013. Both centers consist of at least seven domestic institutions, and UC CEIN also has one participating institution from Europe. Generally, NSF does not support research at foreign institutions, but if there is a clear partnership and expertise provided by a foreign collaborator, as in the case of UC CEIN, a sub-award can be made. Further, both of these centers have participated in European NanoSafety Cluster projects. Finally, CEINT has collaborations with the United Kingdom on the Transatlantic Initiative for Nanotechnology and the Environment (TINE) project; the International Consortium for the Environmental Implications of Nanotechnology (ICEINT), which is based in France; and with the Safe Ecodesign and sustainable Research and Education applied to NANomaterial Development (SERENADE) project, which includes participants from four European countries and Australia. Dr. Tessier stressed that all of these collaborations are driven by individual investigators and that there are many informal international interactions that take place outside of the mechanisms listed above. More information about NSF's awards can be found on the award search website.²¹

¹⁹ www.nsf.gov/funding/pgm_summ.jsp?pims_id=505038

²⁰ www.nsf.gov/funding/pgm_summ.jsp?pims_id=12831

²¹ www.nsf.gov/awardsearch/

4. Bridging NanoEHS Research Efforts

Research in Environment, Health, and Safety of Nanotechnology and Sustainable Nanotechnology

Barbara Karn, U.S. National Science Foundation

Barbara Karn detailed how NSF funds fundamental research at the frontiers of knowledge, across all fields of science and engineering and at all levels of education. NSF is not a regulatory agency, but the results of NSF-funded research can inform regulatory decisions. Dr. Karn described the strong interdisciplinary focus of the Environmental, Health, and Safety of Nanotechnology program in the Engineering Directorate of NSF. Dr. Karn described the six goals of the program:

- Shift emphasis from simple ENMs to more complex, realistic materials and systems
- Provide more detailed materials characterization to facilitate cross-study comparisons
- Apply environmentally benign synthesis methods of nanomaterials, and use nanotechnology to mitigate adverse impacts of current non-nano processes
- Implement a systems approach to nanoEHS research
- Develop the fundamental tools, including models and analytical methods, to measure and predict the EHS impacts of ENMs
- Inform and enable the responsible and sustainable development of nanotechnology

Dr. Karn presented an analysis of 75 research proposals received in 2013. These proposals generally fell into four categories: analytical methods, environmental impacts, fate and transport, and toxicology. Sixty percent of the proposals addressed questions of toxicology, with the remainder of the proposals split among the other three topics. Simple ENMs, such as silver, gold, carbon nanotubes, and titanium dioxide, were the subject of most of the proposals, although a small number of studies were also proposed on cerium oxide and graphene. This led Dr. Karn to further emphasize the need to move toward more complex and realistic systems.

Dr. Karn also discussed the Sustainable Nanotechnology Organization (SNO), which is a non-profit, professional society intended to advance knowledge in all aspects of sustainable nanotechnology, including environmental applications and implications, as well as societal and economic components. SNO is undertaking a variety of activities in the promotion of sustainable nanotechnology, including workshops, conferences, special journal issues, and industrial partnerships. For example, SNO hosted a workshop on nanocerium to address and harmonize the conflicting information on this topic.²² SNO has over 200 members from five countries, and there is a concerted effort to increase international participation. Dr. Karn also mentioned that SNO actively engages graduate students because it sees an opportunity to teach young researchers to consider environmental implications and sustainability in their research and throughout their careers. More information about SNO, including upcoming events and membership opportunities, is available at www.susnano.org/.

²² Note: The results of this workshop were published in *Environmental Science: Nano* after the workshop but before the publication of this report: R.A. Yokel, Introduction to the themed collection on nanocerium research. *Environ. Sci.: Nano* **1**, 514–515 (2014).

4. Bridging NanoEHS Research Efforts

Horizon 2020

Nicolas Segebarth, Directorate General (DG) for Research and Innovation, European Commission

Nicolas Segebarth gave an overview of Horizon 2020, the European Commission's Framework Programme for research and innovation that runs from 2014 to 2020. The European Commission funds approximately 3–5% of all research in Europe and provides critical support for networking and collaboration. The total budget for Horizon 2020 is €77 billion (approximately \$104 billion), which represents a 20% increase over Framework Programme 7 (FP7). Horizon 2020 is intended to address the grand challenges of maintaining and improving European scientific excellence, responding to the economic crisis, and addressing societal challenges.

Nanotechnology was supported in FP7 in thematic programs and under the Nanosciences, Nanotechnology, Materials, and New Production Technologies Programme. This activity addressed grand challenges, such as health, energy, and environmental remediation, as well as cross-cutting issues, including safety, metrology, and standardization. The European Commission funded 48 nanosafety research projects under FP7, representing a total investment of about €177 million. These projects were co-funded by national governments, and the total projects costs were €62 million. Dr. Segebarth noted that the primary goals of nanosafety research are to create safe products for consumers and the environment and to enable a science-based regulatory framework. He also detailed how project clustering under the NanoSafety Cluster is intended to foster synergy, avoid duplication, provide a forum for problem solving and for planning R&D activities, and provide stakeholders with appropriate knowledge.

Horizon 2020 represents a significant departure from previous Framework Programmes; several specific changes were made to simplify the program, support innovation, and emphasize expected impacts over prescriptive topics. Horizon 2020 is built on three interrelated priorities: excellent science, societal challenges, and industrial leadership. Nanotechnology is supported under the Leadership in Enabling and Industrial Technologies program as a Key Enabling Technology. Horizon 2020 is designed to bridge the gap between technological discovery and manufacturing, as evidenced by a new funding instrument for commercializing promising technologies. Projects rated with a Technology Readiness Level between one and six will be funded at 100%, while those with a Technology Readiness Level between five and eight will be funded at 70%. The 2014–2015 Work Programme for Nanotechnologies, Advanced Materials, Biotechnology, and Advanced Manufacturing and Production Technologies was scheduled for publication on December 11, 2013.²³ Five research calls are planned on topics that include international coordination, systems biology and high-throughput approaches, and next-generation tools for risk governance of nanomaterials. Finally, Horizon 2020 has a strong emphasis on leveraging resources and building synergies with member states, industrial partners, and international collaborators. Dr. Segebarth noted that nanoEHS collaboration with the United States is a particularly high priority.

²³ ec.europa.eu/programmes/horizon2020/

4. Bridging NanoEHS Research Efforts

Communities of Research

Stacey Standridge, U.S. National Nanotechnology Coordination Office

Stacey Standridge gave a brief overview of the purpose of the CORs, followed by an explanation of the breakout session logistics. The CORs are modeled on communities of practice in which a group of people who share a common interest are in regular contact to develop a shared repertoire of knowledge and resources. Dr. Standridge described how this mechanism translates to the Communities of Research: scientists from the United States and Europe share an interest in nanoEHS and communicate through emails, teleconferences, and in-person meetings to share information and best practices.

Cross-COR Information Flow

Mark Hoover, U.S. National Institute for Occupational Safety and Health

Mark Hoover encouraged the workshop participants to discuss opportunities for improving the effectiveness of communication and information exchange among the Communities of Research during the breakout sessions. Drawing on recent discussions among nanoinformatics participants in the CORs, he proposed viewing cross-Community communications and collaborations as an “information-to-action continuum” (see Figure 1) in which relevant and reliable information is made available to the CORs through organized ontologies and databases. Outputs of the exposure and hazards communities then enable realistic assessment of risks, which in turn enables informed decision making to manage those risks.

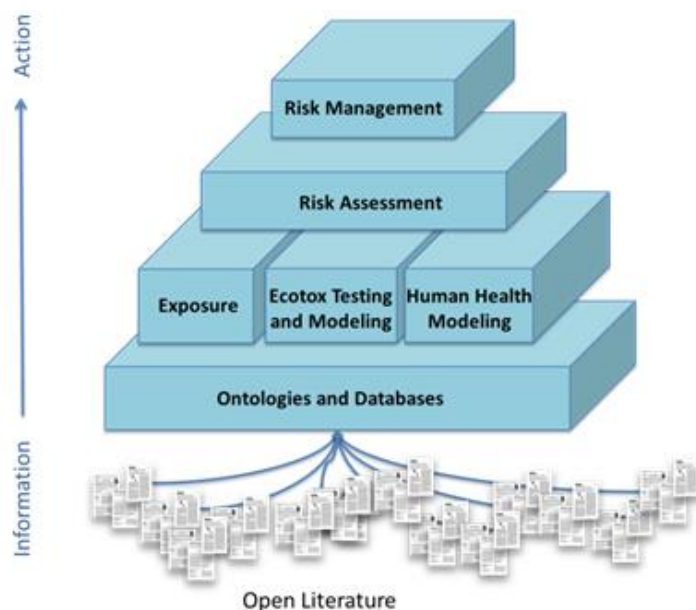


Figure 1. Idealized information-to-action continuum beginning with organized ontologies and databases.

Dr. Hoover described his view of the CORs’ objective (see Figure 2), which is to build and sustain effective *leaders*, *cultures*, and *systems* to enable safety, health, well-being, and productivity in the nanotechnology community. Based on the diverse nature of that community, he further argued that success will best be achieved by incorporating a robust managerial frame of mind, rather than through any specific, proscriptive methods. In particular, Dr. Hoover argued that success in any managerial approach is best achieved and sustained when effective leaders,

4. Bridging NanoEHS Research Efforts

cultures, and systems are in place and well-balanced. If any of these three essential components are lacking, any endeavor, including the work of the CORs, is less likely to be successful.

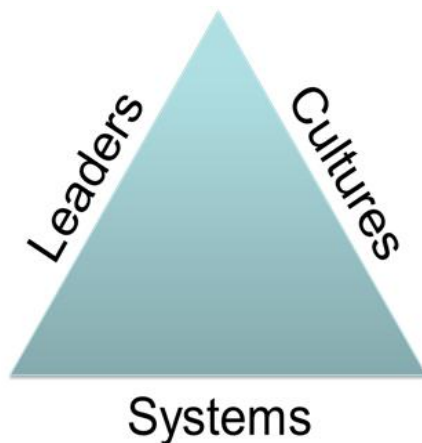


Figure 2. The proposed risk-informed managerial approach, in which well-balanced and effective leaders, cultures, and systems are built and sustained through the CORs.

Finally, Dr. Hoover recommended that the CORs take the following four-pronged approach to achieving community action: (1) engage the community; (2) inform the interested; (3) reward the responsive; and (4) understand and incentivize the reluctant.^{24,25}

²⁴ M. D. Hoover *et al.*, “Toxic” and “nontoxic”: Confirming critical terminology concepts and context for clear communication, *Encyclopedia of Toxicology*, **4**, 610–616 (2014).

²⁵ D. de la Iglesia *et al.*, *Nanoinformatics 2020 Roadmap* (National Nanomanufacturing Network, Amherst, Massachusetts, 2011; eprints.internano.org/607/).

5. COR Breakout Sessions and Plenary Reports

Each of the six CORs held a breakout session on the afternoon of the first day of the workshop to share progress, discuss pressing issues, and propose activities for the coming year. The COR co-chairs served as chairs in their respective breakout sessions, except for the Risk Management and Control session and the Ecotoxicity and Predictive Modeling session. Keld Alstrup Jensen served as the EU co-chair for the Risk Management and Control session, and Richard Handy chaired the Ecotoxicity and Predictive Modeling session.

Further, as illustrated in Figure 3, a one-hour joint breakout session was held with the Exposure through Product Life COR and the Databases and Ontologies COR to discuss a potential joint project. The themes and outcomes from the breakout sessions were reported in a plenary session on the second morning of the workshop. The summaries that follow include both the breakout sessions and the plenary session reports.

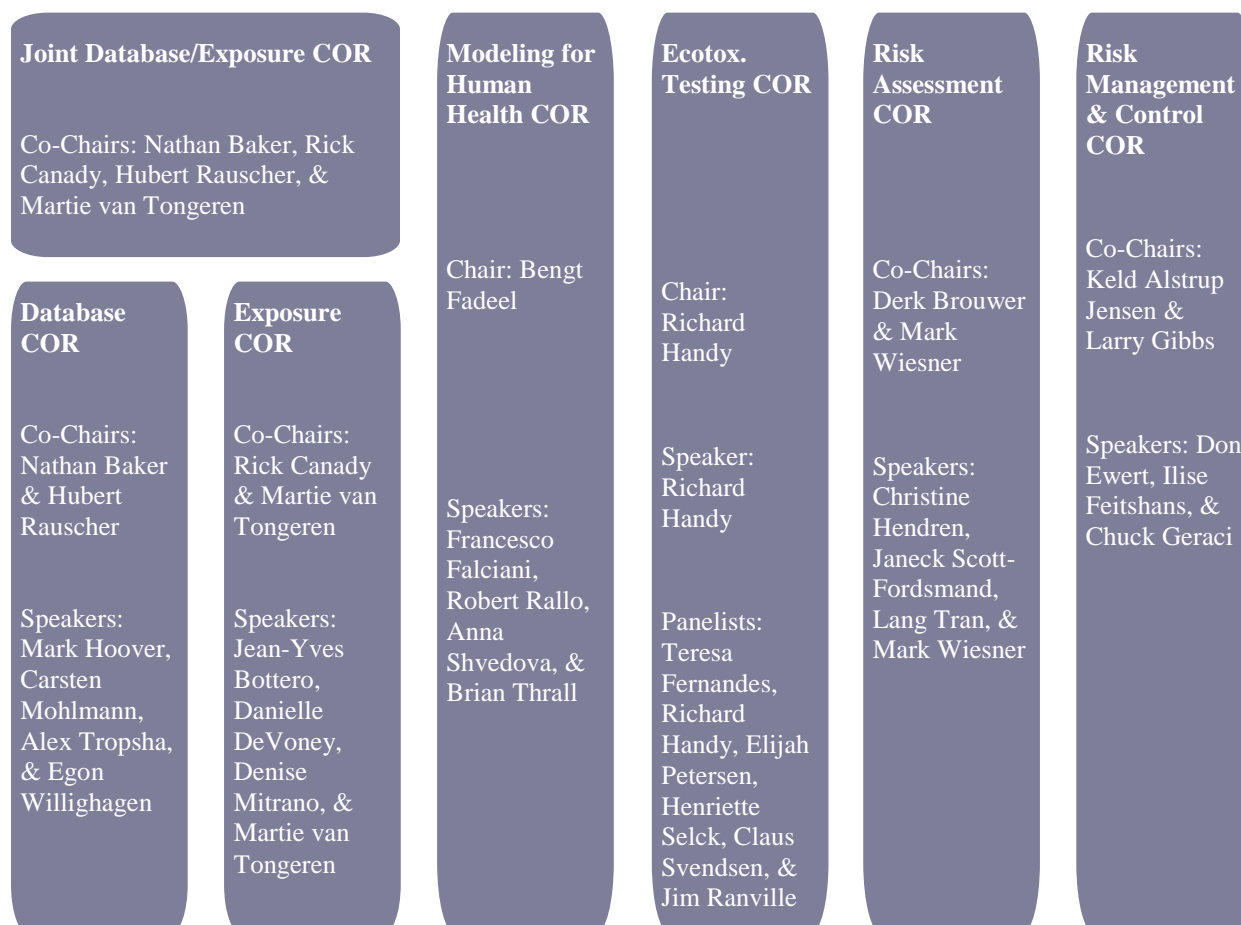


Figure 3. Breakout session format and speakers.

5. COR Breakout Sessions and Plenary Reports

Joint Project Proposed by the Databases and Exposure CORs

Co-Chairs: **Nathan Baker**, Pacific Northwest National Laboratory
Rick Canady, ILSI Research Foundation
Hubert Rauscher, Joint Research Centre, European Commission
Martie van Tongeren, Institute of Occupational Medicine
Rapporteur: **Egon Willighagen**, Maastricht University

Breakout Session Presentations and Discussion

This session focused on a proposed project between the Exposure through Product Life COR and the Databases and Ontologies COR. The project is intended to identify the information that a risk assessor would need in the event of a large-scale spill of ENMs. As the discussion evolved, participants identified a range of relevant information, including how similar spills may have been managed in the past, the toxicological reference values for the materials, and the nature and extent of contamination. Many of the questions that a risk assessor may have are not specific to ENMs, but it can be difficult to answer these questions for ENMs because appropriate methods are context-dependent and there are few standard protocols.

Prior to the workshop, COR members from RTI International drafted a two-page proposal on a database of relevant methods, and workshop attendees discussed this proposal. Participants observed that many relevant databases already exist in a variety of domains and that the integration of these databases would be an easy way to provide information to a risk assessor in the hypothetical situation. However, existing resources must be inventoried before they can be integrated, and several groups, such as the European NanoSafety Cluster's Database Working Group,²⁶ have started assembling inventories.

Attendees recommended two approaches to aggregating the necessary information: (1) a nanoinformatics, workflow approach, similar to the Taverna Workflow Management System,²⁷ and (2) a marketplace approach where information providers and users can meet. Data quality and availability were also recurrent themes during the discussion. One participant noted that the data quality requirements may vary depending on the question of interest; a single definition for data quality is not necessarily beneficial. Another attendee observed that it is easier to share information on methods than it is to share data.

Plenary Report and Discussion

Hubert Rauscher and Martie van Tongeren summarized the breakout session outcomes. Dr. Rauscher noted that it is important to inventory existing resources, and he invited attendees to identify relevant resources. Participants mentioned several projects, including the Nanomaterial Registry²⁸ and the World Health Organization's International Programme on Chemical Safety,²⁹ which established a worldwide risk assessment network.³⁰ Dr. van Tongeren emphasized the need for interlaboratory testing to improve test methods.

²⁶ www.nanosafetycluster.eu/working-groups/4-database-wg.html

²⁷ www.taverna.org.uk/

²⁸ www.nanomaterialregistry.org/

²⁹ www.who.int/ipcs/en/

5. COR Breakout Sessions and Plenary Reports

Databases and Ontologies

Co-Chairs: **Nathan Baker**, Pacific Northwest National Laboratory
Hubert Rauscher, DG Joint Research Centre, European Commission
Rapporteur: **Egon Willighagen**, Maastricht University

Breakout Session Presentations and Discussion

Mark Hoover (U.S. National Institute for Occupational Safety and Health – NIOSH) gave an overview on behalf of the Nanotechnology Knowledge Infrastructure (NKI) Signature Initiative under the U.S. National Nanotechnology Initiative. He described the collaboration, modeling, and cyber-toolbox thrusts of the NKI, including Data Readiness Levels, which provide a descriptor of data quality and maturity.³¹ Dr. Hoover noted that several U.S. and internationally based activities are listed on the NKI cyber toolbox webpage.³²

Carsten Möhlmann (Institute for Occupational Safety and Health of the German Social Accident Insurance) described the Nano Exposure & Contextual Information Database. This tool is managed by the Partnership for European Research in Occupational Safety and Health³³ and will host data on exposure to nano-objects to enable exposure modeling and to provide the basis for a job exposure matrix and further epidemiological studies. As such, the database needs to be flexible to capture information on measurement methods and protocols, as well as material characteristics. The test versions of the input and export modules are ready, with improvements planned. Stand-alone versions are checked and used by third parties.

Alexander Tropsha (RTI International) introduced the Nanomaterial Registry,³⁴ which is positioned as a central data repository for the nanomaterial community to access digitally formatted scientific data. Data included in this resource must be accompanied by Minimal Information About Nanomaterials,³⁵ which is comprised of 12 physico-chemical characteristics and metadata. Another key component of the registry is a well-established curation process that facilitates data management.

Egon Willighagen briefly summarized the activities of the NanoSafety Cluster's Database Working Group and the eNanoMapper project.³⁶ The Database Working Group is undertaking two initial tasks: (1) updating the list of database resources that support nanosafety assessment and (2) creating an overview of and recommendations for data quality. The eNanoMapper project proposes a computational infrastructure for toxicological data management of ENMs based on open standards, ontologies, and an interoperable design to enable a more integrated approach to nanotechnology research.

³⁰ www.who.int/ipcs/network/en/

³¹ Nanoscale Science, Engineering, and Technology Subcommittee of the Committee on Technology, *Nanotechnology Signature Initiative: Nanotechnology Knowledge Infrastructure: Enabling National Leadership in Sustainable Design* (National Science and Technology Council, Washington, District of Columbia, 2012; www.nano.gov/sites/default/files/pub_resource/nki_nsi_white_paper_-_final_for_web.pdf).

³² www.nano.gov/node/828

³³ www.perosh.eu/research-projects/perosh-projects/exposure-measurements-and-risk-assessment-of-manufactured-materials-nanoparticles-devices/

³⁴ www.nanomaterialregistry.org/

³⁵ www.nanomaterialregistry.org/about/MinimalInformationStandards.aspx

³⁶ www.enanomapper.net/

5. COR Breakout Sessions and Plenary Reports

Plenary Report and Discussion

Nathan Baker summarized the breakout session and invited participants to provide feedback on what resources are available. In the subsequent discussion, two key challenges emerged: incentivizing data sharing and ensuring appropriate data quality. Participants recommended several potential approaches to these issues, including blind data entry, providing additional analytical and visualization capabilities to researchers who submit data, and engaging publishers as early as possible.

Exposure through Product Life, with Material Characterization

Co-Chairs: **Rick Canady**, ILSI Research Foundation

Martie van Tongeren, Institute of Occupational Medicine

Rapporteur: **Emeric Frejafon**, INERIS (French National Institute for Industrial Environment and Risks)

Breakout Session Presentations and Discussion

Danielle DeVoney (U.S. Environmental Protection Agency) described how several types of information, including exposure levels and ENM bioavailability, are needed to evaluate the exposure component of risk assessment. Dr. DeVoney emphasized the need to design toxicology studies, both on human health and the environment, such that the data produced can be translated from a controlled, laboratory environment to a real-world release scenario. Further, she recommended defining the characteristics of an ENM that result in biological activity and quantifying exposures based on those characteristics.

Denise Mitrano (Swiss Federal Laboratories for Materials Science and Technology – EMPA) introduced the NanoMILE project.³⁷ NanoMILE is intended to facilitate a safer-by-design approach by correlating specific ENM properties to their aging, transformation, and behavior, as well as by classifying ENMs according to their impacts. Dr. Mitrano presented a case study on the aging and release of silver nanoparticles from textiles, noting that (1) product use dictates relevant aging and transformation processes; (2) multiple, subsequent transformations are likely; and (3) “traditional” additives to textiles may also release nanoscale materials.

Jean-Yves Bottero (Centre Européen de Recherche et d’Enseignement de Géosciences de l’Environnement – CEREGE) presented case studies on nanotechnology-enabled products (i.e., self-cleaning cement, sunscreen, and paint) to illustrate some of the key issues associated with assessing exposure to ENMs along the product life cycle. These issues include the complexity of ENMs in commercial products, ENM variability during the aging process, and multiple release scenarios (e.g., normal use vs. accidental release). Dr. Bottero recommended that more studies be carried out for realistic exposure scenarios on natural systems, as well as the use of a tiered approach to risk assessment.

The discussion during this breakout session led to three concrete recommendations from participants: (1) the development of a decision tree (instead of a case-by-case approach); (2) the use of categorization strategies; and (3) an initial focus on commercially available, high-volume ENMs and products.

³⁷ www.nanomile.eu-vri.eu/

5. COR Breakout Sessions and Plenary Reports

Plenary Report and Discussion

Martie van Tongeren summarized the presentations from the breakout session and related the key ideas that emerged during the discussion of the joint proposal between this COR and the Databases and Ontologies COR. He advocated for use of a decision tree framework that addresses human health and environmental exposure separately and for the development of a database that focuses on methods because it is easier to share information on tools than it is to share data. During the plenary discussion, participants recommended focusing on reference systems instead of reference materials. These systems could be used to validate methods for more realistic exposure scenarios, which would also help to identify critical research needs by highlighting the limitations of the existing protocols.

Predictive Modeling for Human Health, with Material Characterization

Co-Chairs and Rapporteurs: **Bengt Fadeel**, Karolinska Institute
Robert Rallo, Universitat Rovira i Virgili

Breakout Session Presentations and Discussion

The session opened with an overview by Bengt Fadeel summarizing the objectives of the COR along with a presentation on other related activities in the EU and at the international level, including the new Working Group on Systems Biology in the EU NanoSafety Cluster and the 7th International Nanotoxicology Congress. The topics selected for the Nanotoxicology Congress included *in silico* modeling focusing on quantitative structure–activity relationships (QSARs) for nanomaterials, systems biology/computational biology approaches, and animal models for the elucidation of health risks related to (carbon-based) nanomaterials.

Robert Rallo provided an illustrative example of U.S.–EU collaborative research efforts involving UC CEIN and the EU MoDeRn project (Monitoring Developments for Safe Repository Operation and Staged Closure) on the development of structure–activity relationships (SARs) for nanomaterials. He introduced a workflow for analysis and modeling of nanosafety data, which included: (1) data management and preprocessing; (2) data analysis and knowledge extraction; and (3) model development and validation. He also presented some examples of nanoinformatics tools for implementing aspects related to each of the steps in the processing workflow (e.g., HDAT: Tool for analyzing HTS data, nanoDMS, and an ISA-TAB-Nano compliant data management system).

Francesco Falciani (University of Liverpool), a partner in the NanoMILE project, gave a talk on systems biology approaches for studying toxicity of nanomaterials. His presentation focused on recent work on nanosilver in *Daphnia* as a proof-of-concept study, based on RNA sequencing to capture transcriptional responses.

Anna Shvedova (NIOSH), partner of the EU NANOSOLUTIONS project, provided a comprehensive overview of work performed at NIOSH on the effects of nanomaterials using animal models. She discussed data on single-walled carbon nanotubes versus asbestos, along with recent studies of biodiesel. Notably, proteomics studies revealed that the proteins affected

5. COR Breakout Sessions and Plenary Reports

by asbestos were almost entirely a subset of those proteins affected by single-walled carbon nanotubes,^{38,39,40} implying strong similarities in pulmonary responses to these materials.

Finally, Brian Thrall (Pacific Northwest National Laboratory) discussed “omics” approaches in nanosafety research, providing as an example recent studies of amorphous silica and superparamagnetic iron oxide nanoparticles. He highlighted that the field is biased towards acute effects and cytotoxicity of nanomaterials but noted that phenotypic effects of “transcriptional reprogramming” of cells by nanoparticles may not be apparent until cells are challenged; even “benign” particles that lack direct cytotoxicity or proinflammatory effects may alter regulation of hundreds of genes in immune cells.

Plenary Report and Discussion

The COR decided to adopt a broader perspective on “predictive modeling for human health” at the workshop, as exemplified by the four presentations. Several issues were crystallized during the general discussion. First, there is need to define general principles for predictive toxicology, and it is important to make progress with the available tools despite the presence of uncertainty. It was highlighted that UC CEIN has made substantial progress in establishing SARs and predictive models for different nanoparticles (mainly metal oxides), with good agreement between *in vivo*, *in vitro*, and model predictions. There is also a need for data sharing, with an agreed-upon format for data collection; this is something that the EU eNanoMapper project currently is focusing on in collaboration with other EU NanoSafety Cluster projects. Previous examples of successful U.S.–EU collaborations, notably those in the field of systems biology (e.g., NANOMMUNE⁴¹), were mentioned, and plans for further joint research activities between American and European scientists were discussed. Horizon 2020 may offer new opportunities for such collaborations. The MODENA⁴² (modeling toxicity of nanomaterials) COST⁴³ (European Cooperation in Science and Technology) action initiative is another forum for exchanging ideas and results specifically on nanoQSARs. The COR members were in favor of continuing with webinars, for instance, on the importance of the bio-corona for understanding of nano–bio interactions. Finally, the issue was raised whether exposure also should be considered in the COR; interactions with other CORs on this topic were welcomed. Interactions between the U.S.–EU COR and the working groups⁴⁴ on Systems Biology (Chair: Bengt Fadeel) and on Modeling (Chair: Robert Rallo) in the EU NanoSafety Cluster should be considered. It was also noted that the April 2014 7th International Nanotoxicology Congress in Antalya, Turkey, was slated to include one session on systems biology and one session on computational toxicology, featuring prominent scientists from the United States and Europe.

³⁸ A. Elder *et al.*, Effects of subchronically inhaled carbon black in three species. I. Retention kinetics, lung inflammation, and histopathology. *Toxicol. Sci.* **88**, 614–629 (2005).

³⁹ G. Davis, K. Leslie, D. Hemenway, Silicosis in mice: Effects of dose, time, and genetic strain. *J. Env. Pathol. Tox.* **17**, 81–97 (1998).

⁴⁰ R. F. Robledo *et al.*, Increased phosphorylated extracellular signal-regulated kinase immunoreactivity associated with proliferative and morphologic lung alterations after chrysotile asbestos inhalation in mice. *Am. J. Pathol.* **156**, 1307–1316.

⁴¹ www.nanosafetycluster.eu/eu-nanosafety-cluster-projects/seventh-framework-programme-projects/nanommune.html

⁴² www.modena-cost.eu/

⁴³ www.cost.eu/

⁴⁴ www.nanosafetycluster.eu/working-groups.html

5. COR Breakout Sessions and Plenary Reports

Ecotoxicity Testing and Predictive Models, with Material Characterization

Chair: **Richard Handy**, Plymouth University

Rapporteur: **Elijah Petersen**, U.S. National Institute of Standards and Technology

Breakout Session Presentations and Discussion

Richard Handy gave a comprehensive overview of “Progress on Nano Ecotoxicology.” He summarized the potential impacts of nanomaterials on a broad array of test organisms. One critique of microorganism research is that much of it has been conducted on single species, while far fewer studies have investigated more complicated systems. Recent studies have helped fill in data gaps regarding potential toxic effects on marine invertebrate species. Dr. Handy also discussed the effects on terrestrial systems, such as earthworms and plants, noting that uptake into plants is studied less frequently. In vertebrates, multigenerational effects have been observed in fish after TiO₂ exposure. However, fewer studies have been conducted on amphibians, and almost no studies have been performed on reptiles or birds.

Breakout session participants, both those present in the room and those joining by phone, had a lengthy discussion on the bioavailability and toxicity of ENMs in soils and sediments. Standard soil and sediment tests may not always use the most appropriate test media for ENMs because they were not developed for nanoparticle studies. For example, hazard ranking of ENMs may be best conducted by standardized test media, but studies using natural soils and sediments may be more appropriate for modeling. One participant recommended the use of pesticide testing protocols because these tests may be of a longer duration—up to two years. Participants discussed the most relevant metrics for exposure and ecological effects; they identified bioavailability of ENM nanomaterial concentrations in organisms as the most relevant metrics. The group also extensively discussed sources of uncertainty in current test methods.

Stemming from these discussions, the following recommendations were made: (1) comparison of different metrics for ecological endpoints; (2) assessment of long-term effects; (3) thorough characterization of test media for informatics evaluations; (4) single-particle inductively coupled plasma mass spectrometry analysis for *in vivo* characterization and for sediments and soils, as well as extractions from these matrices; (5) identification of ENM aging impacts in sediments in soils; and (6) consideration of new “fit for purpose” test soils. The COR also set a goal of holding one in-person meeting at a scientific conference in the next year.

Plenary Report and Discussion

The plenary discussion focused primarily on the use of Organisation for Economic Co-operation and Development (OECD) test guidelines and the acceptability of current tests.⁴⁵ Several attendees proposed modification of the OECD test guidelines for nanomaterials, but another participant said that it is important to work with the current reference points because there has been a lot of relevant, non-nanotechnology-specific work on these systems. The need for robust, interlaboratory testing was also discussed.

⁴⁵ OECD test guideline revisions were also discussed during the Roundtable Discussion. See page 23 for a summary of that talk.

5. COR Breakout Sessions and Plenary Reports

Risk Assessment

Co-Chairs: **Derk Brouwer**, Netherlands Organisation for Applied Scientific Research (TNO)
Mark Wiesner, Duke University
Rapporteur: **Christine Hendren**, Duke University

Breakout Session Presentations and Discussion

Lang Tran (Institute of Occupational Medicine) gave an overview of the EU NanoSafety Cluster's Risk Assessment Working Group, which was established to coordinate activities in the development of risk assessment approaches and related intelligent testing strategies for ENMs. It is also intended to develop an integrated approach to human and environmental assessment. The MARINA project⁴⁶ specifically addresses identification and evaluation of relevant risk assessment and management tools and methods, as well as the integration of environmental and human health risk assessment and management strategies. Janeck Scott-Fordsmand (Aarhus University) described a research framework to develop an intelligent testing and risk assessment strategy. This strategy will facilitate an informed grouping and ranking of ENMs through the identification of physicochemical priorities, exposure priorities, and hazard priorities. The effort will enable a transition from case-by-case, short-term knowledge to the more generalized understanding needed for more efficient testing and integration with risk management.

Mark Wiesner highlighted the main findings from the U.S. National Research Council report, *Research Progress on Environmental, Health, and Safety Aspects of Engineered Nanomaterials*.⁴⁷ Among the recommendations from the report, two key concepts were highlighted in Dr. Wiesner's presentation: the need to study ENMs in more complex, realistic systems, and the use of an informatics-enabled knowledge commons to link laboratory studies and complex systems. Christine Hendren presented CEINT's approach to separating intrinsic and extrinsic properties, defining reference systems, and developing consistent functional assays that can predict outcomes.

In an initial "tour de table," attendees identified approximately 20 potential topics for prioritization, and these topics were ranked after the presentations through a voting mechanism. The most popular items were (1) an information supply chain, (2) functional assays, (3) harmonized tools for risk assessment, and (4) categorized hazard data that is compatible with risk assessment procedures.

Plenary Report and Discussion

Dr. Hendren summarized the breakout session, noting that the information supply chain and cross-linking efforts were recurring themes. Based on the prioritization activity, she presented a categorization framework (Figure 4) that describes how risk assessment should be framed with a life cycle perspective and with the risk managers' needs in mind. The framework further illustrates how consistent data and harmonized tools can inform a knowledge commons and ultimately enable categorization.

⁴⁶ www.marina-fp7.eu/

⁴⁷ National Research Council, *Research Progress on Environmental, Health, and Safety Aspects of Engineered Nanomaterials* (The National Academies Press, Washington, District of Columbia, 2013; www.nap.edu/catalog.php?record_id=18475).

5. COR Breakout Sessions and Plenary Reports

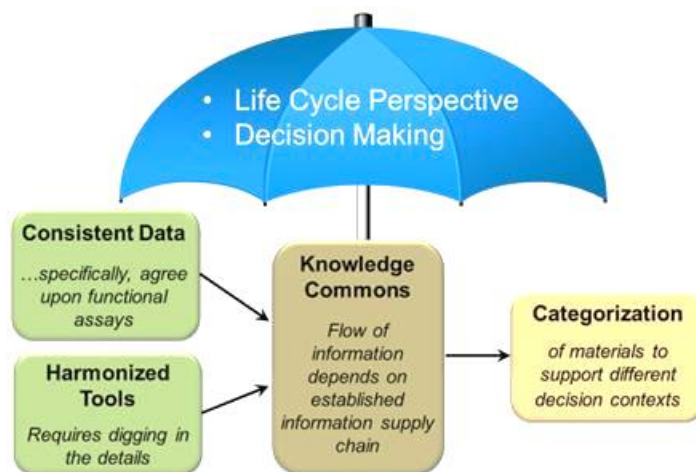


Figure 4. Risk Assessment COR categorization framework.

Dr. Hendren emphasized that harmonizing tools is important across many CORs, but this can only be achieved with detailed discussions; for example, a cross-COR effort to consider linkages could be centered around examples of decision scenarios and the data used to justify and support specific decisions, rather than via abstract discussions.

Risk Management and Control

Co-Chairs: **Keld Alstrup Jensen**, Danish National Research Centre for the Working Environment

Larry Gibbs, Stanford University

Rapporteur: **Keld Alstrup Jensen**, Danish National Research Centre for the Working Environment

Breakout Session Presentations and Discussion

Larry Gibbs gave a brief history of the COR's activities and said that this Community should address the need for an approach to guide the development of globally harmonized risk management procedures.

Ilise Feitshans (University of Lausanne) advocated for international harmonization of nanotechnology laws. She first described the context in which laws are created and the myriad groups that influence, write, and implement nanotechnology-relevant laws. Dr. Feitshans argued that laws are necessary to avoid liability and administrative fines, as well as to prevent injury; furthermore, harmonization of laws will spread best practices, show due diligence, and increase predictability and consistency. She closed by encouraging attendees to educate themselves about existing and potential laws and to participate as informed stakeholders.

Donald Ewert (nanoTox) discussed the prevalence of ENMs in consumer products and the operational needs for regulation. He noted the difference between the European Commission's definition of nanotechnology and that of the U.S. National Nanotechnology Initiative, arguing that a loophole will be created if these discrepancies are not addressed. Dr. Ewert introduced existing occupational, health, and safety management systems and certification programs and proposed a similar certification program, specific to nanotechnology, that would fill the gaps

5. COR Breakout Sessions and Plenary Reports

among existing mechanisms. Such a system would necessitate voluntary stakeholder involvement and the ability to proactively catch early uncertainties.

Charles Geraci (NIOSH) presented principles for safe-by-design ENMs and processes. He said that safe-by-design is a good risk management process, and he described two examples to support this assertion: (1) protective shells on silver nanoparticles to prevent dissolution and (2) functionalization of carbon nanotubes to make them less hazardous.

The group discussed possible mechanisms to learn about market conditions from other risk management programs, and concerns about labeling and hazard communication, particularly with workers. Attendees also identified a range of potential activities that this COR could pursue.

Plenary Report and Discussion

Dr. Gibbs and Dr. Jensen summarized the breakout session. They remarked that this Community resides at the top of the COR pyramid (Figure 1, page 10), and that they look forward to working with the other CORs to collect, communicate, and utilize data that will inform risk management.

6. Roundtable Discussion

The NANoREG Project: a Common European Approach to the Regulatory Testing of Nanomaterials

Keld Alstrup Jensen, Danish National Research Centre for the Working Environment

Dr. Jensen gave a broad overview of the NANoREG project,⁴⁸ which has 61 partners from 15 European countries, as well as the European Commission's Joint Research Centre. It is designed to bridge the gaps between basic research and regulatory decision making and to reduce fragmentation and duplication of regulatory efforts across Europe. The project began in spring 2013 and is funded for a three and half years. The European Commission provides 20% of the total budget, which is approximately €50 million; member countries and industry provide the rest of the support.

The aim of NANoREG is to identify, harmonize, and apply reliable methods for characterization, testing, and risk assessment and management, as well as to establish a grouping paradigm for ENMs to enable faster risk assessment. Toward this goal, the project has three primary objectives: (1) provide legislators with a set of tools for risk assessment and decision-making instruments; (2) develop new characterization and testing strategies; and (3) establish a close collaboration among authorities and industry with regard to the knowledge required for appropriate risk management. Dr. Jensen described how these efforts are expected to have a variety of results and outcomes that will fall under the categories of grouping, regulation, and risk management.

Dr. Jensen said that one of the benefits of the NANoREG structure is that it enables the tracking of specific topics, such as carbon nanotubes, in a single, coherent process. Further, value chain studies will be used to demonstrate the effectiveness of the project. Dr. Jensen explained that the activities of NANoREG fall under eight work packages, six of which have a scientific focus, and he explained the objectives and activities of each work package in detail. For example, 16 regulatory questions have been prioritized under work package one and 19 mandatory core ENMs, out of 70 total, have been identified under work package two. Dr. Jensen acknowledged that it will not be possible to provide answers to the priority regulatory questions before the NANoREG project ends, but the goal is to answer several of the questions and to identify the steps necessary to address the remaining topics.

International collaboration is a critical component of NANoREG. Japan, South Korea, Australia, Canada, Turkey, China, Russia, and Brazil have all shown interest in participating. The project also has links with relevant international organizations, such as OECD and the International Organization for Standardization (ISO), as well as with relevant international projects, including projects under Framework Programme 7. In closing, Dr. Jensen stressed that worldwide participation is encouraged and that there are many opportunities for well-defined collaborations on high-interest topics.

⁴⁸ www.nanoreg.eu/

6. Roundtable Discussion

Opportunities for Collaboration with OECD on Nanomaterials Research

Phil Sayre, U.S. Environmental Protection Agency

Phil Sayre described efforts within the OECD Working Party on Manufactured Nanomaterials (WPMN) to promote international cooperation in addressing nanoEHS issues. He noted that WPMN has ongoing projects in a variety of areas. The most well-known activity is the Sponsorship Programme for the Testing of Manufactured Nanomaterials, in which OECD countries and other stakeholders pool expertise and resources to perform safety testing on a priority list of 13 ENMs.⁴⁹ Dr. Sayre primarily discussed proposed guidance documents and test guidelines, however, because these documents present the greatest opportunity for collaboration.

In 2012 WPMN released a guidance document on *Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials*.⁵⁰ Table 1 lists additional guidance documents and test guidelines that were under consideration, along with the various mechanisms through which scientists could provide input. Dr. Sayre noted that individuals wishing to contribute to these activities could contact their country's Head of Delegation to the WPMN, the BIAC (Business and Industry Advisory Committee to the OECD) Head of Delegation, or the WPMN secretariat.

Table 1. Guidance documents and test guidelines under consideration by WPMN.

Topic	Proposed Action	Opportunities for Collaboration
Inhalation Toxicity Testing of Nanomaterials	Update guidance and test guidelines	Written revisions and possibilities for expert input at a workshop
Aquatic and Sediment Toxicity Testing	Publish guidance	Draft guidance and laboratory evaluation
Assessing the Apparent Accumulation Potential of Nanomaterials	Publish guidance	Draft guidance and laboratory evaluation
Dissolution, Dispersion, and Fate Testing in Water, Soils, and Sediments	Publish decision tree guidance document	Draft guidance and workshop participation
Dispersion and Dispersion Stability	Publish test guideline	Draft test guidelines and workshop participation
Dissolution Rate of Nanomaterials in the Aquatic Environment	Publish test guideline	Draft test guidelines, inter-laboratory testing, and workshop participation
Nanomaterial Removal from Wastewater	Publish test guideline	Draft test guidelines, possible inter-laboratory testing, and workshop participation

⁴⁹ www.oecd.org/science/nanosafety/sponsorshipprogrammeforthetestingofmanufacturednanomaterials.htm

⁵⁰ Organisation for Economic Co-operation and Development, *Guidance on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials* (Report no. ENV/JM/MONO(2012)40, OECD Publishing, Paris, France, 2012; [www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2012\)40&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2012)40&doclanguage=en)).

6. Roundtable Discussion

In the discussion that followed, participants repeatedly highlighted the need to maintain communication, promote collaboration, and reduce duplication among the various international nanoEHS activities, including CORs, the NANoREG project, and the OECD WPMN. One attendee suggested the use of mapping exercises and joint strategic planning to facilitate this cooperation.

Linking Research Outputs to Standardization Bodies for Innovation Objectives: the Case of FP7 CSA nanoSTAIR

Emeric Frejafon, INERIS (French National Institute for Industrial Environment and Risks)

Emeric Frejafon highlighted the European projects that INERIS contributed to in 2013, detailing how these activities have goals that range from developing tools for standards to providing regulatory advice and policy recommendations. The primary objective of the nanoSTAIR project, however, is to build a European platform that supports the transfer of knowledge gained through research to standards documents. As such, this activity, which was scheduled to run from September 2012 to March 2014, focuses on projects with applied outputs that relate directly to standardization.

Dr. Frejafon commented that there is quite a bit of ongoing nanoEHS research, but it is improperly balanced, with more of an emphasis on toxicological studies than on exposure, environmental fate, or end-of-life issues. He further stressed the needs to validate methods and to consider both worker and consumer exposure. All of this should also be done while addressing costs and keeping innovation affordable. Standardization is a tool to address these issues by supporting the dissemination of best practices and knowledge, in addition to providing an opportunity for better regulation.

Standards activities can facilitate nanoEHS research in a variety of topical areas, including measurement infrastructure, toxicology, life cycle considerations, risk assessment and management, and informatics. Dr. Frejafon noted that progress in these areas will be made more efficiently if the various communities (e.g., basic research, industry, standards, etc.) are well linked and can effectively communicate their needs.

The nanoSTAIR project was designed to target these challenges. The nanoSTAIR process can be compared to a turbine (Figure 5) that accelerates the preparation of new proposals by identifying potential candidates, making stakeholder needs explicit, and pooling resources to build a critical mass. In this analogy, the turbine takes inputs from international initiatives and industry, as well as national and EU-wide programs, to more efficiently produce technical specifications and recommendations.

The nanoSTAIR tool analyzes published standards to define keywords and to evaluate how scientific publications are utilized by the standards community. Dr. Frejafon described how the system seems to work well when there is strong topical overlap between the publications and the relevant standards groups, but expert judgment is still valuable, particularly when there is less topical overlap. NanoSTAIR has also produced a web tool that can identify and provide contact information for the most relevant standards group for a particular document and prepare inputs to

6. Roundtable Discussion

standardization.⁵¹ Dr. Frejafon underscored the tool's flexibility and applicability to other topics, such as waste.

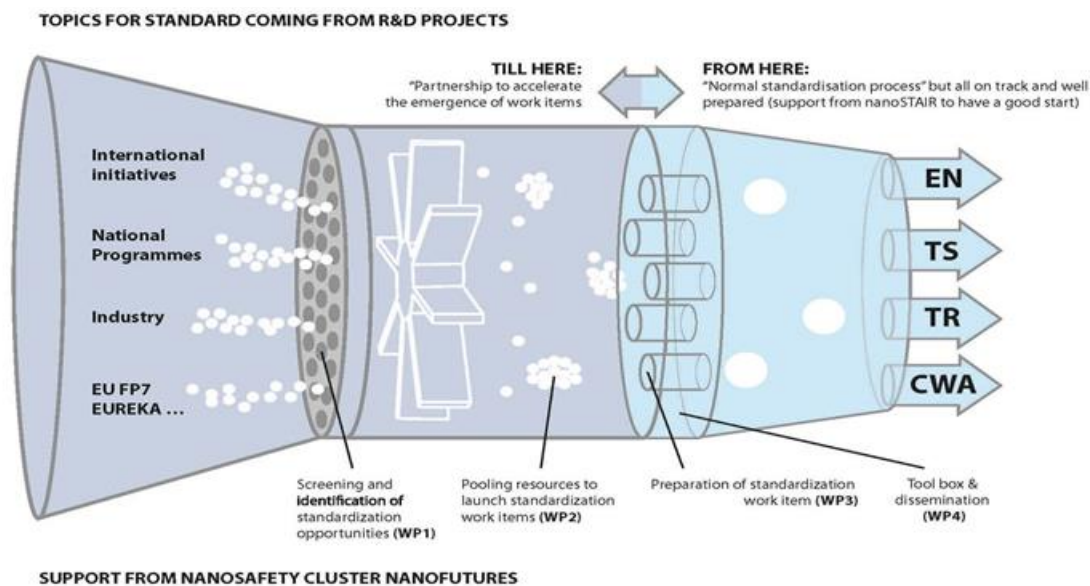


Figure 5. The nanoSTAIR process. The acronyms on the right side of the figure refer to different types of standards. EN is European Norm, TS is technical specification, TR is technical report, and CWA is CEN Workshop Agreement.

Standardization

Ajit Jillavenkatesa, U.S. National Institute of Standards and Technology

Ajit Jillavenkatesa described a few key issues around standardization with the goal of facilitating a robust discussion. He described how the word “standards” refers to a variety of products and how the entire family of standards plays an important role in enabling nanoEHS efforts. Further, he detailed the three common features across the standard development process. The first step is *protocol and tool development*. This stage is crucial because solid protocols, supported by good data and reference materials, reduce the uncertainty and ease *pre-standardization efforts*, which include interlaboratory testing. Pre-standardization efforts build confidence in which elements work and which elements need additional attention, accelerating the *development of consensus standards*.

Dr. Jillavenkatesa detailed how the benefits of international cooperation on nanotechnology standardization can extend beyond reduced duplication and leveraging resources; for example, economic benefits may also accrue, such as getting products to market faster and forming new partnerships. He also noted that significant U.S.–EU collaboration is already taking place. Generally, international cooperation can be most easily initiated in the early stages of technology development before competition and regulatory uncertainty become more prominent. However, the counterpoint to this argument is that standards can also be a powerful tool for competition. It is inevitable that there will be some divergence in standards and standard approaches, but, if a strong culture of cooperation and collaboration exists, that can facilitate bridging differences downstream, including those arising from varying regulatory requirements.

⁵¹ www.nanostair.eu-vri.eu/home.aspx?lan=230&tab=2382&pag=1427

6. Roundtable Discussion

Current nanotechnology standards efforts generally fall into three broad categories: terminology; measurement; and environmental, health, and safety. Dr. Jillavenkatesa asked the CORs to consider if these categories work well for the purposes of the CORs. He recommended that the CORs each identify which standards would be useful to their Community and also prioritize what standards needs exist across the CORs. He urged participants to stay engaged with the standards development process, providing feedback on their utility and applicability.

The benefits and limitations of approaching standardization at a systems level were extensively discussed in the question and answer period. Dr. Jillavenkatesa argued that a standardized framework provides a powerful tool for comparing across systems and accelerating development. However, a big challenge to this approach is that the basic tools are still under development. He stressed the importance of validating the various protocols through rigorous, blind assessments. Another participant recommended focusing on the aspects of protocols that increase reproducibility instead of the minute details of each method. This approach relies on a performance standard instead of a prescriptive standard. Dr. Jillavenkatesa analogized this distinction to requirements that state how quickly a sprinkler should put out a fire instead of requirements that state how far apart the sprinkler heads should be located. He also described how these framework approaches are best implemented with input from the entire community. Finally, one attendee emphasized the importance of forethought when formulating frameworks.

ERA-NET SIINN: a Consolidated Framework for EHS of Manufactured Nanomaterials

Rainer Hagenbeck, Project Management Agency Jülich, Coordinator of ERA-NET SIINN

Rainer Hagenbeck detailed the ERA-NET (European Research Area–Network of national research activities) instrument in which the European Commission funds *international collaboration* on research and each participating country funds *research projects*. Institutions from EU member states that own or manage research funding programmes are eligible to participate in an ERA-NET, and corresponding organizations from other countries can join as associated partners. The ERA-NETs are designed to coordinate national funding programs and to implement joint transnational solicitations.

The Safe Implementation of Innovative Nanoscience and Nanotechnology (SIINN) ERA-NET was launched in 2011. This project is coordinated by the German Project Management Agency Jülich and has 19 partners from 14 countries. The objective of the SIINN ERA-NET is to support three transnational joint calls on nanoEHS topics, including the effects of ENMs on biological systems, exposure assessment, and characterization methods. The first two solicitations have been completed. The third joint SIINN call is planned for 2014, and Dr. Hagenbeck invited U.S. organizations to participate in this call.⁵²

Another deliverable of the SIINN ERA-NET was the development of a consolidated framework to address nanotechnology-related risks and the management of these risks for humans and the environment. Dr. Hagenbeck said that the first draft of this framework is available online,⁵³ and

⁵² Three U.S. agencies (NSF, Consumer Product Safety Commission, and National Institute of Environmental Health Sciences) participated in the third joint solicitation, which opened on October 1, 2014.

⁵³ www.siinn.eu/en/

6. Roundtable Discussion

feedback on the draft is welcome. The framework is a living document, and continuous updates and improvements are expected. This document is not meant to replace full-length texts, but it is organized to give high-level guidance on nanoEHS issues. The framework is meant to identify best practices, potential for synergy, and recommendations for future collaborations, as well as precautionary measures, pre-normative work, and steps toward regulations. Dr. Hagenbeck closed by noting that the framework was expected to be updated, based on user feedback, and published online in 2014.

In the discussion that followed, U.S. participants had specific questions about how SIINN is coordinated and how the European Commission is involved. Dr. Hagenbeck described how a SIINN-internal group of experts suggests scientific topics for the joint calls. Project proposals are vetted by an external advisory board, and the ministries from each national government make the final funding decisions. The national ministries do not interact directly with the European Commission; instead the ERA-NET coordinator interfaces with the Commission.

Wrap up for Day 2 and Concluding Remarks

Chris Cannizzaro, U.S. Department of State

Nicolas Segebarth, DG for Research and Innovation, European Commission

Chris Cannizzaro thanked the participants for the quality of discussion during the workshop and invited additional feedback on the CORs by email. In particular, he encouraged comments on the aspects of the CORs that are, or are not, working well, if the current COR topics are the right areas, and if the number of Communities needs to be increased or decreased.

Nicolas Segebarth reiterated Dr. Cannizzaro's request, adding two additional observations from the meeting: (1) the topic of materials characterization is embedded in all of the CORs, but it was not discussed during the workshop; and (2) the importance of standardization was repeatedly emphasized during the event. Dr. Segebarth urged the participants to consider how these two topics can be more appropriately incorporated in the Communities. He closed by noting that the next *EU-U.S.: Bridging NanoEHS Research Efforts* workshop will be held in Europe.⁵⁴

⁵⁴ The fourth EU-U.S. nanoEHS workshop is scheduled for March 12–13, 2015, in Venice, Italy.

Appendix A. Workshop Agenda

Monday, December 2, 2013

8:30 am Registration

Session 1: Welcome Remarks

Moderator: C. Cannizzaro

9:00 am **Words of Welcome**

Mihail C. Roco (U.S. National Science Foundation)

Robert Pohanka (U.S. National Nanotechnology Coordination Office)

9:10 am **Welcome on Behalf of the EU**

Elke Anklam (Joint Research Centre, European Commission)

9:20 am **Purpose and Goals of the 2013 Workshop**

Chris Cannizzaro (U.S. Department of State)

Session 2: NanoEHS Research Priorities

9:30 am **Overview of Nanosafety in Europe 2015 – 2025**

Kai Savolainen (Finnish Institute of Occupational Health)

10:00 am **Overview of the 2011 NNI EHS Research Strategy**

Trey Thomas (U.S. Consumer Product Safety Commission)

10:30 am **Coffee Break**

Session 3: Bridging NanoEHS Research Efforts

11:00 am **International Dimensions of NSF Projects**

Barbara Karn & Alan Tessier (U.S. National Science Foundation)

11:20 am **Horizon 2020**

Nicolas Segebarth (DG Research and Innovation, European Commission)

11:40 am **Communities of Research (CORs)**

Stacey Standridge (U.S. National Nanotechnology Coordination Office)

12:00 pm **Cross-COR Information Flow**

Mark Hoover (U.S. National Institute for Occupational Safety and Health)

12:30 pm **Lunch**

Appendix A. Workshop Agenda

Breakout Sessions

1:30 pm	See Breakout Session Table (next page) for detailed information
5:00 pm	Wrap up for Day 1
5:30 pm	Adjourn
6:00 pm	Reception and Group Dinner (no host)

Tuesday, December 3, 2013

Session 4: COR Reports and Discussion

Moderator: N. Segebarth

8:45 am	Vision for Information Flow among CORs Nicolas Segebarth (DG Research and Innovation, European Commission)
9:00 am	Databases & Ontologies Co-Chair: Nathan Baker (Pacific Northwest National Laboratory) Co-Chair: Hubert Rauscher (Joint Research Centre, European Commission) Predictive Modeling for Human Health Chair: Bengt Fadeel (Karolinska Institute) Ecotoxicity & Predictive Models Chair: Richard Handy (Plymouth University)
10:15 am	Coffee Break
10:45 am	Exposure through Product Life Co-Chair: Rick Canady (ILSI Research Foundation) Co-Chair: Martie van Tongeren (Institute of Occupational Medicine) Risk Assessment Co-Chair: Derk Brouwer (Organisation for Applied Scientific Research) Co-Chair: Mark Wiesner (Duke University) Presenter: Christine Hendren (Duke University) Risk Management & Control Co-Chair: Keld Alstrup Jensen (Danish National Research Centre for the Working Environment) Co-Chair: Larry Gibbs (Stanford University)
12:00 pm	Lunch

Appendix A. Workshop Agenda

Breakout Sessions (Monday, December 2, 1:30 – 5:00 pm)

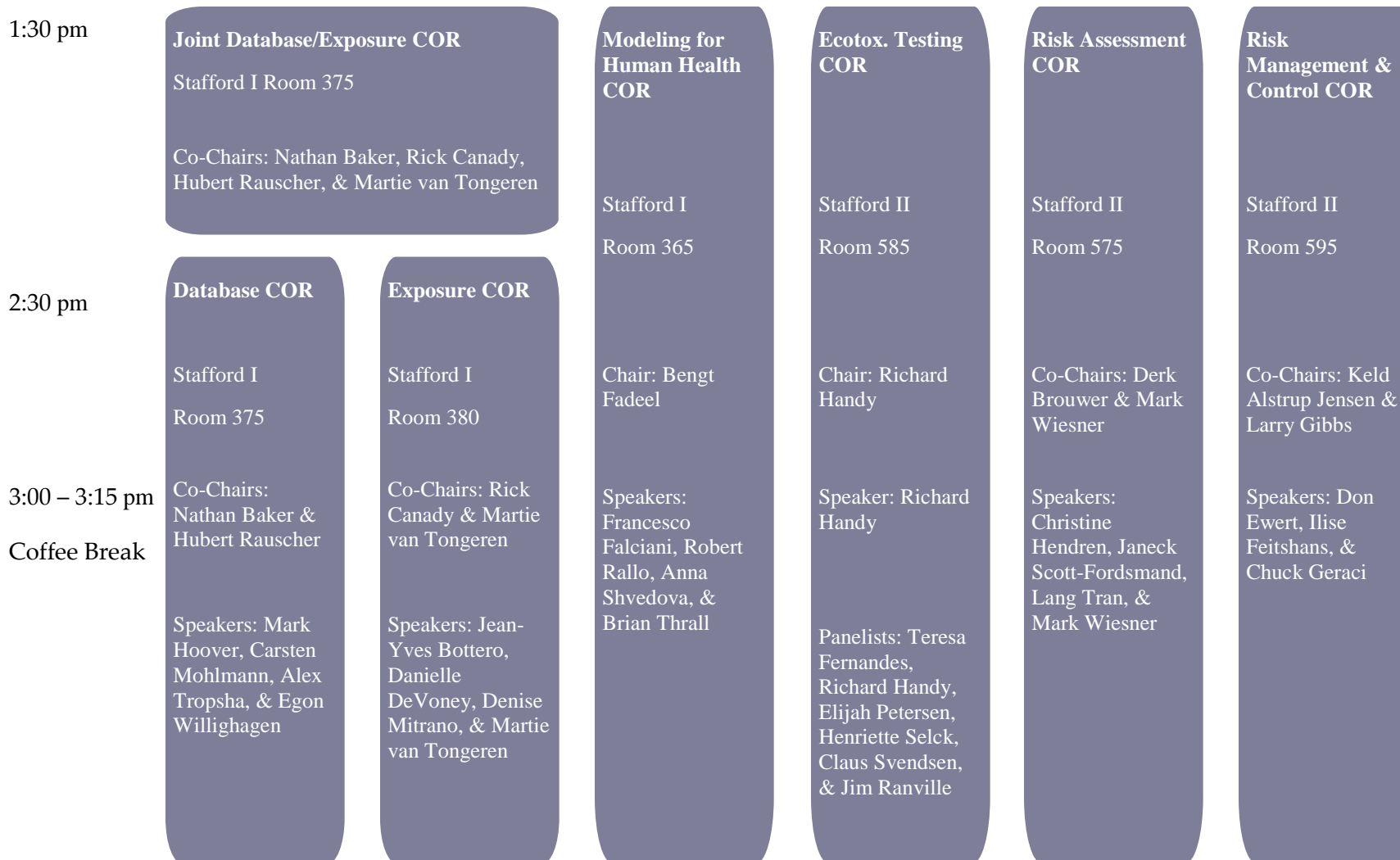


Figure 5. Breakout session schedule and speakers.

Appendix A. Workshop Agenda

Tuesday, December 3, 2013 (con't.)

Session 5: Roundtable Discussion

Moderators: E. Anklam & C. Geraci

- 1:00 pm **Connecting the CORs to Other Efforts**
NANoREG
Keld Alstrup Jensen (Danish National Research Centre for the Working Environment)
OECD Working Party on Manufactured Nanomaterials (WPMN)
Phil Sayre (U.S. Environmental Protection Agency)
Discussion
Standardization (e.g., ISO, ASTM, CEN, and VAMAS)
Emeric Frejafon (INERIS–French National Institute for Industrial Environment and Risks)
Ajit Jillavenkatesa (U.S. National Institute of Standards and Technology)
Discussion
ERA-NET SIINN Consolidated Framework for EHS of Manufactured Nanomaterials
Rainer Hagenbeck (Project Management Agency Jülich, Coordinator of ERA-NET SIINN)
Discussion
- 3:15 pm **Wrap up for Day 2 and Concluding Remarks**
Chris Cannizzaro (U.S. Department of State)
Nicolas Segebarth (DG Research and Innovation, European Commission)

Appendix B. Participant List

Affiliations are as of December 2013.

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Appendix C. Abbreviations and Acronyms

CEINT	Center for the Environmental Implications of NanoTechnology
COR	Community of Research
DG	Directorate General (of the European Commission)
EHS	environment(al), health, and safety
ENM	engineered nanomaterial
ERA-NET	European Research Activity Network
FP7	Framework Programme 7 (2007–2013) (EU)
Horizon 2020	EU Framework Programme for Research and Innovation (2014–2020)
IRES	International Research Experience for Students (U.S. NSF)
nanoEHS	nanotechnology-related environment(al), health, and safety
NIOSH	National Institute for Occupational Safety and Health (U.S.)
NKI	Nanotechnology Knowledge Infrastructure (NSI)
NNI	U.S. National Nanotechnology Initiative
NSF	U.S. National Science Foundation
NSI	Nanotechnology Signature Initiative (U.S. NNI)
OECD	Organisation for Economic Co-operation and Development
PIRE	Partnerships for International Research and Education (U.S. NSF)
QSARs	Quantitative structure–activity relationships
SARs	Structure–activity relationships
SIINN	Safe Implementation of Innovative Nanoscience and Nanotechnology ERA-NET
SNO	Sustainable Nanotechnology Organization
UC CEIN	Center for Environmental Implications of Nanotechnology
WPMN	Working Party on Manufactured Nanomaterials (OECD)