Bridging international approaches on nanoEHS

The challenge of assessing the scope and magnitude of risk from nanomaterials is urgent for society and ignoring risks could be detrimental for development. This challenge is bigger than the individual capacities on each side of the Atlantic, but effective cross-Atlantic collaboration can solve essential riddles about the use of nanomaterials.

Janeck James Scott-Fordsmand, Mónica João de Barros Amorim, Camille de Garidel-Thoron, Vincent Castranova, Barry Hardy, Igor Linkov, Ilise Feitshans, Gregory Nichols, Elijah Joel Petersen, David Spurgeon, Sally Tinkle, Ulla Vogel, Paul Westerhoff, Mark Robert Wiesner and Christine Ogilvie Hendren

Nanomaterial environmental, health and safety (nanoEHS) work enables researchers to produce information that can be used directly in regulatory systems to support predictability and coherence in policymaking, to answer questions raised by the general public, to reduce uncertainties that may limit investment in new technologies and to avoid future liabilities to commercial enterprises. These research results will potentially affect billions of people's lives.

Research initiatives focusing on nanoEHS issues have highlighted the need to ensure societal and global trust. This includes trust in fundamental issues of scientific integrity, reproducibility, knowledge and data-sharing, local and global governance, and broader communication as they relate to nanoEHS[1–6].

Bridging communication between stakeholders from the scientific, regulatory, business and public sectors is thus essential for the advancement of science in society as it induces trust in the outcome[7–10]. Knowledge translation between scientists and regulators from different geographical areas and cultures is equally critical. Although geographical collaboration is highly promoted, there is a lack of integrated project-minded funding structures.

One prominent nanoEHS initiative is the US–EU Communities of Research (CoR), which aims to build connections between risk-related disciplines that support their collective goals[11]. Here we describe the progress of this collaboration to date, and offer observations on differences and similarities in approaches used under different jurisdictions as well as future perspectives on nano risk evaluation.

Relevance, reliability and repeatability of scientific methods

Fundamental scientific testing and guideline developments are based on relevant transparent protocols that deliver reproducible results[9,12] as this is a key point for the societal implementation of nanoEHS regulations. Reproducibility is obtained through the development of robust standard methods. For nanoEHS the MALTA initiative[13] supports the relevant organizations, for example, the Organisation for Economic Co-operation and Development Working Party on Manufactured Nanomaterials (OECD WPMN) and standards organizations such as the International Organization for Standardization (ISO).

Societal implementation involves transparent and sustainable risk-based decisions that are acceptable to stakeholders such as manufacturers, workers, regulators, insurers and consumers. Risk-based decisions must include test systems covering all steps of the nanomaterial/product lifecycle, since each step may be relevant for different stakeholders. Hence, this includes initial production of pristine materials, their incorporation into products, to the end of life for a nanomaterial-containing product.

In the USA, the National Institute for Occupational Safety and Health (NIOSH) assesses worker exposures and recommends exposure limits and worker protections, while the Occupational Safety and Health Administration (OSHA) sets permissible occupational exposure limits. The Food and Drug Administration (FDA), the Consumer Product Safety Commission (CPSC), and the US Environmental Protection Agency (EPA) are responsible for setting standards for public use of nanomaterials and nanomaterial-containing products. These agencies perform human health risk assessments within their own areas of responsibility[9]. To achieve consistency, agencies have developed measurement tools and approaches that can be applied across all sectors[10]. In the EU, chemicals are regulated through Registration, Evaluation, Authorization and Restriction of chemicals (REACH) and Classification, Labelling and Packaging (CLP) regulations, because they are covered by the definition of a chemical 'substance' in both regulations. The general obligations in REACH and CLP apply for any substance, with no provisions referring explicitly to nanomaterials. However, the EU Commission recently adopted revision of several Annexes of REACH, clarifying the registration requirements for nanomaterials.

A critical need for both environmental and human health testing is the availability of broadly available reliable and repeatable quantitative nanomaterial characterization methods that are useful in relevant testing media. There simply are not yet broadly available methods that can characterize nano-specific parameters (possibly with the exception of size) in complex media.

The environmental approaches for exposure assessment and hazard testing are broadly similar in the EU and the USA. These methods have evolved from generic tools to tools that increasingly allow a greater focus on nano-specific issues[14,15]. Whereas early exposure models were simple general mass flow models, newer nanoEHS models include nano-specific release, transport and fate processes, relevant to specific nanomaterial lifecycles[16,17]. There is a marked focus on including uncertainty parameters in the models, because (among other reasons) it is difficult to obtain exact volume/tonnage data on nanomaterial production and releases across various life stages and because fate models are still in development[18]. However, despite the similarities in the US and EU approaches, there is no consensus on these exposure assessment and modelling approaches. The hazard measurement methods adopted in the USA and EU are also similar in many respects, again targeting nano-specific tools compliant with current standard methods[19–22]. However, the USA has a further focus on higher trophic levels as the targets of protection, whereas the EU introduced more legislative guidelines aimed at protecting lower trophic levels.

With regard to human health, the most notable difference between the USA and the EU approaches is that in the USA, responsibility for regulating risks of nanomaterials is distributed across several federal agencies, whereas in the EU the responsibility is distributed between different Directorate-Generals within the EU commission and within individual member states. It has proven difficult to apply current guidelines to nanomaterials in both the USA and the EU, making it challenging to perform quantitative risk assessments for nanomaterials. However, the USA NIOSH proposed occupational exposure limits for three specific nanomaterials: ultrafine TiO_2, multiwalled carbon nanotubes and silver nanoparticles in 2011, 2013 and 2015, respectively. To date, these recommended exposure limits have not been implemented as permissible exposure limits. The EU Commission has implemented an occupational exposure limit for the process-generated diesel engine exhaust. Member States have to comply with the new level by 21 February 2023 at the latest (3 years later for the sectors of underground mining and tunnel construction) (https://dieselnet.com/standards/eu/ohs.php). However, the Netherlands applied a 5-fold lower occupational exposure limit for diesel exhaust on 1 July 2020. Some states (for example, Germany and Finland) have established voluntary agreements between the labour market partners (based on non-health reference values for exposure), while other member states currently have no nano-specific regulations.

With regard to test methods, a primary goal for both environmental and human health is a further alignment of exposure and hazard testing systems (already developed and new systems) within each geographical region. Efforts include a focus on how and when to use such testing systems in a broader risk governance perspective. Concurrently, alignment between regions should be sought.

Data sharing and openness

Data sharing and openness have been emphasized in the cross-continental work of the US–EU CoR. In both places, there is an increased emphasis on all public funded research data (when possible) adhering to findable, accessible, interoperable and reusable (FAIR) principles. There is an ongoing debate about data compilation, that is, the creation of structured datasets incorporating published and unpublished findings from reliable sources. Datasets that are amenable to computational analysis, modelling and theory development. The sharing, comparison and reuse of data requires the development of common ontologies, access criteria, formats and standards for data curation and completeness[23–26]. There has been an extensive discussion about data standards in the nanoEHS field, with the elaboration of the ISA-TAB-Nano file format (developed within the US-based National Cancer Informatics Program Nanotechnology Working Group, NanoWG)[27] serving as an example of mutual adoption and joint development between the USA and the EU. A cross-continental NanoInformatics 2030 Roadmap[28] identifies the key needs and obstacles in this area. A related issue is that of data access for wider stakeholder communities via institutions such as the European Union Observatory for Nanomaterials (EUON)[29]. Investment in the development of a cyber infrastructure, associated communication processes and tools to support data compilation is required for successful advancement of nanoEHS (see also ref. [30]).

With the expansion of the nanoEHS field, it is clear that much of the data, experience and knowledge generated to date can (with due diligence) be used to draw inferences about 'similar' materials/scenarios and to develop general models. Models that reduce the need for testing and case-by-case evaluation are a critical need, generally referred to as read-across approaches[31,32]. Both the USA and the EU have initiatives to identify such methods. In Europe two large project funded under the call NMBP-14-2018 are specifically dealing with developing read-across techniques and computational models.

Policy perspective

The USA and the EU use traditional risk-based approaches to identify and manage risks associated with nanomaterials. Such approaches involve assessing a material's inherent hazards, exposure pathways and related effects, in a dose-response type approach. While such approaches have a long history of success (with notable exceptions) with mature and/or well-characterized chemicals, they may have limited efficacy given the uncertainty surrounding[33] nanomaterials across their lifecycle.

Despite similarities in risk assessment practices, the US and EU have generally adopted differing outlook policy prescriptions for how nanomaterials should be governed. The US and the EU both signed the Rio Declaration Principle 15 in 1992, which proposed a precautionary approach to new chemicals and materials to avoid potentially serious or irreversible harm to the environment. In 2000, the European Commisison translated this more informal 'approach' to a more formal 'principle' and set out specific cases in which this principle applies. The USA maintained its commitment to the precautionary approach, but did not endorse the translation into a principle. The USA considers a chemical or nanomaterial safe until it is proven harmful[34]. This indicates that the EU regulates based on the potential for hazard, whereas the USA regulates based on risk (where Risk = Hazard × Exposure). However, there are many similarities between USA and EU laws governing the use in commerce of toxic or hazardous substances. Both represent a coherent body of unified legislation, both are beholden to protect from risk while promoting public trust and both are challenged to adapt regulatory approaches to an emerging or rapidly changing technology[35]. They each have a mature infrastructure to examine new rules, enforce compliance with law and make use of global harmonization of chemical safety (GHS, see ref. [36]) when applicable, depending on agency requirements. A key difference is the starting points of their analysis for risk, as seen above. The EU's legal concept presumes materials are unsafe, but this is a rebuttable presumption that can be overcome by following specific steps using defined regulatory criteria for testing. However, regulation has begun to narrow the difference between the EU and US systems as they begin to align. For instance, the revisions of the US Toxic Substances Control Act (TSCA) in 2016 allows an enhanced system of scrutiny and pre-registration before items enter the market, and the EU is increasingly moving towards avenues for redress through administrative penalties and litigation. Coherence in emerging technology policy requires continuous planning and extensive discussion across the continents to ensure that consistency of language is paired with consistency in methods and meanings, including frameworks that encourage collaboration with practical deliverables[35].

Communication

Rapid, reliable and efficient communication is required to support governance of nanomaterials[5]. In the EU, risk management is supervised by the European Parliament, the European Council and the European Commission, while risk communication is performed by the European Commission, European agencies and scientific committees, besides the risk management performed by member states. Conversely, in the USA, risk assessment, management and communication are decentralized and performed by various Federal Agencies and other organizations, as

discussed above[37]. Overall, the approaches to risk communication in the EU and USA are broadly convergent. In both cases, communication with authorities, professional users and consumers is based on the best available scientific understanding and knowledge, with an emphasis on independence, competence, quality and transparency. Efforts have been focusing on increasing the availability of information with regard to the presence of nano web platforms and national registers set up by government, industry and academia (that is, registers by Sweden, Denmark, Belgium and France, and the EUON). The EU and USA both have rules and guidance relating to conflicts of interest, transparency, stakeholder involvement, regulatory impact assessment, peer review, collaboration and coordination within the governmental structure. Moreover, both the USA and the EU have identified control banding as a suitable risk control method for managing nanomaterial exposure[38,39]. Both have developed Material Safety Data Sheets (MSDS), training modules and guidance for handling nanomaterials. In the EU, nano-related risk is communicated to authorities and consumers via the CLP and the REACH Chemical Safety Assessment regulations, which are intended to improve the protection of human health and the environment from risks presented by chemical substances (and nanomaterials). REACH provides the legal instrument and ensures communication through the supply chain. Conversely, the USA generally uses federal agency-specific regulations such as the TSCA for the EPA, or the Food, Drug and Cosmetic Act (FDCA) for the FDA. To align the risk communication strategies of these two jurisdictions, it will be necessary to agree upon and implement coordinated solutions and products. An effective and proactive risk communication strategy[8] that includes established and new ways to communicate would help to build trust along supply chains and reassure both professional users (for example, manufacturers, regulators and insurers) and consumers[5]. Core principles shared by the EU and USA provide a foundation for developing a common set of principles that emphasize an approach using the best available science for nano risk communication.

Way forward

In many aspects the fundamental scientific methods adopted in the EU and the USA are aligned, although on both sides there is still a need for further methods that can describe nano-specific effects. Hence, the cross-Atlantic focus should ensure that commonly accepted methodologies are easily available, for example. Although there is a common agreement on which nano-parameters are relevant, it is still only possibly for a few laboratories to measure these in environmental relevant media. Further, for exposure and fate modelling, the focus should be on a common understanding of how to include uncertainty parameters (for example, those of measurements of nanomaterials, their biological impact and the uncertainty related to the exposure and fate models) into the risk assessment models. In some areas such as human health, it seems that an in-depth correspondence between the USA and the EU can only take place after an internal alignment (that is, alignment within the USA and within the EU), as described in the human health section.

Investment in mutually accepted cyber-infrastructure, associated communication processes and tools to support data compilation are required for successful advancement of nanoEHS. This obviously includes an agreement on which nano-specific descriptors are the most important for specific outcomes and how these descriptors should be reported. Given the strong impact of surrounding media conditions on the behaviour of the nanomaterials, the appropriate metadata are at least as important as the nano-characteristics. These issues are assessed and implemented within international regulatory bodies, for example, the OECD WPMN[40].

In the policy domain, there are many similar actual risk assessment and risk management practices, but the starting point for risks assessments differs in the EU and the USA. The EU's legal concept presumes that materials are unsafe, but this is a rebuttable presumption, while the USA considers a chemical or nanomaterial safe until it is proven harmful. Although progress has been made in aligning these presumptions, this area should be an obvious point for further emphasis.

In both places, broad communication plays an important role, with communication based on best available scientific knowledge. The emphasis is on independency, competence, quality and transparency and addressing the various stakeholders needs. In light of the progress in the technical areas of nanomaterials risk assessment, an obvious focus should be continued sharing of information with stakeholders with the perspective of having a broadly accepted nano governance. This includes a trustworthy and objective international governance scheme, which promotes a proactive role of the stakeholders to reach for resilient risk governance[41].

It is widely appreciated that the challenge at hand is bigger than the capacities on each side of the Atlantic, and that solutions are urgently needed. However, to make progress this consensus needs to be accompanied by an organizational structure that can facilitate easy and direct cross-Atlantic collaboration. Attempts have been made to achieve this; however, further emphasis must be placed on this collaborative aim as the alternative may well be slower technological progress in the USA and the EU than could otherwise be achieved. ❐

Janeck James Scott-Fordsmand[1]✉, Mónica João de Barros Amorim[2,3], Camille de Garidel-Thoron[4], Vincent Castranova[5], Barry Hardy[6], Igor Linkov[7], Ilise Feitshans[8,9], Gregory Nichols[10,17], Elijah Joel Petersen[11], David Spurgeon[12], Sally Tinkle[13], Ulla Vogel[14], Paul Westerhoff[15], Mark Robert Wiesner[16] and Christine Ogilvie Hendren[16,18]

[1]*Aarhus University, Silkeborg, Denmark.* [2]*Department of Biology, University of Aveiro, Aveiro, Portugal.* [3]*CESAM, University of Aveiro, Aveiro, Portugal.* [4]*Aix Marseille Univ, CNRS, IRD, INRA, Coll France, CEREGE, Aix en Provence, France.* [5]*West Virginia University, Morgantown, WV, USA.* [6]*Edelweiss Connect, Basel, Switzerland.* [7]*US Army Engineer Research and Development Center, Concord, MA, USA.* [8]*European Scientific Institute, Archamps, France.* [9]*Work Health and Survival Project, Haddonfield, USA.* [10]*Homeland Defense and Security Information Analysis Center, Oak Ridge, TN, USA.* [11]*National Institute of Standards and Technology, Gaithersburg, MD, USA.* [12]*NERC Ctr Ecol & Hydrol, Wallingford, England.* [13]*IDA/Science and Technology Policy Institute, Washington, DC, USA.* [14]*National Research Centre for the Working Environment, Copenhagen, Denmark.* [15]*Arizona State University, Tempe, AZ, USA.* [16]*Duke University, Durham, NC, USA.* [17]*Present address: GP Nichols & Company, Knoxville, USA.* [18]*Present address: Appalachian State University, Boone, NC, USA.*
✉*e-mail: jsf@bios.au.dk*

Published online: 20 May 2021
https://doi.org/10.1038/s41565-021-00912-5

References

1. Nel, A. E. *Science* **355**, 1016–1018 (2017).
2. *Nat. Cell. Biol.* **19**, 741–741 (2017).
3. Jasny, B. R. et al. *Science* **357**, 759–761 (2017).
4. Nosek, B. A. & Errington, T. M. *Elife* **6**, e23383 (2017).
5. Murphy, F. et al. *Nat. Nanotechnol.* **12**, 717–719 (2017).
6. Wiesner, M. R. et al. *Environ. Sci. Technol.* **43**, 6458–6462 (2009).
7. Kenny, C., Washbourne C.-L., Tyler, C. & Blackstock, J. J. *Palgrave Commun.* **3**, (2017).
8. Service, E. P. R. *Scientific advice for policy makers in the EU* (European Parliamentary Research Service, 2015).
9. Garraway, L. *Nature* **543**, 613–615 (2017).
10. Martin, J. *Nature* **546**, 577–577 (2017).
11. Friedersdorf, L. E. et al. *Nat. Nanotechnol.* **14**, 996–998 (2019).

12. *Nature* **546**, 8–8 (2017).
13. The Malta Intiative. *Bundesumweltministerium* https://www.bmu.de/en/topics/health-chemical-safety-nanotechnology/nanotechnology/the-malta-initiative (2020).
14. Scott-Fordsmand, J. J. et al. *Int. J. Environ. Res. Public Health* **14**, 1251 (2017).
15. Scott-Fordsmand, J. J. et al. *Nano Today* 7–10 (2017).
16. Westerhoff, P. et al. *Nat. Nanotechnol.* **13**, 661–669 (2018).
17. Hendren, C. O. et al. *Environ. Sci. Technol.* **47**, 1190–1205 (2013).
18. Svendsen, C. et al. *Nat. Nanotechnol.* **15**, 731–742 (2020).
19. Amorim, M. J., Roca, C. P. & Scott-Fordsmand, J. *J. Environ. Pollut.* **218**, 1370–1375 (2016).
20. Petersen, E. J. et al. *Environ Sci Technol* **49**, 9532–9547 (2015).
21. Hund-Rinke, K. et al. *Nanotoxicology* **10**, 1442–1447 (2016).
22. Scott-Fordsmand, J. J. et al. *Environ. Pollut.* **218**, 1363–1364 (2016). ß.
23. Marchese Robinson, R. L. et al. *Nanoscale* **8**, 9919–9943 (2016).
24. Hartmann, N. B., Ågerstrand, M., Lützhøft, H.-C. H. & Baun, A. *NanoImpact* **6**, 81–89 (2017).
25. Tropsha, A., Mills, K. C. & Hickey, A. J. *Nat. Nanotechnol.* **12**, 1111–1114 (2017).
26. Powers, C. M. et al. *Beilstein J. Nanotechnol.* **6**, 1860–1871 (2015).
27. Thomas, D. G. et al. *BMC Biotechnol.* **13**, 15 (2013).
28. Hasse, A., Klassig F. *US Roadmap Nanoinformatics 2030* (EU Nanosafety Cluster, 2018).
29. *European Union (EU) Observatory for Nanomaterials (EUON) 2017* (ECHA, accessed 1 February 2020); https://euon.echa.europa.eu/
30. *CEP Final Report: The promise of evidence-based policymaking* (Commission on Evidence-Based Policymaking, 2017).
31. Godwin, H. et al. *ACS Nano* **9**, 3409–3417 (2015).
32. Oomen, A. G. et al. *Int. J. Environ. Res. Public Health.* **12**, 13415–13434 (2015).
33. Grieger, K. et al. *Nat. Nanotechnol.* **14**, 998–1001 (2019).
34. Holdren, J. R., Sunstein, C. R. & Siddiqui, I. A. *Principles for Regulation and Oversight of Emerging Technologies* (Executive Office of the President of the United States, 2011).
35. Feitshans, I. L. *Global Health Impacts of Nanotechnology Law: A Tool for Stakeholder Engagement* (Panstanford publications, 2018).
36. *Recommendation of the Council on the Safety Testing and Assessment of Manufactured Nanomaterials* (OECD, 2013).
37. Malloy, T., Trump, B. D. & Linkov, I. *Environ. Sci. Technol.* **50**, 6822–6824 (2016).
38. Schulte, P. et al. *J. Occup. Env. Hyg.* **5**, 239–249 (2008).
39. Trump, B. D., Hristozov, D., Malloy, T. & Linkov, I. *Nano Today* **21**, 9–13 (2018).
40. *Approaches to Develop or Use Concept of Grouping, Equivalence and Read-Across Based on Phyical-Chemical Properties (GER-PC) of Nanomaterials for Their Human Health and Ecosystem Hazard Assessment in Regulatory Regimes: Analysis of A Survey* (Organisation for Economic Co-operation and Development, 2016).
41. Linkov, I. et al. *Environ. Sys. Dec.* **38**, 170–176 (2018).

Acknowledgements

Financial support to CESAM (UIDB/50017/2020 + UIDP/50017/2020), to FCT/MCTES through national funds (PIDDAC), and the co-funding by the FEDER, within the PT2020 Partnership Agreement and Compete 2020. Excellence Initiative of Aix-Marseille University - A*MIDEX, a French "Investissements d'Avenir" program, through the Labex SERENADE. National Science Foundation (EEC-1449500) Nanosystems Engineering Research Center on Nanotechnology-Enabled Water Treatment. The views and opinions expressed in this article are those of the individual authors and not those of the US Army, European Commission or other sponsor organizations.

Competing interests

The authors declare no competing interests.