A common European approach to the regulatory testing of nanomaterials

Inventory of Safety Assessment Issues and New Approaches to Research and Governance Deliverable 6.2

Introduction

One of the aims of the NANoREG project is to fill the increasing gap between innovation and risk analysis regarding manufactured nanomaterials (MNMs). This deliverable helps to understand this issue by providing information on:

- Social and technical issues currently inhibiting robust safety assessment of MNMs;
- Key bottlenecks inhibiting the ability of researchers to deliver answers to regulatory questions.

It also usefully explores ways to overcome these challenges by providing a review of:

- High throughput screening and organ-on-a chip as new approaches to safety testing, including a discussion of their challenges and limitations;
- Safe-by-Design (SbD) and Responsible Research and Innovation (RRI) as new approaches to the governance of MNMs, including a discussion of their challenges and limitations;
- How the identified challenges, obstacles and risks may be turned into business opportunities.

Description of Work

The work presented in this deliverable has been developed through reviewing relevant literature and running several dedicated dialogue workshops with nanosafety researchers. The issues canvassed during these workshops were ideas concerning what constitutes good science and innovation, how this relates to the notion of responsible research and innovation, how responsibilities for the safety of MNMs are seen to be distributed and enacted, and what the obstacles for achieving responsible research and safe innovation are.

Main Results

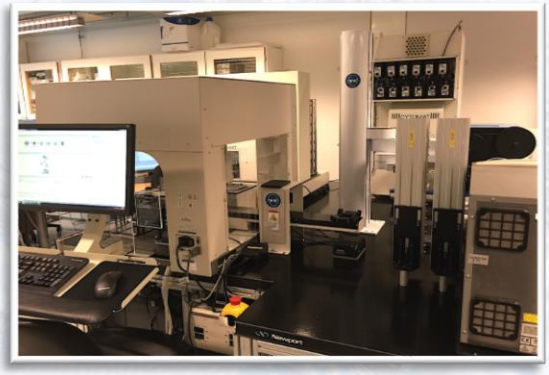
Safety assessment issues and key research bottlenecks

The literature review and dedicated workshops identified a great number of barriers currently prohibiting the practice of risk analysis and safety assessment from a value chain perspective. This includes: (1) *conceptual barriers* posed by issues such as the lack of agreed definitions, the huge diversity of MNMs, and the variety of applications across several sectors, (2) *scientific barriers* posed by issues such as the nascent nature of validated and standardised test methods, the range of possible exposure routes, and the limited knowledge on toxicology, transformation, fate and bioaccumulation, (3) *practical barriers* such as the availability of limited funding for nanosafety research and the current time lag between rapidly advancing commercial applications and the careful development of reliable safety testing, and (4) *regulatory barriers* such as non-harmonised regulatory requirements and systems.

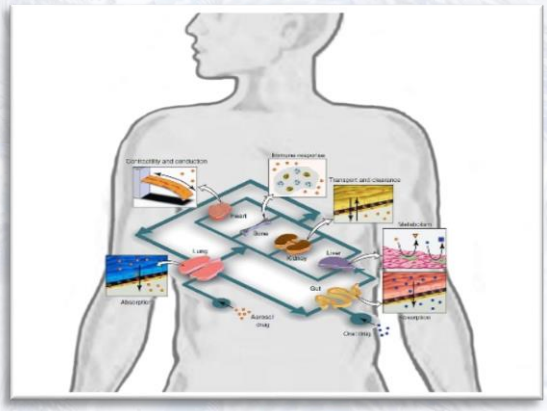
Furthermore, with a focus on environment, health, and safety (EHS) research, three key bottlenecks were defined and elaborated, including (1) knowledge of the basic properties of MNMs, (2) understanding of MNM interactions with biological systems and (3) required infrastructure and instrumentation.

To canvas possible ways to overcome these safety assessment issues and research bottlenecks, the deliverable reviews both *technical options,* including two new approaches for safety testing of MNMs (high throughput screening and organ-on-a-chip), and *socio-political options,* including two new approaches to the governance of MNMs (safe-by-design and responsible research and innovation).

New approaches to EHS testing



There is a huge demand from both the scientific community and legislative institutions to come up with rapid, cost-effective, and reliable ways to conduct MNM safety testing. The deliverable reviews the approach of *high throughput screening* (HTS). It describes the (potential) benefits as including the generation of large amounts of reliable data, reduced need for animal testing and reduced time and costs. Potential challenges and limitations of HTS techniques are also described, for example how toxicology screening needs to be coupled with characterization of MNMs in the exposure medium and how this still needs to be developed for HTS techniques. Furthermore, validation of in vitro HTS tests for in vivo situations and the development of HTS approaches able to assess dose- and time-dependent toxicity predictive of in vivo adverse effects, are also still required.



The deliverable also explores the potential of *organ-on-a-chip* systems (OCs). An OCs is a microfluidic device containing miniaturized bioreactors in which living cells are cultured in a precise spatial arrangement and under a continuous flow of culture fluid in order to simulate the physiology of an entire living organ. Potential benefits of the device include that it may allow high-resolution, real-time imaging of the cultured cells as if they were in a living organ. The deliverable provides an extensive overview of the state of the art regarding the use of OCs and concludes that although the development of OCs for toxicity testing is still in its infancy and in many cases still requires validation, OCs may be usefully used to explore three types of models for toxicity testing: (1) tissues representing tests under healthy conditions, (2) tissues representing tests under pathological conditions or (3) tissues representing barriers such as the gut wall, blood-brain-barrier, placenta, etc. The relatively long viability of OCs and their dynamic character may make these systems more suitable to mimic repeated dose experiments than conventional static in vitro systems. One of the potential limitations, however, is uncertainty regarding the criteria regulators and safety scientists may use to judge the feasibility and acceptability of OCs for repeated dose experiments.

New Approaches to Governance

The deliverable also analyses two new approaches for MNM governance: *Safe-by-Design (SbD)* and *Responsible Research and Innovation (RRI).* Both of these approaches are designed to try and address some of the limitations that relying on regulation through risk assessment of final products currently faces for MNMs. The deliverable describes the history of the development of these two concepts as well as their potential benefits and challenges for implementation. It is concluded that integration of some of the key features of RRI into the NANoREG SbD stage gate model would be advantageous. The most relevant elements to be added to the stage gate model include a) the alignment of innovation with social needs, b) the involvement of civil society groups, non-governmental organisations and members of the public, c) an emphasis on reflecting on underlying values, assumptions and uncertainties throughout the innovation process, d) a specific commitment to transparency and accessibility, and e) an interest in anticipating impacts beyond risks to health and safety, including ethical issues, socio-economic impacts and questions regarding sustainability.

Business Opportunities

The deliverable ends with an overview of how some of the challenges and limitations identified can be turned into potential business opportunities. This includes areas such as the synthesis of well-defined nanomaterials and the development of new tools for characterisation and testing in complex media.

For more details about NANoREG please visit the official website **www.nanoreg.eu.**

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