Regulatory Questions & Issues Deliverable 1.1

Introduction

The NANoREG project is a “demand driven project”: the R&D work of this project is guided by key questions and issues in the area of regulatory toxicology and risk assessment of nanomaterials as formulated by regulatory authorities and other stakeholders.

NANoREG Deliverable D1.1 "Report on a Virtual Workshop to identify, formulate and prioritize issues/questions" presents the result of this virtual workshop: a list of 16 questions and issues on which the NANoREG project will be focussed. A public version of the Deliverable is available on the NANoREG web-site.

Main Results

In the Description of work of the NANoREG project, an initial set of key issues and questions was presented on which the NANoREG project should focus. This set was based on the conclusions of Reach Implementation projects on Nanomaterials (RIP-oN), recommendations of the EU Scientific Committees and opinions of several national and international regulatory agencies.

During the first month of the NANoREG project this initial set of questions and issues has been refined and extended by consultation of the REACH Competent Authorities Subgroup on Nanomaterials, the NANoREG National Coordinators and the internal European Commission Interservice Group on Nanotechnologies.

The result of this process is presented in the table below.

Table 1: *Refined set of key questions from a regulatory perspective to be addressed in NANoREG*

No.	Issue / question
1	**Measurement and characterization - Identification:** How can MNMs be identified according to the EC recommendation for a definition of MNMs and for regulatory purposes (i.e. the implementation of the EC definition in e.g. REACH, CLP, cosmetics, novel food, etc.), including other jurisdictions (global harmonisation)? Can we develop robust measurement protocols which enable assessment of whether a NM falls under, or not, the EC definition? Are there robust measurement protocols available (and for which matrices) that enable identification?
2	**Measurement and characterization**: Could an "intelligent characterisation strategy" be defined? What is a minimal set of physical (and/or chemical) characteristics that should be available for risk assessors within the context of regulatory toxicology? What are the relevant features to characterise MNMs, e.g. size, form, aspect ratio, rigidity, flexibility and coating? What methods (SOPs) should be developed / used to determine the physical chemical characteristics of MNMs throughout their different life cycle stages within the context of regulatory toxicology?

3	**Characterisation/Transformation**: What testing should be performed to identify surface modifications that occur once a MNM has been released into the environment or taken up into the body? How can transformation, including agglomeration surface modification, dissolution and incineration, be determined and considered in the exposure and hazard assessment and how do they change the intrinsic toxic properties and biodistribution Do we need to know the details of such surface modifications or of what is bound, or do we need some simple test systems that actually determine the behaviour and transformation of MNM in relevant media throughout all life cycle stages? Is a nano-derived material still nano when it becomes agglomerated? Take into account relationship with questions 7-9.
4	**Metrology and dose metrics**: Which metrics (metrology) should be used for MNMs in regulatory toxicology?
5	**Extrapolation and grouping:** What guidance can be provided on how to decide when information from different forms of MNMs (or from the bulk material) can be "re-used" in the sense of read-across, categorisation and grouping? Should / could guidance be based exclusively on physical-chemical properties or could exposure related (eco)toxicological and mechanistic information (as Mode of Action) be used as well and how?
6	**Fate, persistence and long-term effects:** Can effective in vitro and alternative models to understand long-term effects be developed? Will MNMs accumulate in humans, the environment, environmental species and the food chain and what are the driving forces? Is this mechanistically different from bulk materials? Will nanomaterials present long-term and/or cause deferred effects? How will coatings or surface modifications or the bio-based nature of the MNM affect biopersistence / biodegradability rates?
7	**Kinetics and fate, determination:** How and when should information on absorption from the various routes of exposure, on deposition (e.g. lung burden), on biodistribution, on potential persistence and bioaccumulation, and on internal exposure (taking into account dose, duration, coating and interaction with biological systems) be generated and used?
8	**Kinetics and fate, extrapolation:** How and when can information on kinetics and fate be used to justify grouping / read across or testing triggering / waiving and for building knowledge on the relationship between physical-chemical properties and toxicity? In other words: to what extent are the kinetics and fate of MNMs (e.g. environmental distribution or deposition and biodistribution in the lung) different from the bulk material? Are there ways to extrapolate this information from the bulk material or from several forms (size, shape, coating, etc.) of the same chemical and how should this extrapolation be made?
9	**Mode of action:** What are the physical and chemical properties driving exposure and (eco)toxicity of MNMs at all stages of their life cycle? How is MNM interaction with biological systems affected? What are critical characteristics of MNMs that need to be considered and included / excluded when developing MNMs to ensure they are safe and which materials have a known increased toxicity in the nanoform vs. the bulk form, and why? How will this facilitate the regulatory safety assessment of new nanomaterials?
10	**Hazard:** Which methods should be used to assess the human and environmental toxicity? What is the applicability of conventional testing methods for nanomaterials? Is adaptation of the conventional methods needed, for example by including nano-specific endpoints or additional guidance on sample preparation? What testing is relevant at all stages of the nanomaterial life cycle?
11	**Exposure:** What are the main determinants for occupational and consumer exposure to MNM and what are the duration and type of exposure?
12	**Exposure:** How should human and environmental exposure be assessed in practice (determining exposure scenario, quantify input parameters for models, assumptions and use of proxy indicators, background and uncertainty estimation)?
13	**Exposure and life cycle analysis:** Which scenarios could denote potential exposure and what information do we have on them? Can we develop standardized and efficient testing procedures for estimating release of nanoparticles (NP) from powders and NPs in matrices? What are situations in which MNM exposure is expected to be negligible / high? Are the amount and the nature of releases of MNM similar to regular chemicals, when common recycling and end-of-pipe techniques are used?
14	**Risk Assessment:** What are the no-adverse-effect or benchmark dose levels of long-term (low dose) exposures and can they be derived from short-term exposures (acute and subacute)? If not, what kind of information should be generated?

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15	**Risk Management:** How can exposure to MNMs be minimized / eliminated? Are risk management measures (RMM), in particular existing personal protective equipment, effective and sufficient when hazards and/or risks are high, uncertain or unknown? Should the RMM be different from bulk powders? Are currently available control banding tools appropriate for NPs or will these need to be further evaluated, improved (related to exposure assessment, too)?
16	**Health surveillance:** What are the triggers to indicate that biological monitoring or health surveillance of (occupational) exposed individuals is needed? Can an 'intelligent strategy' be developed?

Follow-up

All NANoREG tasks have been linked to relevant questions and issues as listed in table 1; the results of the tasks will be grouped along the lines of these questions and needs and discussed with relevant stakeholders like assessors, policymakers and industry. Periodical review and update of the Questions and needs is foreseen in the NANoREG project.

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

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