Workshop Proceedings

EU–U.S.: Bridging NanoEHS Research Efforts
Joint Workshop

March 12–13, 2015
Venice, Italy

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This document is the report of the United States–European Union (U.S.–EU) Joint Workshop on Bridging Nanotechnology Environmental, Health, and Safety (nanoEHS) Research Efforts, held on March 12–13, 2015, in Venice, Italy. The workshop was sponsored by the European Commission and the U.S. National Nanotechnology Initiative. It brought together European and American scientists engaged in nanoEHS 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 Danail Hristozov from University Ca' Foscari Venice (on behalf of the European Commission).

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1. Introduction and Background

The *2015 EU–U.S.: Bridging NanoEHS Research Efforts* joint workshop was held on March 12–13, 2015, at the premises of University Ca' Foscari in Venice, Italy. The workshop was organized by the U.S. National Nanotechnology Initiative (NNI) and the European Commission. Approximately 90 participants attended the meeting in person, and over a third of the attendees travelled from the United States. Attendees included scientists, policy makers, regulators, administrators, and authorities from the European Union and the United States[1].

The purpose of this fourth EU–U.S. nanoEHS workshop was to further deepen and promote EU–U.S. collaboration on nanomaterials-related environment, health, and safety (nanoEHS) research. Additionally, the aim was to publicize progress towards 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 *EU–U.S.: 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 Modelling 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 http://us-eu.org/2015-eu-u-s-workshop/2015-agenda/.

2. Welcome Remarks & Goals

Words of Welcome

Antonio Marcomini, Ca' Foscari University of Venice

Prof. Antonio Marcomini opened the workshop by welcoming the participants on behalf of the Department of Environmental Sciences, Informatics, and Statistics of Ca' Foscari University of Venice, which hosted the event. He explained that the growing number of nanotechnology products reaching the market poses pressing questions regarding their environmental, health, and safety (EHS) implications. Timely consideration of nanoEHS issues is essential to facilitate societal acceptance of nanotechnology, which is key to ensuring sustainability in the innovation of this technology. In order to achieve these goals, cross-disciplinary thinking is essential, and ethical, legal, and societal implications need to be taken into consideration.

U.S. Opening Statement

Chris Cannizzaro, U.S. Department of State

Dr. Chris Cannizzaro welcomed attendees to the event on behalf of the NNI. He explained that the responsible development of nanotechnology is one of the four primary goals of NNI. This is emphasized in the *2011 NNI Environmental, Health, and Safety Research Strategy*, which describes the need for developing nanoEHS knowledge, data, and tools and for their widespread dissemination[2]. He further noted that several of the NNI's Nanotechnology Signature Initiatives (NSIs)[3] are focused on sustainability or nanoEHS, with the potential for establishing or further strengthening linkages to the CORs.

EU Opening Statement

Elke Anklam, Joint Research Centre Institute for Reference Materials and Measurements of the European Commission

Dr. Elke Anklam welcomed the workshop participants on behalf of the European Commission. She mentioned that nanotechnology and nanoEHS are important topics to the Commission, as evidenced by its activities supporting the implementation of the European Union (EU) chemical

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

[3] Please see www.nano.gov/signatureinitiatives for more information on the NNI Nanotechnology Signature Initiatives.

safety, cosmetics, food safety, etc. regulations for nanomaterials. Dr. Anklam shortly introduced Horizon 2020[4], the European Union's new research funding programme. Nanotechnology is one of the key emerging technologies identified in the EU 2020 Strategy[5]. Horizon 2020 funds nanoEHS research, which is key to ensuring the sustainability of the nanotechnology industry in the EU.

In order to facilitate nanoEHS research, it is important for scientists to communicate and collaborate effectively. Therefore, international cooperation is of key importance and should be encouraged to align research agendas in the EU and United States, enabling the nanoEHS field to progress more rapidly. This progress will promote responsible nanotechnology R&D, leading to increased innovation and economic growth.

Purpose and Goals of the 2015 Workshop

Georgios Katalagarianakis, Directorate General for Research and Innovation of the European Commission

Dr. Georgios Katalagarianakis introduced the purpose of the CORs: to establish communities of practice in which groups of people in the EU and United States who share common interests in the nanoEHS research area are in regular contact to develop shared knowledge and resources. This purpose has been achieved mainly through networking, which could be further broadened and strengthened to facilitate research cooperation. Research cooperation has been challenged so far by resource limitations, lack of awareness and common understanding of certain COR goals, and sometimes by insufficient or ineffective coordination of activities between the CORs.

The following steps are needed to make the CORs more effective and efficient: (1) focus the COR activities, adapting their objectives to the available resources; and (2) establish mechanisms of interactions among the CORs through realignment or regrouping of their activities.

Focusing the COR activities can be achieved through defining specific goals and/or drafting roadmaps. One example of an interaction mechanism among CORs is the nanoEHS Scrimmage activity performed as part of this workshop (c.f. Section 3), as it can facilitate the identification and setting of common goals. Some examples of COR realignment and regrouping are the introduction of the new COR on "Characterization" and shifting the scope of the COR on "Human Toxicity" to more experimental research (e.g., biological uptake and bioaccumulation, testing, systems biology approaches). The seven Communities of Research now address the following topics:

- Characterization
- Databases & Computational Modelling for NanoEHS
- Exposure through Product Life
- EcoToxicity
- Human Toxicity

[4] ec.europa.eu/programmes/horizon2020/

[5] European Commission. Europe 2020: A European strategy for smart, sustainable and inclusive growth. 2013.

- Risk Assessment
- Risk Management & Control

Cooperation could also be promoted through new COR activities. Dr. Katalagarianakis gave some useful suggestions for such initiatives. One option could be to draft a publication on harmonization of methods as a pre-standardization activity that would transparently present future needs. Moreover, he further suggested that the CORs could put forward ideas for potential adoption by research funding programs in the United States and EU or author focus paper(s) on the state of the art and the research gaps within the topics of the CORs.

Dr. Katalagarianakis suggested that the COR chairs rotate every two to four years, with a Steering Committee including representatives form industry, academia, and governments. Some future directions of the COR activities should target more networking between nanoEHS excellence centres in the EU and United States, as well as strengthening cooperation on the topic of "safer by design".

3. NanoEHS Scrimmage

Purpose and Goals

Prof. Mark Wiesner from Duke University introduced the purpose and goals of the Scrimmage activity, an interactive exercise designed to promote engagement and interaction across the CORs. The Scrimmage was essentially a simulated decision process with the following objectives:

- Explore how communication processes among the CORs function, and may sometimes fail, to address the information and actions needed to support the responsible development of nanotechnology.
- Incorporate input from multiple communities of experts across the nanoEHS field.
- Provide insight into how the U.S.–EU CORs should advance and set goals by shedding light on three key questions:
    - What are the critical disconnects between the CORs?
    - What information deficits are present that could be addressed by the CORs?
    - Are the CORs properly aligned for successful information sharing?
- Avoid the automatic response of "we can't give you a number yet" that would result in a general discussion of data gaps.

Prof. Wiesner also explained the methodology behind the scrimmage activity. In its hypothetical scenario, each participant would assume that (s)he is a citizen of a Country X, having the expertise and sector affiliations (s)he holds in real life. Elections are coming up shortly, and due to a strong public demand for action, immediate regulatory decisions are being required by the Country X leadership to impose strict limits on occupational, consumer, and environmental exposures to two specific engineered nanomaterials, i.e., nano-TiO_2 and CdSe-sensitized nano-TiO_2.

The recommended regulatory limits developed as part of this exercise were not intended to serve as actual policy recommendations; rather, the activity was intended to generate recommendations pertaining to the process of arriving at a collective answer in response to the simulated challenge.

The workshop participants were divided into ten teams: five teams focused on nano-TiO_2 (A Teams), and five teams focused on the CdSe-sensitized nano-TiO_2 (B Teams). The CORs represented these teams charged with developing the required recommendations, which would depend on academic, industrial, and regulatory information. The idea was that all members of the EU–U.S. CORs should work together to meet a unified goal.

Table 1: *"A" and "B" teams, with team leaders, in the nanoEHS Scrimmage.*

Nano-TiO_2		CdSe-Sensitized Nano-TiO_2	
Exposure A	Rick Canady	Exposure B	Martie van Tongeren
Human Health A	Robert Rallo	Human Health B	Yoram Cohen
Ecotoxicity A	Elijah Petersen	Ecotoxicity B	Henriette Selck
Risk Assessment A	Derk Brouwer	Risk Assessment B	Mark Wiesner
Risk Management A	Larry Gibbs	Risk Management B	Tom van Teunenbroek

Scrimmage Steps

The objective of each team was to collect as many points as possible by answering questions on a scorecard. The "A" teams competed among each other in collecting points, and so did the "B" teams. Each team had to answer the same set of questions in four categories: (1) Occupational workplace limit, (2) Consumer production concentration limit, (3) Environmental exposure limit for freshwater, and (4) Ambient air quality exposure limit.

Each of the 96 questions was worth one point, so the team answering the most questions would win. By nature of the scenario and design of the event, the questions spanned a broad array of disciplines and sectors with respect to the expertise required to address them. Successful completion of the exercise therefore depended on prioritizing the most important issues and consulting strategically with the groups who could best address the questions of interest.

Figure 1: *An example nanoEHS Scrimmage scorecard.*

NanoEHS Scrimmage Scorecard

Team: Exposure A **Material:** **TiO_2**

	Question	Answer	Resource
1	**What should be the occupational workplace limit?**		
2	**What are the recommended numerical bounds?**		
3	In what matrix/form is the ENM expected to be encountered during the fabrication process?		
4	What detection methods may be used to detect the presence of these materials in the workplace and/or the environment?		
5	What is the expected release rate of the ENMs from the product matrix?		
6	Who will be impacted by exposure to the selected nanomaterials (human populations)?		
7	What ecosystems will be impacted by exposure to the selected nanomaterials?		
8	What environmental processes/ ecosystem services may be impacted by exposure to the selected nanomaterials?		
9	What are the likely exposure vectors to the workplace environment? (dust from raw material handling or material transfer emitted to air, leakage during operations to liquid waste streams…)		
10	What are the likely exposure pathways in the body? (dermal, inhalation, ingestion..)		
11	What environmental compartments are likely to be the release points and the accumulation points for these materials? (air, water, soil…)		
12	What should be the regulatory mechanism to address these exposure limits?		
13	How will we identify the presence of these materials?		
14	What is the toxicity of these materials to model organisms?		
15	What are the known or hypothesized mechanisms of toxicity for these materials?		
16	What sublethal toxic endpoints are relevant for these materials?		
17	Is there potential for trophic or maternal transfer of these materials?		

The exercise began with teams working amongst themselves for ten minutes to rank the importance of the four protective limits for their assigned nanomaterial, and then to begin answering questions on the scorecards for any of the limits they chose to address. After this initial round, the CORs of the A and B groups of teams interacted in four consecutive rounds of "speed-consulting", rotating

every ten minutes so that each of the "A" teams interacted with each of the "B" teams. Each round of speed-consulting was divided into halves so the group could address the A teams' nano-TiO2 questions for the first five minutes and the B-teams' CdSe-sensitized nano-TiO2 questions for the second five minutes. In this way, each COR was able to interact with all other COR and draw on varying expertise to meet the challenge presented. Throughout the activity, every participant was exposed to the nuances of both the data-rich, application-agnostic nanomaterial and the data-poor, specified application nanomaterial. Finally, each COR had a closing round of ten minutes to finalize answers to the scorecard questions and revisit their prioritization of the four recommended protective limits.

Results of the nanoEHS Scrimmage

Because this scrimmage was a pilot event of a newly developed type of activity, the goal was to gain an understanding of what was useful and what could be improved and further developed for future iterations. See Table 2: NanoEHS Scrimmage Results for detailed responses from all contributing CORs.

Of the seven groups that ranked the four protective limits, 100% ranked occupational exposure limits as the most important. Next, the consumer production concentration limit and the environmental exposure limit for freshwater ranked about equally, and the ambient air quality exposure limit was most often ranked last. Five of the seven groups had at least one minor change to their rankings at the conclusion of the exercise, potentially due to considerations brought about from their interactions across CORs.

The Ecotoxicity "A" group, focused on nano-TiO_2, was the clear victor of the scrimmage with answers submitted for 92 of the 96 questions. The range of scores was quite interesting, with the smallest number of answered questions being 12 of 96. This suggests that different teams took very different approaches in prioritizing their use of discussion time. Some groups focused primarily on rich investigations of their top priority protective limit; some groups focused on leveraging answers for one limit wherever possible to inform other limits. As shown in the results table breakdown of recorded sources, several groups reported significant influence of other CORs in answering their questions. Other CORs indicated that outside sources, including benchmark regulatory limits, agency guidance documents, or published literature, were the bases of their answers to specific questions.

In the end, six quantitative recommendations were proposed for Occupational Exposure Limits, with multiple CORs proposing the same limit and two other CORs providing guidance without specifying the precise limit. One COR proposed a Consumer Product Limit, while another questioned the rationale for setting such a limit altogether. Three CORs proposed freshwater limits, with two others providing directional guidance. Three CORs proposed ambient air limits, with two utilizing the same recommendation as proposed for an occupational limit.

Figure 2: *Round-robin consultations.*

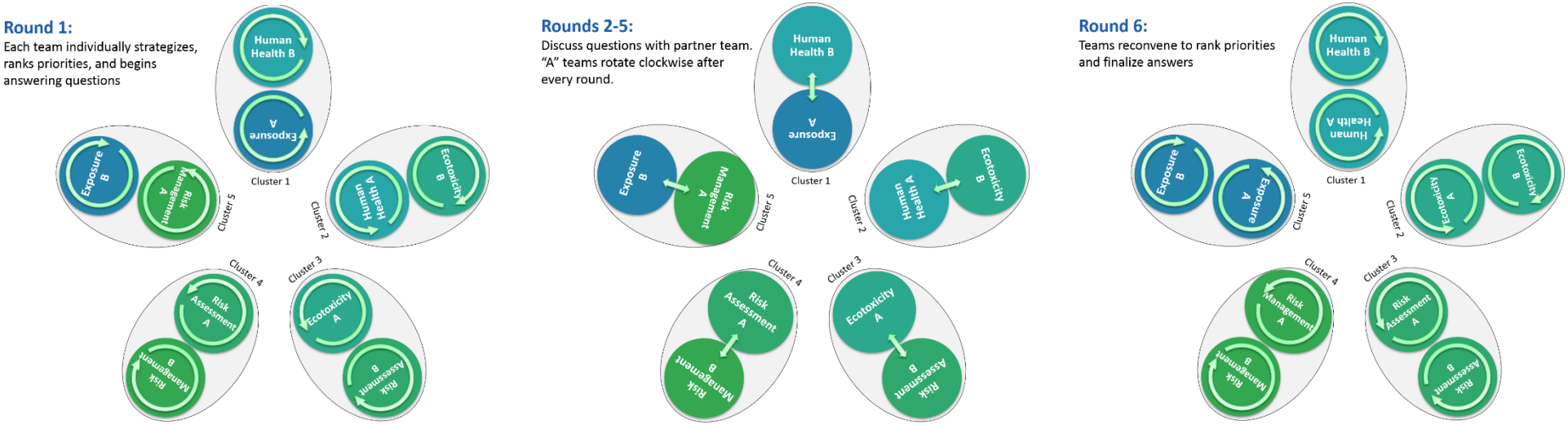

Table 2: *NanoEHS Scrimmage Results.*

TEAM		Product-Agnostic Nano-TiO_2					Quantum-dot Sensitized Nano-TiO_2 for Photovoltaics				
		Ecotoxicity A	Exposure A	Human Health A	Risk Assessment A	Risk Management A	Ecotoxicity B	Exposure B	Human Health B	Risk Assessment B	Risk Management B
Score		92 / 96	65 / 96	No scorecard provided	12 / 96	40 / 96	26 / 96	41 / 96	72 / 96	43 / 96	24 / 96
Questions with Recorded Sources	"Self"	-	41		5	1	-	-	None recorded, notes taken	None recorded, notes taken	6
	COR Consultations	-	55		7	-	2	-			14
	Specified Sources	42			1	11	4	2			4

Discussion of the Results and Recommendations

The inaugural nanoEHS scrimmage activity successfully orchestrated interactions among CORs in tackling a common challenge to synthesize environment, health, and safety data to provide protective guidance based on the best available knowledge on specified engineered nanomaterials.

A variety of American and European regulatory bodies and risk projects were cited as sources that guided answers to specific questions, and the teams worked together to agree on preliminary proposed limits (which again were solely proposed as part of this demonstrative exercise and not as actual regulatory recommendations).

This event was the first of its kind and created many opportunities for focused engagement between experts in pursuit of a common goal. Feedback from participants was largely positive in this regard but also included constructive comments on how the event could be more clearly structured and prepared. Future activities will incorporate this feedback and could take a variety of forms. One exercise could further dissect these responses and their initial sources to highlight very specific data gaps that would advance the discussions to support risk-based decisions like the hypothetical one presented in this scrimmage. From the priority areas identified here based on COR input, a more detailed scrimmage activity could be designed that includes preparatory information gathering and more concrete background information so that a follow-up scrimmage would be less hypothetical. Existing risk assessment tools might be used to organize and facilitate the sharing of these data among COR in a future live interactive event, or in an online format for increased participation. In the upcoming year, the Risk Assessment COR will take as its guiding agenda the task of designing follow-up interactions and tools in support of future activities inspired by this NanoEHS Scrimmage event.

4. COR Breakout Sessions and Plenary Reports

Each of the seven 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 Databases and Computational Modelling, Human Toxicity, EcoToxicity, and Risk Management and Control COR breakout sessions took place in the first half of the afternoon, before the Exposure, Risk Assessment, and Characterization sessions in order to give participants the opportunity to participate in multiple sessions. The COR co-chairs served as chairs in their respective breakout sessions and presented the discussion results in the subsequent plenary session reports.

EcoToxicity COR

U.S. co-chair: **Elijah Petersen**, National Institute of Standards and Technology

EU co-chair: **Henriette Selck**, Roskilde University

The EU COR co-chair introduced the U.S. co-chair and highlighted the proposed session structure. An introductory presentation described the scope of the COR, the work done by the COR to date, and future aims. This was followed by three stimulus presentations, which focused on nanomaterials in an agricultural context, aspects of environmental risk assessment and realism, and thoughts on grouping and categorization of nanomaterials. A vigorous discussion followed on the required level of characterization for different environmental matrices (water, soil, sediment). Characterization in complex media and in studies that use low concentrations is often difficult, and so scientists must be realistic and not expect full comprehensive characterization of engineered nanomaterials (ENMs) in such studies. There is also a strong interest in detailed characterization and in publishing all relevant data to facilitate modelling. Additional discussions focused on the need to work very closely with collaborators who specialize in characterization and to make sure they are involved in the experimental design at an early stage. A very important point mentioned was the absolute need to report experimental details (e.g., medium recipe; mixing method/time; pH, temperature; dispersant, if any; feeding/non-feeding; etc.) as much and as widely as possible to allow revisiting data once we have a better understanding of fate (including transformation) in the environment.

An EcoToxicity COR focus article drafted by the COR Steering Committee is nearly complete and highlights the work done to date by the COR, including summarizing breakout session discussions from previous EU–U.S. meetings, as well as gaps and potential ways forward. At this breakout session there was a strong interest expressed in writing a peer-reviewed perspective manuscript on the level of characterization needed for nanoecotox studies in different matrices. In addition, several other ideas for potential research were also discussed.

Human Toxicity COR

EU co-chair: **Robert Rallo**, Universitat Rovira i Virgili

U.S. co-chair: **Yoram Cohen**, University of California, Los Angeles

The session started with a briefing from both co-chairs with the purpose of introducing the organization of the breakout session and the two invited speakers. Before the presentations, the original COR scope was briefly discussed, together with the implications of the changes resulting

from the COR realignment. It was mentioned that the aim of the COR will now shift towards more general issues related to possible human toxicity implications of nanomaterials.

The introduction was followed by two invited presentations. The first talk was by Dr. Tina Bahadori (U.S. Environmental Protection Agency - EPA) who discussed the EPA's present R&D efforts for assessing human exposure to and evaluating the toxicity of nanomaterials. Dr. Bahadori highlighted that, to date, most of the assessments have been carried out on pristine nanomaterials. She stressed that evaluations should now focus on more realistic scenarios involving "aged" nanomaterials and their degradation by-products. There is a need for well-established assessment protocols in these new scenarios. Moreover, it is important to conduct the toxicity evaluation in the proper context by taking into account a variety of factors, such as the interaction of nanomaterials with other materials already present in the environment and the use of life cycle analysis to identify where relevant exposures are likely to occur. The second presentation was by Dr. Dario Greco (Finnish Institute of Occupational Health) who provided his vision regarding the current challenges in systems nanotoxicology. Dr. Greco emphasized the need to differentiate between "omics" and systems biology. Systems biology deals with interactions, and in this context data integration is a key element. The integration of different types of data (e.g., structural, physicochemical, and bioactivity) tends to improve a model's overall performance. He noted that fuzzy methods can be used to integrate heterogeneous data; however, additional challenges remain such as the selection of best model features (or descriptors) and the development of a robust computational framework for systems nanotoxicology.

The discussion that followed both presentations served to identify a number of key issues relevant for the COR objectives. The key questions and issues that emerged from the discussion are summarized below:

- Data relevance to toxicity modelling
    - What are the limitations of currently available (public) data for modelling endpoints/metrics that are relevant to human health?
    - Do we generate a sufficient number of replicas to ensure statistical consistency?
    - What are the limitations of toxicity data?
    - What are the suitable approaches to evaluate/quantify variability of biological systems and diversity of technical approaches/models?
- Modelling nanomaterial toxicity
    - Data-driven models should be developed based on the integration of available data (i.e., body of evidence).
    - Modelling targets should include quantitative (e.g., EC50) as well as qualitative (e.g., ranking of severity of impact, toxicity classes) endpoints.
    - There is a need for systems biology models that focus on interactions due to exposure to single and multiple types of ENMs. The key question is whether computational systems biology is at a sufficient stage of development to provide useful models for predictive toxicology.
    - There is a need to develop understanding of modes of action (toxicity mechanisms) to increase models' performance.
    - Feature (descriptor) selection is critical for model development.
- Relevance of exposure to toxicity outcomes
    - Most toxicity evaluations are focused on pristine materials. There is a need to evaluate the relevance of mixtures (e.g., ENMs and chemicals), as well as to develop standardized protocols for quantifying aging and degradation of ENMs.

- There is a need for a clear and acceptable methodology for ascertaining the relevance of the material that is being evaluated (e.g., in its actual application) relative to the pristine material.
- It is critical to evaluate toxicity at the expected critical routes and exposure levels throughout the life cycle of ENMs (i.e., integrating life cycle analysis with exposure assessment).

In addition to the above, there is a need to have modellers participate in the process of experiment planning and data generation. It is important to involve modellers at an early stage of the experimental design to ensure that the generated data will be useful for validation of mechanistic models and for development and validation of data-driven models. It was also pointed out that there is a need to revisit the current Organisation for Economic Co-operation and Development (OECD) guidelines for quantitative structure-activity relationship development to deal with the special characteristics of nanomaterials and the available nanosafety data (e.g., limited size of nanoparticle datasets).

Databases and Computational Modelling for nanoEHS COR

U.S. co-chair: **Nathan Hodas**, Pacific Northwest National Laboratory

EU co-chair: **Barry Hardy**, eNanoMapper

There were a wide variety of views expressed in the data and modelling COR discussion. Many participants commented on the need for open data and protocols to be made available to the community in a transparent and useful manner. Open data would also improve data quality due to the increased scrutiny and discussion "enabled by the crowd" through improved access to and evaluation of the data by the scientific community. It was acknowledged that commercial concerns, such as those related to patenting and exploitation, also need consideration.

Many resources have been developed in recent years in both the United States (e.g., caNanoLab at the U.S. National Cancer Institute) and Europe (e.g., OpenTox), but an interoperability effort is required to bring resources together to add value to both the scientific field and for practical applications such as risk assessment. Concrete use cases and application implementations supporting goals shared by the different CORs is a high priority action to be pursued. In this respect the scrimmage organized at the meeting was an inspiration in providing guidance to an application that could be developed to support the complex discussions and decision making required in evaluating the safety of nanomaterials and in making related regulatory decisions. The Data and Modelling COR set a goal to specify and develop such a knowledge application, which could be prototyped and used at next year's EU–U.S. COR workshop.

It would be useful to organize data resources that are less fragmented and, along with the scientific review and publication process, contribute to a sustainable data infrastructure. Guidance on interoperability and related implementation would make more data available in a useful way. It is also important to have a clear, common meaning on context and metadata as promised by a shared ontology; although funding in this area has been insufficient to achieve knowledge safety infrastructure goals. Current running projects such as eNanoMapper and ProSafe could help accelerate progress in related open standards, ontology, and interoperability.

Increased availability of reference information on well characterized systems would provide a critical body of knowledge for the study of complex interactions and data mining for relationships,

making it an enabler. Some differences of opinions were expressed on whether predictive models could be built if sufficient physicochemical information were available. There is a need to include more exposure data and modelling in the infrastructure and applications for risk assessment and safer-by-design purposes.

Opportunities to relate methods and results to carefully characterized systems and protocols is an important goal and could be supported by interactions between the Data and Modelling COR and the new Characterization COR. Could differences be traced, for example, between zeta potentials and particular components of a protocol? Could the relevance of a particular characterization for the risk assessment or management context be determined?

The Data and Modelling COR will be most successful and have the greatest impact if different existing parties are willing to collaborate and link their existing resources together to support complex discussions and decision making. That solution will not be one larger database, but a database that could bring heterogeneous knowledge representations into the context of conversations and support. Such a database would also capture annotations and arguments around data and models leading to the answering of questions (as trialed at the scrimmage) and to a decision. A goal for the COR in coming months will therefore be to decide, in collaboration with the other CORs, on the details of use cases to be supported, which could then guide a prototype implementation effort. A sustainability strategy will also be developed in parallel.

There was much enthusiasm in the group for an action-oriented approach and implementation, providing an optimistic start to this next phase of COR activities.

Exposure through Product Life COR

EU co-chair: **Martie van Tongeren**, Institute of Occupational Medicine, Scotland

U.S. co-chair: **Richard Canady**, International Life Sciences Institute

The Exposure through Product Life COR discussed a series of questions focusing on the exposure part of the scrimmage exercise as a way to stimulate consideration of what defines COR expertise areas. The discussion also helped identify the types of expertise that should be solicited. The scrimmage seemed to assume the nanoform was persistent (e.g., from released entity to a water quality criteria value for the same entity) rather than looking at occurrences as a cycle of components or performing a fate analyses to predict what might occur for subsets of heterogeneous released particles. One immediate conclusion from the scrimmage was that the characterization of exposure is obviously important, but it is also very difficult and expensive. Therefore exposure characterization has to be weighed with the decision needs. Since determining dose is difficult and costly, hazard will tend to rule in decisions. Characterization is also difficult because exposure needs to be determined for different scenarios along the life cycle, which adds variability to the release processes and transformation pathways that need to be understood and measured, further complicating the process. Nevertheless, exposure may be easier to manage by preventing it, even if it is difficult to measure exposure precisely. Using a worst-case assumption of the most hazardous agents to determine exposure mitigation objectives or research needs may be justified if you don't know anything about the agent. Tiered toxicity approaches and "threshold of regulation" approaches could be applied.

A concept or analysis approach is needed to determine when something is no longer a nanoparticle or a nanoparticle of concern. Transformation analysis provides context for the evolution of

nanoparticles to "safe ends" or when something persists or is enriched as a "not safe" entity. Fate is critical to understanding how to do "safer by design", particularly when a nanoscale component enables the application. Research into designing "kill switches", similar to those for pharmacology biotech where the genomes are constructed so that the microbes cannot survive in the wild, could be done. However, modifying nanomaterials to add "kill switches" or to reduce toxicity may change desired properties and hence usefulness. So reducing exposure may be a more realistic approach. In addition, designing pathway analysis approaches like "Hazard Analysis and Critical Control Point" (HACCP) plans for food safety could be another strategy.

Several topics were addressed during the discussion but need further consideration: relevant metrics (e.g., mass vs. surface area) for exposure assessments; the techniques that could help to differentiate between (natural) background and engineered nanomaterials; and the nature of "anthropogenic" vs. "non-anthropogenic" nanomaterials. The key points from these discussions included (1) consideration of the combination of elements occurring together in a nanomaterial and the increase of such elements in certain media may give some indication of environmental release; (2) isotope analyses may be useful; (3) standard metals geochemistry and fate from releases may be an area of research that informs nanoscale metals/oxides evaluation.

In regards to the organization of the COR, the group concluded that continuity is lacking and therefore they explored ways to build activity and participation. The ideas fell into ways to organize and run the COR, ways to promote the COR, and ways to provide incentive to participate. This discussion resulted in the following suggestions:

- Establish a "core" group of four to eight people, consisting of occupational, consumer, and environment, and food (release and exposure) experts. The "core" would meet (via conference call) more often than the full COR to plan specific activities.
- Revisit and establish a comprehensive e-mail circulation list, branching out from the expertise areas of the "core" group.
- The COR should have a teleconference or webinar every quarter initiated perhaps by a brief seminar highlighting a nano-exposure topic of importance in both Europe and the United States.
- Development of a work plan (by the "core" group, with input from the full COR) with a list of deliverables. The work plan could include ideas such as:
    - White paper or description of:
        - What differentiates a COR for nanomaterial exposure from a COR for exposure to chemicals or to macro particles?
        - Evaluation of tools and methodologies (models, release experiments already being done).
        - Identify actual synergies between projects in the area of exposure assessment.
    - Database of analytical and modelling methods for exposure assessment.
    - Data sharing, either of measurement data or libraries of exposure scenarios with estimates of exposure.
- Plan a nano exposure conference. In addition, The COR co-chairs were invited to participate in the Quantifying Exposure to Engineered Nanomaterials from Manufactured

Products (QEEN) Workshop to be held July 7-8, 2015, near Washington, DC[6]. The purpose was to provide information on the COR activities and to attract new participants.

- Include the International Society of Exposure Science, the Society of Environmental Toxicology and Chemistry, or other exposure-oriented societies in the COR planning, and potentially establish a NanoExposure specialty group at those or other scientific societies.
- Develop symposia at scientific society meetings and other workshops (such as the July 2015 QEEN workshop).
- Invite senior researchers to provide the webinar at each quarterly COR call.
- Develop and maintain a list of funding opportunities (make a calendar that the funding agencies can add to).
- Provide opportunities to write joint papers.
- Provide a meeting place for collaborations.
- Provide a forum to learn about activities and training.
- Create an international U.S.–EU exchange program on exposure.

Risk Assessment COR

U.S. co-chair: **Mark Wiesner**, Duke University

EU co-chair: **Janeck Scott-Fordsmand**, Aarhus University

In the Risk Assessment COR breakout session the following agenda was discussed:

- Follow up on NanoEHS Scrimmage from the plenary session.
- Discuss U.S. and EU progress on risk assessment (identify common targets in the progress).
- Define concrete and workable Risk Assessment COR goals for 2015 (e.g., databases).
- Outline practical issues (e.g., meeting frequency, etc.).

The agenda points were discussed with emphasis on (1) summarizing the activities for the last year, (2) evaluating the usefulness of the scrimmage game approach for further meeting, and (3) setting concrete goals for the coming year.

The last year has been an active year for the Risk Assessment COR with frequent phone meeting where the U.S. and EU partners have presented their progress in the risk area and had general discussion on risk assessment issues. The main focus has been to keep an open communication to exchange knowledge and ideas, and this focus has functioned well. It was decided to continue the open non-formal communication, besides defining the concrete goals, in the coming year.

The scrimmage activity worked well, despite the fact that it took a bit of time for the participants to get used to the approach.

For the coming year the concrete goals are:

- Progress with State of Art on Risk Assessment review (to be finished before summer).

[6] www.nano.gov/qeenworkshop

- Based on Risk Assessment approaches, identify data types from other areas (hazard, exposure, etc.).
- Identify risk scenarios where the driver is exposure and where the driver is hazard (to be finished by end of year).
- Build on simple case studies.
- Continue the scrimmage game approach to promote collaboration.

The Risk Assessment COR will progress through bimonthly meetings on fixed dates.

Risk Management and Control COR

EU co-chair: **Tom van Teunenbroek**, Dutch Ministry of Infrastructure and the Environment

U.S. co-chair: **Lawrence Gibbs**, Stanford University

The Risk Management and Control COR breakout session was attended by the two co-chairs and eight additional participants. After self-introductions around the table, the co-chair Lawrence Gibbs introduced Ms. Camilla Pease, Senior Manager with ENVIRON UK, Ltd., who provided a presentation on the existing requirements of the United States and the EU that involve regulation of nanomaterials. The presentation was well received and highlighted that there is a current scattering of regulation in both Europe and the United States, but that there is no clear approach to regulation of nanomaterials. Significant discussion followed about the challenges of developing a risk management approach that would be able to cover the many and diverse uses and applications for nanomaterials throughout the life cycle. Treye Thomas indicated that the Consumer Protection Safety Commission has great interest in better understanding the risks of nanomaterials in consumer products and that exposure assessment plays an important role in understanding the potential health risks of materials incorporated into manufactured products.

The discussion then moved on to reviewing what possible COR activities might be appropriate for the group to work on over the next three to six months. Considerable discussion ensued about how to focus the conversation on risk management processes as opposed to risk and exposure assessment, which is the focus of other CORs. There was a comment that significant resources have been poured into nanotoxicology and other nanoEHS research, with little substantive information that has evolved for use in developing reasonable science-based risk management programs through the material life cycle. Another comment was proffered that there is inclination by some within the EU to move forward with an approach to the regulation of nanomaterials based on the tenets of the ProSafe process and procedures.

There was no general agreement on specific activities for the Risk Management COR. The direction of cooperation could be towards identifying approaches and procedures that could be applied to nanomaterial risk management in the variety of environments where exposure to different populations and biosystems could occur. Identification of possible activities for the Risk Management COR will be further explored after the workshop.

Characterization COR

U.S. co-chair: **Anil Patri**, U.S. Food and Drug Administration

EU co-chair: **Kenneth Dawson**, University College Dublin

The Characterization COR breakout session was attended by the two co-chairs and about ten additional participants. The discussion focused on the need to support nanoEHS science through developing standard characterization protocols focusing on properties relevant to biological impacts that are reproducible across laboratories. In addressing this need, it is of high importance to avoid any duplication of efforts with the ongoing activities in the OECD Sponsorship Programme and other initiatives such as the EU Flagship Programme and NANoREG. As a result of these activities, important issues such as reproducibility, manufacturability, and batch-to-batch variability are now becoming possible to study (and potentially resolve) meaningfully. There is a need for reference ENMs, which has been addressed by the U.S. National Institute of Standards and Technology through the development of 10, 30, 60 nm colloidal gold, silver, and silica reference ENMs.

Characterization of ENMs in complex environmental and/or biological matrices is complicated because the results are largely dependent on the nature of dispersion media and other "exposure" conditions, such as pH or ionic strength. It is still a major challenge to distinguish ENMs from background materials of similar chemical composition that are generally ubiquitous in the environment. This challenge always requires the use of a combination of analytical tools, which is often unpractical and/or expensive. In order to optimize this burden of proof, it is important to find the suitable balance between "absolute" characterization and "appropriate" characterization that is sufficient from regulatory point of view.

As an additional resource, scientists who investigate potential nanoEHS risks should be connected to scientists who develop ENMs as delivery vehicles for drugs. Their assistance would help in the design of interlaboratory studies and in assigning precision and bias to measurements.

In order to achieve the above, important steps should be taken, which could involve (1) exchanging faculty and students to promote skills; (2) conducting interlaboratory studies to support the development of guidance and standards; and (3) conducting a review between EU and U.S. scientists.

The Characterization COR breakout discussion raised the following important questions:

- Which properties/aspects of nanomaterials characterization are key in defining their biological impacts from a data reproducibility standpoint?
- How can those properties be identified and measured qualitatively and quantitatively by current techniques?
- Which aspects of the total systems (ENM properties, exposure conditions, environment etc.) must be fixed or controlled to render the system reproducible and fully characterized from biology/nanomedicine point of view?
- If new methods are required to accomplish these tasks, what are the technical challenges, and how should they be developed into robust reproducible assays?
- What standards are needed to facilitate regulatory review and commercialization?

The COR will continue to look for answers to these questions in the coming years of EU–U.S. nanoEHS cooperation.

5. Research Strategies

Quality Assurance for the Characterization of Nanomaterials and Implementation of Labelling Requirements for Food and Consumer Products

Elke Anklam, Joint Research Centre Institute for Reference Materials and Measurements of the European Commission

Dr. Elke Anklam described how measurements are important to regulation and policy making because millions of measurements are performed every year and key decisions are taken on this basis. In this context, standardization is very important as it can increase the compatibility, interoperability, repeatability, and quality of these measurements, which is of benefit to:

- *Industry*: through enhanced competiveness and innovation.
- *Producers and authorities*: through facilitated implementation of legislation.
- *Trade*: through facilitated movement of goods.
- *Environment*: through more sustainable processes.
- *Consumers*: through safer and higher quality products.

The harmonization and standardization of measurement protocols is an essential prerequisite for consumers' acceptance of nanotechnologies as they can enable the following:

- Labelling requirements based on the definition of "nanomaterials."
- Risk assessment of nanomaterials, which requires comparable data.
- Control of final products on the market (analytical methods, sampling, etc.).
- Quality assurance tools (reference methods and materials, proficiency testing).

Dr. Anklam introduced the labelling requirements based on the definition of "nanomaterials." In 2011 the European Commission adopted a recommendation on such a definition:

> "*A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm…"*

Under the Food Information to Consumers 1169/2011 regulation, all food ingredients present in the form of engineered nanomaterials shall be clearly indicated in the list of ingredients followed by the word "nano" in brackets. Similarly, under the EU Cosmetics Regulation 1223/2009, all ingredients present as nanomaterials have to be indicated on the package with the term "nano" in brackets.

In order to properly comply with these regulatory requirements, industries need appropriate analytical and quality assurance tools that are able to measure the physicochemical properties of ENMs in different media. Therefore, the development of standard sample preparation and characterization protocols for ENM dispersions that are reproducible across laboratories is currently a major area of research.

In this context several international standardization efforts are underway. For instance, Comité Européen de Normalisation (CEN) is working on the standardization of "nano" nomenclature and developing standard protocols for measuring ENMs in complex matrices. The International Organisation for Standardisation (ISO) Technical Committee 229 has focused on harmonization of nano terminology and developing standards for physicochemical characterization of specific nanomaterials (e.g., quantum dots, carbon nanotubes), as well as basic particle sizing instrument standards, protocols for dispersion stability and characterization, and reference materials.

Moreover, EU projects have developed standards for detecting nanomaterials in complex matrices. For instance, the Nanolyse project developed sample preparation and characterization protocols specifically for ENMs in food.

In order to facilitate the safety assessment of ENMs there is need for (1) quality assurance tools such as Certified Reference Materials; (2) fit-for-purpose validated analytical methods; (3) proficiency tests; (4) documentary standards and guidance on measurements; (5) increased collaboration of measurement communities; and (6) scientific advice to policy makers.

The European Commission's Joint Research Centre (JRC) is working towards addressing these needs. In doing this, JRC staff have developed methods for detection, quantification, and analysis of nanomaterials in consumer products, validated fit-for-the-purpose analytical procedures, and standardized protocols for toxicity testing of ENMs, as well as testing strategies and risk assessment methodologies. JRC hosts the NANOhub database (www.napira.eu/) and a repository of representative nanomaterials that are used in a variety of research projects for testing.

Dr. Anklam concluded that quality assurance and cooperation are important to ensure reliable data and, therefore, to reduce costs from duplication of measurements and increase confidence in risk assessment results. This increase results in consumer confidence and could facilitate trade.

U.S. Progress Review on the Coordinated Implementation of the NNI 2011 EHS Research Strategy

Treye Thomas, U.S. Consumer Product Safety Commission

Dr. Treye Thomas introduced the U.S. National Nanotechnology Initiative, which was launched in 2000 to promote and coordinate nanotechnology R&D in the United States. He described how 20 Federal departments, independent agencies, and independent commissions collaborate, leverage resources, and share data. The four goals of the NNI are to (1) advance a world-class nanotechnology R&D program; (2) foster the transfer of new technologies into products for commercial and public benefit; (3) develop and sustain educational resources, a skilled workforce, and a dynamic infrastructure and toolset to advance nanotechnology; and (4) support the responsible development of nanotechnology.

The Nanotechnology Environmental and Health Implications (NEHI) Working Group addresses nanoEHS issues, which mainly relate to the fourth goal of the NNI to support the responsible development of nanotechnology. NEHI produced the *2011 NNI Environmental, Health, and Safety*

Research Strategy[7]. 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, incorporating risk assessment, risk management, and life cycle analysis to inform specific research principles. The life cycle perspective is a new and distinguishing aspect of the 2011 strategy as compared to the 2008 edition. It is inspired by the need to account for the various transformations that ENMs can undergo in different life cycle stages, which further complicates the analysis of their fate and transport in the environment and their effects in living organisms. There are six core research areas supporting the strategy: (1) Nanomaterial Measurement Infrastructure; (2) Human Exposure Assessment; (3) Human Health; (4) Environment; (5) Risk Assessment and Risk Management Methods; and (6) Informatics and Modelling.

Dr. Thomas introduced the *2014 NNI EHS Progress Review*[8]. It was developed jointly by the NEHI participating agencies and follows the structure of the *2011 NNI EHS Research Strategy*. The review contains annotated examples of nanoEHS research activities undertaken by the NEHI agencies, including intramural and extramural research from 2009 to 2012. It is neither a technical review of the current state of progress in nanoEHS research, nor a comprehensive review of all nanoEHS research supported by the U.S. Federal Government, but it demonstrates coherence in the coordination and collaboration among the NEHI agencies.

The review shows that the NEHI agencies and grantees generated over 400 nanoEHS publications from 2009 to 2012. It also demonstrates that the 2011 strategy has effectively facilitated collaboration among U.S. Federal agencies through agreements and collaborations with multistakeholder groups to assess the state of the science in key areas. Moreover, the NNI has supported:

- International and voluntary standards development (e.g., consensus standards with ISO and ASTM International, 15 published standards on ENM physicochemical characterization, and other standards on ENM biological tests).
- University-based nanoEHS research centres. The National Science Foundation (NSF) and EPA established two centres for the environmental implications of nanotechnology: CEINT, led by Duke University, and UC CEIN, led by University of California Los Angeles.

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[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] Nanoscale Science, Engineering, and Technology Subcommittee of the Committee on Technology, *Progress Review on the Coordinated Implementation of the National Nanotechnology Initiative 2011 Environmental, Health, and Safety Research Strategy* (National Science and Technology Council, Washington, District of Columbia, 2014; www.nano.gov/2014EHSProgressReview).

- Federally funded nanoEHS databases and information platforms including the Nanomaterial Registry, nanoHUB.org, and the cancer Nanotechnology Laboratory (caNanoLab) portal. The NNI also has a Nanotechnology Signature Initiative on the Nanotechnology Knowledge Infrastructure, which has a strong emphasis on informatics to advance nanoEHS research.

The progress review has led to important benefits. It enhanced communication of research activities among the NEHI Working Group's member agencies. Moreover, it helped to identify synergistic ongoing and planned activities as well as potential research gaps that can lead to new interagency collaborations and leveraging of existing agency resources. The review has also provided informed guidance to the NEHI participating agencies in the formulation of their own intramural and extramural research portfolios and allocation of their resources, in the context of their agency-specific missions. It facilitated integrated development of potential new interagency initiatives or thrust areas that can provide opportunities for enhancing and optimizing investments. The review also contributed significantly to stakeholder involvement in terms of facilitating communication with myriad stakeholders about research accomplishments and priorities and about implementation and coordination of the *2011 NNI EHS Research Strategy*. Finally, it helped identify opportunities for stakeholders to participate in or leverage ongoing or planned research of the NEHI agencies.

Research Needs and Data Gaps

Tina Bahadori, U.S. Environmental Protection Agency

Dr. Tina Bahadori introduced chemicals, including emerging (nano)materials, as a lynchpin of innovation in today's economy. Sustainable innovation requires designing, producing, and using chemicals in safer ways. Information and methods are needed to make better-informed, more-timely decisions about chemicals, many of which have not been thoroughly evaluated for potential risks to human health and the environment. Scientific understanding is required to anticipate potential for adverse impacts on human health or wildlife populations based on knowledge from data-rich chemicals.

Nevertheless, the rate that new engineered nanomaterials are being developed makes it impossible to evaluate them on a case-by-case basis, and traditional testing approaches may be inappropriate for ENMs. It is essential to understand how the physicochemical properties of nanomaterials influence their behaviour in complex environments and to identify intermediate properties of nanomaterials that can predict exposure and/or hazard. In order to achieve this understanding, it is important to develop methods to (1) estimate the release of ENMs from consumer products along the product life cycle, (2) characterize them in complex media, and (3) assess their fate, transport, and transformation in environmental media. Such alternative testing strategies may be used to identify adverse outcome pathways, including the potential for impacts to human health and the environment.

Dr. Bahadori emphasized that there are still significant research needs and data gaps with respect to conventional chemicals, so the above issues are not unique to ENMs. Only a tiny fraction of the compounds around us have been tested for safety. There are roughly 50,000 to 80,000 chemicals used by U.S. consumers and industry, while only 300 have been comprehensively tested. In this context Dr. Bahadori asked the logical question: What is so different about nanomaterials? Then she listed some of the EPA nanoEHS research priorities: (1) develop a core library of

nanomaterials; (2) build analytical capabilities; (3) develop nanoEHS databases and decision support tools; (4) study the fate, transport, and transformation of ENMs across their life cycles; and (5) study their effects on the human health and on the ecosystems.

Dr. Bahadori stressed the need for nanoEHS analysis throughout the life cycle of nanotechnology-enabled products that can account for their physicochemical transformations in different environments. Such analyses should seek to identify and measure key physicochemical properties of ENMs released from the products in the environment, where they age under realistic conditions. This approach would involve identification of ENM release hot spots, critical for formulation of potential exposure scenarios. Moreover, the transport (from manufacture or product use scenarios) and the transformations of the ENMs in the (complex) environment or at the nano–bio interface should be accounted for in order to estimate realistic exposure. This knowledge can be used not only for risk analysis, but also to develop safer-by-design ENMs.

In this context, Dr. Bahadori introduced *Design and Evaluation of Safer New Chemicals: A Framework to Inform Government and Industry Decisions*. It is a project sponsored by EPA, where an ad hoc committee developed a decision framework for evaluating potentially safer substitute chemicals as determined by human health and ecological risks. The committee has identified the scientific information and tools required by regulatory agencies and industry to improve and increase consideration of potential health and environmental impacts early in the chemical design process. The decision framework shall be capable of integrating multiple and diverse data streams to support early consideration of potential health and environmental impacts as a part of fit-for-purpose decision making.

Regulatory Research Roadmap

Tom van Teunenbroek, Dutch Ministry of Infrastructure and the Environment

Dr. Tom van Teunenbroek introduced the European NanoSafety Cluster *Regulatory Research Roadmap*. He explained that the use of a diverse array of ENMs in a wide array of consumer, industrial, and medical applications has led to an increased interest in improving our understanding of issues pertaining to their safe use. The European Commission funded many projects in the 6th and 7th Framework Programmes (FP6 and FP7, over 170 million euro), which initially set out to identify whether there were significant safety issues relating to nanomaterials and then, based upon this evidence, moved on to identify whether nanomaterials are adequately regulated in Europe (through NANoREG). These activities will be further enhanced in Horizon 2020 with the funding of NANoREG II and other new projects (e.g., funded via the NMP-30-2015 call: Next generation tools for risk governance of nanomaterials).

While some changes are already in place or being considered, there remain significant gaps in knowledge and procedures that need to be addressed in order to generate appropriate and proportionate regulation for nanomaterials that is informed by a sound evidence base. The *Regulatory Research Roadmap* aims to identify the major areas that need to be considered, pointing out relevant activities that have or are being conducted in relation to each and highlighting those for which more work is needed. This work is distributed among academic research, standardization/validation, and integration of evidence with social and political considerations in order to generate acceptable and trustworthy regulation. The major areas or knowledge gaps to be addressed are presented as hexagons in a diagram that provides an indication of how they might be prioritized over time in order to achieve this final goal. However, the diagram is flexible and

can be updated as knowledge is acquired and the questions are adjusted. For each major area to be addressed a short narrative has been generated to further explain the relevance of the major area and to reference relevant activities that contribute to this major area.

In putting together this report, the NanoSafety Cluster participants have drawn upon the knowledge of cluster members and the following key activities:

- NANoREG gap analysis and NANoREG's set of questions relevant for regulators.
- ITS-NANO hexagon diagrams and text.
- MARINA tiered approach for risk assessment.
- Nanonext.nl – Dutch nanotechnology development programme (€250 million 2012-2016) project.
- SANOWORK, SUN, and GUIDEnano safer-by-design strategies.
- Registration, Evaluation, Authorization, and restriction of CHemical substances (REACH) regulation input through the European Chemical Agency.

The research priorities are set out using hexagons according to the style established by the ITS-NANO project. The hexagon diagram design has been chosen, since a strictly consecutive approach is considered inappropriate. Instead the hexagon diagrams show that for each issue (hexagon) there is more than one way to progress. The strategy sets a priority for each area corresponding to a hexagon. It is proposed that the topics deemed of highest priority should be addressed (or begin to be addressed) in the short term, while lower priority areas should be addressed in the longer term based on when information is needed. This does not mean that the lower priority areas are less important, rather that they will be easier to address in the longer term when more relevant information becomes available. Some work on the longer term goals needs to start now in order to frame the short-term work required.

It is worth noting that not all of the major areas are academic research, but that this overall plan will also require input from standardization and validation experts as well as risk assessors, policy makers, and other interested stakeholders (e.g., industry and consumers).

EU Closer to the Market Roadmap

Kai Savolainen, Finnish Institute of Occupational Health

Prof. Kai Savolainen started with the statement that the safety of a technology is a market itself. The level of safety achieved from any nanotechnology application varies with space and time and is related to the benefits the new technology offers. However, the development of new rules/practices should be based on solid scientific knowledge. New knowledge can be derived by exploratory (basic) research, but there is also the need for research to generate the knowledge supporting the development of regulations and provide the (hazard and exposure) tools to facilitate the assessment of human and environmental risks, as well as to develop safer-by-design processes and products of nanotechnology. Prof. Savolainen gave NANoREG as a pronounced example of a project generating such "regulatory" knowledge and also provided reference to the *Regulatory Research Roadmap* (c.f. previous section).

Prof. Savolainen described the scope of the *Closer to the Market* roadmap: it addresses important nanotechnology translational aspects, such as the provision of the technology, skills, and processes necessary to achieve science-based practices for ensuring safety in both industrial and commercial

activities, as well as the minimum requirements for developing essential skills in employees. He stressed that building capacity through creation of jobs is key in a number of domains, including risk monitoring, risk control, risk prevention, risk mitigation, standardization, education, training, and certification. The challenge of building such capacity is now being addressed by a number of NanoSafety Research Centres such as the Finnish NanoSafety Research Centre, the Danish Nano Safety Centre, the Namur NanoSafety Centre, EURO-NanoTox, LEITAT, RIVM, TNO, EMPA, INRS, etc. In order to adequately address this challenge, international collaboration is key. In this regard, the *Closer to the Market* roadmap discusses the current situation of NanoSafety research in the United States, Asia, and Latin America. There is a new research call between EU and China on Nanoscience and Nanotechnology. Other important international collaborations include the SIINN (Safe Implementation of Innovative Nanoscience and Nanotechnology) ERA-NET (European Research Activity NETwork) that allows funding of joint EU–U.S. nanoEHS projects, as well as the new EU–Brazil, EU–Korea, and EU–Japan collaborations in the frame of the NANoREG programme.

Prof. Savolainen stressed the need to establish a market for nanosafety services, but acknowledged that there are significant bottlenecks. For instance, sustainable marketing requires employees and employers to be confident in the safety of the processes applied in the occupational settings and consumers to be confident in the safety of the products. He proposed actions that could remove some bottlenecks in the medium to the long term. These include, but are not limited to, networking, benchmarking, data collection, reporting, communication, standardization, certification, assistance to newcomers, feedback for fixing next research priorities, assistance to regulators, training, and certification of skills. Taking such actions could guide market actors (industry, public authorities) towards identifying best practices and standards to achieve environmental protection and operational certification.

In this context, Prof. Savolainen proposed an EU-funded Coordination and Support Action (CSA) topic that brings together the investments member states have made to build staff and operate nanoEHS management platforms and institutes. The goal is to get the topic published by the end of 2015 and the action operational by the end of 2016. The CSA will develop further actions and provide services and support for different stakeholders (e.g., industry, governments, researchers, etc.) to sustainably create marketable, societally approved products and goods.

6. Collaborations and Funding Opportunities

U.S. Funding Opportunities

Srikanth Nadadur, National Institute of Environmental Health Sciences

Dr. Srikanth Nadadur introduced the current activities and the future plans with respect to the nanotechnology research performed by the U.S. National Institute of Environmental Health Sciences (NIEHS). The mission of NIEHS is to reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease. Dr. Nadadur presented the NIEHS nanoEHS overarching goals with respect to the *NNI EHS Research Strategy* focus areas: (1) to gain fundamental understanding on the relationships between physicochemical characteristics and the biological interactions of ENMs; (2) to prioritize ENMs for research based on production, use, and physicochemical properties, as well as integrated approaches for hazard ranking; and (3) to address nanoEHS public health issues and regulatory needs.

Dr. Nadadur presented the ARRA Nano Grand Opportunity Consortium, which aims to develop (1) reliable and reproducible methods to assess biological response/toxicological endpoints for ENMs; (2) standardized protocols and methods for ENM dispersion and characterization in cell culture media; and (3) *in vitro* and *in vivo* models that can reliably predict biological response and reproducible data across labs using well-characterized ENMs.

Dr. Nadadur introduced also the NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR), which are currently working on three key nanoEHS projects. The first project focuses on *in vitro* work aiming to understand basic ENM-biological interactions (molecular, cellular, and organ level) using diverse cell phenotypes, representing portals of entry. The second project performs *in vivo* work to investigate how ENMs influence physiological pathological outcomes in target/secondary organs as well as translocation across different organs. The third project on Risk Assessment Translation is developing a collaborative/integrated risk assessment framework.

Dr. Nadadur also described the Chemical Effects in Biological Systems database (CEBS, http://cebs.niehs.nih.gov), which houses toxicological information of interest to health scientists. CEBS has a public and a private component. The public component houses raw data and metadata from over 9000 toxicological studies. Data from the NCNHIR consortium efforts are being moved into CEBS and will be accessible to investigators and partners.

The above projects and initiatives identified a number of knowledge gaps and needs to be addressed by future research. These include uncertainties around key nano-bio interactions that are difficult to elucidate due to the complexity introduced by existing and emerging ENMs. This calls for the development of molecular predictive toxicological approaches, animal models using multiple routes of exposures, long-term studies, predictive biomarkers for target and secondary organ responses, and common mechanism(s) of action across ENMs and routes of exposure.

In order to address some of the above issues, Dr. Nadadur proposed a focused approach targeting a limited set of ENMs that are pre-identified with input from regulatory agencies. These ENMs would be supplied by a materials resource core centre. Participating research projects would

investigate diverse routes of exposure and organ systems by means of molecular and pathophysiological approaches in order to create comprehensive toxicity profiles of the ENMs.

Dr. Nadadur concluded that in the context of the above activities there are ample opportunities for EU–U.S. collaborations in terms of mechanisms for sharing materials, experimental protocols, and specific data needs of regulatory agencies.

Nora Savage, National Science Foundation

Dr. Nora Savage explained that the NSF supports fundamental research across all fields of science and engineering and at all levels of education, highlighting the strong interdisciplinary focus of the Environmental, Health, and Safety of Nanotechnology program in the Engineering (ENG) Directorate. She explained that NSF values globally engaged U.S. scientists and engineers. In this context she presented the international dimensions of NSF projects, focusing on the mechanisms for promoting international collaborations. She stressed that although NSF does not support research at foreign institutions, NSF could provide funding to U.S. researchers for international travel as part of research collaboration. In addition, when the U.S. primary investigator demonstrates improved benefits resulting from international collaboration where critical expertise is provided by a foreign collaborator, international travel for the U.S. primary investigator may be supported.

Dr. Savage introduced two sizeable NSF-coordinated nanoEHS activities that have international dimensions, i.e., the SIINN ERA-NET 3rd Call and the "Nanomanufacturing" ENG multidivision activity. SIINN ERA-NET promotes the safe and rapid transfer of research results in nanoscience and nanotechnology into industrial applications. National and regional resources have been virtually pooled to create a transnational programme of research in which the United States contributed at least $2 million. The "Nanomanufacturing" activity supports Nanoscale Interdisciplinary Research Teams with grants up to $1.5 million for a period of four years. This activity promotes collaborative multidisciplinary research in order to overcome barriers to nanomanufacturing and includes nanoEHS challenges.

Dr. Savage introduced also the revised NSF Nano Program, which targets fundamental science in the area of nanomaterial behaviour mechanisms. Having previously managed two NSF programs–Nano EHS and Interfacial Processes and Thermodynamics, Dr. Savage was able to note the cross-cutting topics of these programmes, including interfacial characterization, interfacial dynamics, and surface properties. Some specific activities that have received financial support investigated the role the protein corona in the interaction of ENMs with organisms and a concept of label-free, high-throughput cell sorting based on surface free energies.

NANoREG Progress Report, ProSafe and NANoREG II

Tom van Teunenbroek, Dutch Ministry of Infrastructure and the Environment

Dr. Tom van Teunenbroek explained that over €170 million and ten years of research have been invested in nanoEHS research in the EU, resulting in a dramatic increase in the number of publications presenting data on physicochemical properties, release, kinetics, mode of action etc. Yet, there is no clear answer to the question "are nanomaterials a serious environmental and health threat?" Dr. van Teunenbroek argued that this shortcoming is due to the absence of central coordination in nanoEHS research, which has developed mostly in a bottom-up manner. Although

a bottom-up approach may be appropriate for general science and innovation, it is rather inefficient for addressing societal concerns.

Dr. van Teunenbroek presented an equation to describe the value of generated nanoEHS regulatory data, which is a function of the data's reliability (currently unknown), relevance (still questionable), exchangeability (limited due to the absence of standardized ontology), and comparability (insufficient due to differences in methods, materials, and operating practices). The experience of practitioners so far shows that there is a strong need for a top-down approach focusing on regulatory needs in addition to scientific needs; in other words, methods and data that can be used in a regulatory context are needed. Acquiring this information, in a nutshell, is the basic philosophy of NANoREG.

NANoREG is a large-scale EU research project, with 66 partners from 14 EU member states and two associated states, and strong industry involvement. In addition, NANoREG has collaboration agreements with Brazil and South Korea as well as tight links to international organizations (e.g., the European Chemicals Agency, OECD, ISO) and to ongoing EU FP7 projects such as SUN and MARINA. Its total funding is about 50 million euro for 42 months, making it into one of the largest nanoEHS programmes in the world.

The general goal of NANoREG is to develop a common European approach to the regulatory testing of nanomaterials. The specific objectives of the project are to

- Provide regulators with a set of tools for risk assessment and decision-making instruments for the short to medium term, by gathering data and performing pilot risk assessment, including exposure monitoring and control, for a selected number of nanomaterials used in products.
- Develop for the long term, new characterization and testing strategies adapted to a high number of nanomaterials where many factors can affect their environmental and health impact.
- Establish a close collaboration among authorities and industry with regard to the knowledge required for appropriate risk management, and create the basis for common approaches, mutually acceptable datasets, and risk management practices.

Given the regulatory context of the NANoREG project, reliability, comparability, and exchangeability of the generated EHS data is a key condition for its success. To meet these demands, the NANoREG Guidance Document was developed for the partners involved in *in vivo*, *in vitro*, and ecotoxicity experiments. The document sets minimum requirements for quality checks during toxicity testing by (1) harmonizing key test conditions, like the dispersion Standard Operating Procedures (SOPs) to be applied; (2) providing benchmark data; and (3) limiting the number of different nanomaterials to be tested.

The development of the regulatory framework for addressing the safety of ENMs and the creation of the NANoREG toolbox has just started. The same applies for the sub-projects on "Safety in the Value Chain Case Studies" that will link the results of the R&D work to the conceptual work.

The toolbox includes SOPs for the creation of ENM dispersions for measurement and toxicity testing. Specifically, SOPs have been developed for, for example, probe-sonicator calibration, size and stability analysis, and measurement of primary particle sizes. Preparation for round-robin testing is in progress. Minimum characterization requirements for the toxicological studies have been set and prescribed and relevant OECD Technical Guidances have been evaluated

theoretically. Instruments, tools, and methods have been identified for exposure measurements, including portable devices and stationary instrumentations for which SOPs will be developed. The generated measurement data will be integrated into the Nano Exposure and Contextual Information Database (NECID - http://www.perosh.eu/development-of-a-nano-exposure-and-contextual-information-database-necid/).

Long-term inhalation studies with CeO_2 and $BaSO_4$ were performed. In addition, a 90-day oral administration study based on the OECD guideline 408 including genotoxicity and fertility analysis with SiO_2 was completed, and some first results are available. With respect to genotoxicity and fertility, no adverse effects have been recognized so far. *In vivo* genotoxicity and immunotoxicity studies on nanofibrillar cellulose were performed. Moreover, several *in vivo* ecotoxicity tests have been carried out. Materials tested included TiO_2, CeO_2, and Ag.

Initial thoughts on categorization, read-across, and extra/interpolation have been exchanged by the partners. In addition, decision trees or strategies for risk assessment are under development to facilitate the integration and harmonization of the different risk assessment tools developed in NANoREG and to contribute to their future acceptance and implementation within and outside the project.

Dr. van Teunenbroek linked the objectives of NANoREG with ProSafe, which is a Coordination and Support Action to facilitate and promote the acceptance of the safer-by-design concept within the EU member states, national organizations, OECD, and globally. ProSafe is designed to have a central, supporting, and coordinating position in the chain of EU and international relationships, including ongoing initiatives and projects such as NANoREG, NANoREG II, new Horizon 2020 projects, industrial relations, and through the Inter Service Group to the European Commission.

The main objective of this project is to coordinate and support the aims of the EU member and associated states in their domestic and international efforts (e.g., OECD) for risk assessment, management, and governance by streamlining data acquisition, collection, and management on regulatory-oriented toxicology testing of nanomaterials, exposure monitoring, life cycle analysis, and disposal and treatment of waste nanomaterials. Consideration is also given to regulatory policy developments on both the national and international level, including challenges raised by the convergence between nano- and biotechnologies.

In this context, ProSafe will produce a white paper with the intention of providing the broadly accepted basis for regulators and industries to cover EHS aspects of ENMs, including safer by design. The ProSafe long-term research goals (2015-2020 and 2020-2025) include funding arrangements for EU–U.S. research collaboration.

James Baker, SELOR

Dr. James Baker presented the scope and objectives of the NANoREG II project, which was scheduled to start in July 2015. Its main aims are to (1) develop and demonstrate safer-by-design regulatory approaches for ENMs; (2) validate the tools and methodology, as well as their background data-sets that will lead to the manufacture of safer-by design-ENMs; and (3) address barriers for the application of these safer-by-design tools as standard industry practice.

The project essentially will seek to establish principles for grouping of nanomaterials according to their assumed modes of toxicological action for regulatory purposes. Out of each group, a few representative materials should be selected and a toxicological profile shall be assessed. The project will take into account future dossier requirements under REACH or other related EU legislation to

limit the required additional information, especially animal testing, to the essential minimum. The project will actively engage industrial partners to ensure collaboration between them and regulators.

EU Funding Opportunities

Nicolas Segebarth, Directorate General for Research and Innovation of the European Commission

Dr. Nicolas Segebarth gave an overview of Horizon 2020, the European Commission's Framework Programme for research and innovation that runs from 2014 to 2020. 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.

The total budget for Horizon 2020 is €77 billion (approximately $104 billion), which represents a 20% increase over 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.

Horizon 2020 is based on the principle of general openness. Cooperation with the United States is set as a highest priority, but the funding of U.S. partners is not automatic, except if provided for in the Work Programme (e.g. Health), deemed essential for the action/project, or provided for in a relevant bilateral agreement or any other relevant arrangement. There have been several successful cases of non-EU-funded U.S. participation in the EU nanoEHS projects NANOMMUNE, NEURONANO, MODERN, NANOSOLUTIONS, NANOMILE, and others.

Cooperation between the United States and Europe is possible at two different levels:

- At the project level, through (1) direct participation of U.S. partners in an EU grant or (2) through cooperation between independent projects sharing research agenda and having coordination mechanisms. See the next opportunities for the period 2016-17 below.
- At the programme level (government and funding agencies) through (1) joint calls, (2) coordinated/synchronized calls with ex post cooperation, or (3) joint calls through ERA-NET or CSA projects (e.g., SIINN, ProSafe).

The next opportunities for forming international nanoEHS consortia under Horizon 2020 are currently being prepared and will focus on the following topics:

- Analytical techniques and tools in support of nanomaterial risk assessment.
- Promoting safe innovation through global consolidation and networking of nanosafety centres and strengthening the European nanosafety capacity.
- Framework and strategies for nanomaterial characterization, classification, grouping, and read-across for risk analysis.
- Advanced and realistic models and assays for nanomaterial hazard assessment.

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%.

Karl Hoehener, TEMAS AG

Dr. Karl Hoehener presented the Coordination Action ProSafe, which aims at coordinating (1) the implementation of the safe-by-design concept in industrial innovation process for (specific) products, (2) the creation of a common database supporting this concept, and (3) the generation of data for the exposure and risk assessment along the value chain of nano-enabled products. This will be achieved through linking of existing initiatives and approaches as well as promoting the acceptance/uptake of the safe-by-design concept on national and international (e.g. OECD) levels. In order to do this, ProSafe is offering two main mechanisms:

- Common calls to fund joint innovation projects addressing the development of nanomaterials or nanoproducts with the respective processes integrating the safe-by-design concept along the entire value chain.
- Twinning of projects: Collaboration with the innovation funding agencies on a national scale participating in calls for supporting the safe-by-design concept with methods, training, and other activities.

Appendix A. Workshop Agenda

Download the PDF version at http://us-eu.org/wp-content/uploads/2014/12/2015-EU-US-NanoEHS-CoRs-agenda_final1.pdf.

Slides for selected presentations are available at http://us-eu.org/2015-eu-u-s-workshop/2015-agenda/.

Thursday, 12th March, 2015

8:30 – 9:00	**Registration**

Session 1: Welcome Remarks & Goals – Moderator Georgios Katalagarianakis

9:00 – 9:05	**Words of Welcome** Antonio Marcomini, Ca' Foscari University of Venice
9:05 – 9:15	**U.S. Opening Statement** Chris Cannizzaro, U.S. Department of State
9:15 – 9:25	**EU Opening Statement** Elke Anklam, JRC-IRMM European Commission
9:25 – 9:40	**Purpose and Goals of the 2015 Workshop** Georgios Katalagarianakis, DG Research and Innovation
9:40 – 10:15	**Facilitated Discussion and Instructions for Breakout Sessions**

Session 2: nanoEHS Scrimmage – Moderator Treye Thomas

10:15 – 10:30	**Introduction to nanoEHS Scrimmage** Mark Wiesner, Duke University
10:30 – 10:50	**Coffee break & Transition to nanoEHS Scrimmage Room**
10:50 – 12:00	**NanoEHS Scrimmage Activity**
12:00 – 13:00	**NanoEHS Scrimmage Plenary #1:** Convene for facilitated discussion, led by a U.S.–EU COR leadership member who would have been floating throughout multiple CORs to observe. This is designed to highlight successes, surprising results, etc.

Session 3: COR breakouts (full afternoon) – Moderator Nicolas Segebarth

14:00 – 14:20	**NanoEHS Scrimmage Plenary #2:** Announce winners of NanoEHS Scrimmage
14:20 – 14:30	**Transition to Breakout Session Rooms**
14:30 – 16:00	**First Breakout** <u>Databases and Computational Modelling for NanoEHS</u> o Discussion Leaders: Barry Hardy, Douglas Connect Nathan Hodas, Pacific Northwest National Laboratory <u>Human Toxicity</u> o Discussion Leaders: Yoram Cohen, University of California, Los Angeles Robert Rallo, Universitat Rovira i Virgili o Discussant: Tina Bahadori, U.S. Environmental Protection Agency o Speaker: Dario Greco, Finnish Institute of Occupational Health <u>EcoToxicity</u> o Discussion Leaders: Henriette Selck, Roskilde University Elijah Petersen, National Institute of Standards and Technology o Speakers: Jason White, Connecticut Agricultural Experiment Station Claus Svendsen, Natural Environment Research Council – Centre for Ecology & Hydrology Phil Sayre o Rapporteur: Teresa Fernandes <u>Risk Management and Control</u> o Discussion Leaders: Lawrence Gibbs, Stanford University Tom van Teunenbroek, Dutch Ministry of Infrastructure and the Environment o Speaker: Camilla Pease, ENVIRON

16:30 – 18:00	**Second Breakout** Exposure ○ Discussion Leaders: Richard Canady, International Life Sciences Institute Martie van Tongeren, Institute of Occupational Medicine Risk Assessment ○ Discussion Leaders: Derk Brouwer, TNO: Netherlands Organisation for Applied Scientific Research Mark Wiesner, Duke University Janeck Scott-Fordsmand, Aarhus University Characterization ○ Discussion Leaders: Anil Patri, U.S. Food and Drug Administration Kenneth Dawson, University College
18:00 – 18:10	**Transition to Plenary Room**
18:10	**Wrap-up Day 1 and Adjourn** Nicolas Segebarth, DG Research and Innovation

Friday, 13th March, 2015

8:40 – 9:00	**Quality assurance for the characterization of nanomaterials and implementation of labelling requirements for food and consumer products** Elke Anklam, JRC-IRMM European Commission

Session 4: COR Breakout Reports – Moderator Georgios Katalagarianakis

9:00 – 10:25	**EcoToxicity COR** U.S. co-chair: Elijah Petersen, National Institute of Standards and Technology EU co-chair: Henriette Selck, Roskilde University **Human Toxicity COR** U.S. co-chair: Yoram Cohen, University of California, Los Angeles EU co-chair: Robert Rallo, Universitat Rovira i Virgili **Databases and Computational Modelling for NanoEHS COR** U.S. co-chair: Nathan Hodas, Pacific Northwest National Laboratory EU co-chair: Barry Hardy, Douglas Connect **Exposure through Product Life COR** U.S. co-chair: Richard Canady, International Life Sciences Institute EU co-chair: Martie van Tongeren, Institute of Occupational Medicine **Risk Assessment COR** U.S. co-chair: Derk Brouwer, TNO: Netherlands Organisation for Applied Scientific Research EU co-chair: Mark Wiesner, Duke University **Risk Management and Control COR** U.S. co-chair: Lawrence Gibbs, Stanford University EU co-chair: Tom van Teunenbroek, Dutch Ministry of Infrastructure and the Environment **Characterization COR** U.S. co-chair: Anil Patri, U.S. Food and Drug Administration EU co-chair: Kenneth Dawson, University College Dublin

Session 5: Research Strategies – Moderator Treye Thomas

11:00 – 11:15	**U.S. Progress Review on the Coordinated Implementation of the NNI 2011 EHS Research Strategy** Treye Thomas, U.S. Consumer Product Safety Commission
11:15 – 11:30	**Research Needs and Data Gaps** Tina Bahadori, U.S. Environmental Protection Agency

11:30 – 11:45	**EU Regulatory Research Roadmap** Tom van Teunenbroek, Dutch Ministry of Infrastructure and the Environment
11:45 – 12:00	**EU Closer to the Market Roadmap** Kai Savolainen, Finnish Institute of Occupational Health

Session 6: Collaborations and Funding Opportunities – Moderator Chris Cannizzaro

13:30 – 13:45	**U.S. Funding Opportunities** Srikanth Nadadur, National Institute of Environmental Health Sciences
13:45 – 14:00	**U.S. Funding Opportunities** Nora Savage, National Science Foundation
14:00 – 14:15	**NANoREG Progress Report & NANoREG II** Tom van Teunenbroek, Dutch Ministry of Infrastructure and the Environment James Baker, SELOR
14:15 – 14:30	**EU Funding Opportunities** Nicolas Segebarth, DG Research and Innovation Karl Hoehener, Temas AG
14:30 – 15:00	**Discussion**
15:00	**Wrap up for Day 2 and Concluding Remarks** Georgios Katalagarianakis, DG Research and Innovation Lisa Friedersdorf, U.S. National Nanotechnology Coordination Office
15:15	**Closure of the Meeting**

Appendix B. Participant List

Affiliations are as of March 2015.

Monica Amorim, University of Aveiro, Portugal

Elke Anklam, European Commission-JRC-IRMM

Tina Bahadori, U.S. Environmental Protection Agency, United States

James Baker, SELOR, the Netherlands

Jean-Yves Bottero, CEREGE-CNRS, France

Derk Brouwer, TNO, the Netherlands

Marcello G. Cacace, Institute for the Study of Nanostructured Materials, National Council of Research, Italy

Richard Canady, ILSI Europe, Belgium

Chris Cannizzaro, U.S. Department of State, United States

Yoram Cohen, UCLA, United States

Hugues Crutzen, European Commission - DG JRC, Belgium

Kenneth Dawson, UCD, Ireland

Maria Diez-Ortiz, LEITAT Technological Center, Spain

Agnieszka Dobrak-Van Berlo, FPS Health, Food Chain Safety and Environment, Belgium

Elina Drakvik, Finnish Institute of Occupational Health, Finland

Stephen Ebbs, Southern Illinois University, United States

Teresa Fernandes, Heriot-Watt University, United Kingdom

Lisa Friedersdorf, U.S. National Nanotechnology Coordination Office, United States

Lawrence Gibbs, Stanford University, United States

Carine Gorrebeeck, FPS Health, Food Chain Safety and Environment, DG Environment, Belgium

Stefania Gottardo, European Commission Joint Research Centre, Italy

Barry Hardy, Douglas Connect GmbH, Switzerland

Nathan Hodas, PNNL, United States

Danail Hristozov, Ca' Foscari University, Italy

Hoehener Karl, TEMAS AG, Switzerland

Georgios Katalagarianakis, European Commission, Belgium

Ademar Lugao, IPEN, Brazil

Victor Maojo, Universidad Politecnica de Madrid, Spain

Antonio Marcomini, Ca' Foscari University, Italy

Steve Morris, Portland Communications, United Kingdom

Srikanth (Sri) Nadadur, NIEHS/NIH, United States

Anil Patri, FDA, United States

Camilla Pease, ENVIRON, United Kingdom

Elijah Petersen, NIST, United States

Joris Quik, RIVM, the Netherlands

Robert Rallo, Universitat Rovira i Virgili, Spain

Hubert Rauscher, European Commission Joint Research Centre, Belgium

David Rickerby, European Commission Joint Research Centre, Belgium

Juan Riego Sintes, European Commission Joint Research Centre, Italy

Jerome Rose, CEREGE CNRS, France

Nicole Sani-Kast, ETH, Switzerland

Nora Savage, U.S. National Science Foundation, United States

Kai Savolainen, Finnish Institute of Occupational Health, Finland

Phil Sayre, OECD, United States

Janeck J. Scott-Fordsmand, Aarhus University, Denmark

Nicolas Segebarth, European Commission, Belgium

Henriette Selck, Roskilde University, Denmark

Elena Semenzin, Ca' Foscari University, Italy

Claus Svendsen, NERC-CEH, United Kingdom

Treye Thomas, U.S. Consumer Product Safety Commission, United States

Sara Totaro, European Commission Joint Research Centre, Italy

Bas van Sikkelerus, SABIC, the Netherlands

Tom van Teunenbroek, Ministry of Infrastructure & Environment, the Netherlands

Martie van Tongeren, IOM, United Kingdom

Socorro Vázquez-Campos, LEITAT Technological Center, Spain

Jason White, CT Agricultural Experiment Station, United States

Mark Wiesner, Duke University, United States

Margrethe Winther-Nielsen, DHI, Denmark

Olga Zaytseva, University of Hohenheim, Germany

Christian Micheletti, Veneto Nanotech, Italy

Carlos Fito, ITENE, Spain

Maida Domat, ITENE, Spain

David Spurggon, CHE-NERC, United Kingdom

Stavros Anagnou, National Technical University, Greece

Markus Jensen, Hesser Associated International, United States

Aiga Mackevica, DTU, Denmark

Eva Valsami-Jones, University of Birmingham, United Kingdom

Rainer Hagenbeck, Infineon Technologies AG, Germany

Appendix C. Abbreviations and Acronyms

CEBS	Chemical Effects in Biological Systems database
COR	Community of Research
CSA	Coordination and Support Action
EHS	Environment(al), health, and safety
ENM	Engineered nanomaterial
ENG	Directorate for Engineering (NSF)
EPA	Environmental Protection Agency (U.S.)
ERA-NET	European Research Activity NETwork
EU	European Union
FP6	Framework Programme 6 (2002–2007) (EU)
FP7	Framework Programme 7 (2007–2013) (EU)
Horizon 2020	Framework Programme for Research and Innovation (2014–2020) (EU)
ISO	International Organisation for Standardisation
JRC	Joint Research Centre (European Commission)
nanoEHS	nanotechnology-related environment(al), health, and safety
NCNHIR	NIEHS Centers for Nanotechnology Health Implications Research
NEHI	Nanotechnology Environmental and Health Implications Working Group (NNI)
NIEHS	National Institute of Environmental Health Sciences (U.S.)
NNI	National Nanotechnology Initiative (U.S.)
NSF	National Science Foundation (U.S.)
OECD	Organisation for Economic Co-operation and Development
R&D	Research and development
REACH	Registration, Evaluation, Authorization, and restriction of CHemical substances (EU regulation)
SIINN	Safe Implementation of Innovative Nanoscience and Nanotechnology ERA-NET
SOP	Standard Operating Procedure