A common European approach to the regulatory testing of nanomaterials

NANoREG

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[1] Renamed, see section 3 on deviations from work plan
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Table of Content

1 Description of task (as copied from the Description of Work - DoW)

Task 1.1: Refinement of problem identification and formulation of questions and requirements, including interaction with stakeholders.

The collection of regulatory issues/questions requiring scientific answers will be provided by the national coordinators (WP 7 Task7.2) and consolidated in common workshops on the basis of the feed-back given by regulators and other stakeholders (e.g. industry, NGOs, international organisations). Preliminary ideas on how regulatory issues/questions will be addressed will also be shared during the workshop. Collaboration and communication with Tasks 7.1 and 7.2 will be established for organising these workshops and the feed-back activities under task 1.3 and 1.4. This task will mainly rely on the proven experience from the core group formed by RIVM, JRC, TUKES and AIT to interface between regulators and other stakeholders and the scientific community for implementation of REACH and other regulations (e.g. regulations covering Cosmetics, Biocidal Products, Food and Feed as well as food contact materials, etc. should also be addressed) and the OECD WPMN Sponsorship and WNT Test Guidelines Programmes. FOPH will be the pivotal link with the activities of WP 7. NRCWE will concentrate on interacting with the Danish NanoNetwork and on establishing research cooperation with the Danish Nanosafety centre. INRS, in addition to providing an interface with ANSES and the French Labour Ministry, will integrate input from the OECD WPMN SG 6 (Cooperation on Risk Assessment) and SG 8 (Exposure measurement and Exposure Mitigation) with a particular focus on occupational safety and health. TUKES will collaborate closely with nanocellulose industry and with the Nanosafety Centre (coordinating EU nanosafety research) at the Finnish Institute of Occupational Health, who are also partners in WP4 and WP5. VN will bring a direct feedback on industrial needs, areas of interest and research, in particular from SMEs. ISS will exploit the already existing close cooperation with the National Coordinator (Ministry of Health), in particular within the implementation of REACH and CLP regulations for which the NC is the Competent Authority, maintaining also the dialogue with national stakeholders. ENEA will exploit its participation in national and international networks in the field of REACH regulation and LCA (ECHA committees, SEAC, SETAC, National REACH Helpdesk, OECD working groups, Italian LCA network and other) for identifying representative stakeholders to be consulted. BfR will play a similar role within the German regulatory community of experts. TEKNIKER will contribute in regulatory issues related with the use of nanoparticles in lubricants, in relation to REACH and ECOLABEL definition.

(Lead: JRC, contributors: RIVM, AIT, NRCWE, FOPH, ISS, ENEA, TUKES, VN, INRS, BfR, TEKNIKER, TEMAS)

2 Description of work & main achievements

2.1 Summary

This document presents the outcome of a *consultation* with representatives of regulatory authorities and other stakeholders regarding the prioritization and refinement of the initial set of key questions and issues in the area of regulatory toxicology and risk assessment of nanomaterials, which are to be addressed by the NANoREG project. The information was mainly gathered via the REACH Competent Authorities Subgroup on Nanomaterials, the NANoREG National Coordinators and, towards the end of 2013, through the internal European Commission Interservice Group on Nanotechnologies.

The main objective of this consultation was to ensure that NANoREG stays focused on the issues that regulatory authorities are facing and on the information they need when assessing risk of nanomaterials and deciding on risk management measures.

These identified regulatory issues and questions will guide the research to be carried out within NANoREG. This research will provide means for (partially) answering the questions and generating the information that is critically needed by regulatory authorities and policymakers.

Results of this consultation will be shared with the NANoREG advisory boards and, together with the results of Task 1.2, will form the main basis for the work under Tasks 1.3 and 1.4. This document is the main deliverable of Task 1.1 (D1.1). This task remains active and is closely linked with Tasks 1.3 and 1.4, to keep pace with both scientific and regulatory developments. Accordingly, during the project, updates of the list of questions/issues are anticipated. It cannot be discarded that some questions/issues may be identified too late for resolution within the timeframe of NANoREG.

In this document, more insight is given on how the list of policy issues identified at the time of preparing the NANoREG project proposal match (or do not match) the questions that regulators need to address in their actual work. New policy issues have been identified in some of the national kick-off meetings (see Table 6).

The results of this consultation confirm that the selected themes and questions/issues made by the NANoREG consortium were accurate and relevant. However, a number of additional questions have been indicated as priorities during the consultative process: the need for further explanation of the meaning of the questions and more indications on what is expected from the researchers seem to be needed. *An evident lack of exposure-related* questions in a context of risk assessment was detected.

Table 5 (end of section 2.6) shows the outcome of the consultation: an updated set of questions to be addressed by NANoREG. This constitutes the actual deliverable of the activities described here.

There will be the need to re-assess these questions at some instant in the execution of NANoREG, to decide whether they can be addressed with the remaining NANoREG time and resources available, or some of them will have to be looked into in a possible NANoREG II.

2.2 Introduction

The intention of the NANoREG project is to i) analyse the applicability of current testing and assessment instruments to manufactured nanomaterials (MNM), ii) suggest an overall framework for testing and assessment of MNM and iii) a tool box and other instruments to implement such a framework. Work package 1 (WP1), "Scientific answers to regulatory issues", defines the project's desired outputs. It collects and defines the regulatory issues/questions to be addressed by the scientific work packages (WPs) and will deliver the framework and the toolbox.

The elaboration of the framework and tools relies on the success of other WPs to address the key questions/issues identified by WP1. The questions originate from issues that the regulatory authorities are facing and their information needs when assessing risk of nanomaterials and deciding on risk management measures. The questions define the work and help to ensure that NANoREG stays focused on the actual needs so the project delivers results reflecting the actual regulatory needs.

The scientific WPs of the project have planned their initial work around the first set of general questions and demands from authorities, which was preliminarily identified during the preparation of the NANoREG proposal. The set is based on e.g. the RIPoN[3] 2 and 3 projects, the recommendations of EU Scientific Committees and opinions of several national and international regulatory agencies. The questions and issues relate to regulatory environmental and human toxicology and risk assessment of nanomaterials.

[3] RIPoN = REACH Implementation Project on Nanomaterials

Of course, policy discussions are also based on factors that are not in NANoREG's scope. In this sense, the set of questions is an element for the policy discussions and it will not, by itself, lead to definitive answers or replace the political debate.

To avoid overlooking any crucial questions or duplication and replication of work already carried out in other current or earlier projects, Task 1.1 must validate and refine the initial set via *consultation* of partners, national project coordinators and regulators. This consultation allows developing new or updated questions for NANoREG. The validation is also based on an initial gap analysis (Task 1.2, D1.2) performed within WP1 during the first months of the project.

The original plan of the project foresaw that the consultation with stakeholders would take place in a dedicated workshop at M4 (D1.1). However, given the complexity, variety of issues, the short time available and the huge increase of involved stakeholders, it was agreed with the Management Committee to organise a *virtual workshop* in which the involved partners would report on the inputs from their national coordinators and other stakeholders' contacts. This information forms the basis of an updated set of issues/questions to be addressed by the scientific WPs. As Task 1.1 will run during the whole project, there will be further occasions for consultations at later stages, in addition to the workshops organised by WP7 and the feed-back workshop due at M22 (D1.5).

This document presents the process and reports on the first consultation with representatives of regulatory authorities and other stakeholders regarding the prioritisation and refinement of the initial set of questions and issues. The information was mainly gathered via the REACH Competent Authorities Subgroup on Nanomaterials (CASG Nano), the NANoREG National Coordinators and, towards the end of 2013, through the internal European Commission (EC) Interservice Group on Nanotechnologies (ISG Nano).

Further consultations are foreseen during the project and it can thus be anticipated that the results presented here will be regularly updated.

2.3 Initial set of questions

The initial set of key issues/questions defined at the start of the project (and listed in the DoW) are presented in Table 1, which gives an overview of these questions relevant for regulators per domain.

As the initial focus of the project proposal was on regulatory (eco)toxicity testing for hazard identification and characterization, some questions on exposure and risk assessment were not included in the initial set. These are among the issues that, as mentioned later in this document, regulators would like to see included in the project activities.

Table 1: Initial set of key issues or questions from the perspective of regulatory authorities, as included in the NANoREG project proposal and DoW.

No	Issue/question
1	***Measurement and characterization:*** How can MNMs be identified for the purpose of risk assessment as well as according to the EU definition of MNMs?
2	***Identification:*** Is a MNM (particles, fibres) always a MNM? Or are there circumstances that result in MNMs being transferred into something which does not fit into the EU definition of MNMs?
3	***Metrology and dose metrics:*** Which metrics (metrology) should be used for MNMs in regulatory toxicology?
4	***Extrapolation***: 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'?

5	***Persistence and long-term effects:*** Will MNMs accumulate in man, the environment and environmental species and what are the driving forces?
6	***Kinetics and fate:*** To what extent is the dosimetry for MNMs (e.g. deposition, biodistribution) different from the bulk material?
7	***Kinetics and fate:*** What are the options to extrapolate information on these aspects from bulk material or different sizes of the same chemical to the NM range?
8	***Mode of action:*** What are critical characteristics of MNMs that need to be considered to develop safer MNMs?

The short list presented in Table 1 is actually a condensation of an extended list of key issues and questions identified by NANoREG on the basis of the conclusions of the RIPoN 2 and 3 projects, the recommendations of the EU Scientific Committees and opinions of several national and international regulatory agencies. The extended list is presented in Table 2 and was supplied to the regulators during the consultation as background information to help them in formulating new questions. It was also used to reformulate the initial questions based on the feedback received.

Table 2: Extended list of key issues and questions identified by NANoREG at the time of approval of the project proposal.

Extended list of key issues and questions
Characterisation:
Generation of information on properties, including when MNM occur in 'complex matrices' (i.e. tissue, soil, sediment, biological fluids…). This includes what is the stability of MNMs including coatings, aggregates in both the test system (solubility issues) as well as during storage and how should be assessed.
1. How can MNMs be identified for the purpose of risk assessment as well as according to the EU definition of MNMs? Provide guidance.
2. What are the characterization needs to determine the physical properties driving (eco) toxicity for MNMs at any stage of the life cycle based on existing knowledge? What are the major gaps in knowledge and how can these be reduced within the NANoREG project duration as well as beyond?
3. What methods (SOPs) are available to address the characterization needs and what needs to be developed to be able to apply this in a regulatory setting? How can these be used for designing safer MNMs?
4. How should surface modifications of MNMs be determined?
5. Is a MNM (particles, fibres) always a MNM? Or are there circumstances that result in MNMs being transferred into something which does not fit into the EU definition of MNMs? What examples can be provided and how will this affect exposure assessment?
6. What are appropriate reference materials for which route of exposure and toxicity tests?
7. What are appropriate procedures to prepare samples for testing in a regulatory setting (considering all properties (physico-chemical, toxicity and ecotoxicity) and all relevant routes of exposure) that can be transferred in to testing guidelines? Develop SOPs for regulatory purpose including test for solubility. Assessments in various appropriate media.
Metrics:
Related to toxicity characterisation and of key importance for the entire risk/safety assessment process:
8. Which metrics (metrology) should be used for MNMs in regulatory toxicology? Are these the same for all types of MNMs? What is a minimal set of physical (and/or chemical) characteristics/metrics that should be available for risk assessors within the context of regulatory toxicology
9. What is a minimal set of physical (and/or chemical) characteristics that should be available for risk assessors within the context of regulatory toxicology?
External and internal exposure assessment throughout the life cycle:
10. What are situation in which high NM exposure can occur (using different metrics, consider also release of MNMs from a matrix and scenario analysis)?
11. Will MNMs accumulate in man, the environment and environmental species? What are properties that promote accumulation and degradation? To what extent can accumulation and degradation due to long term exposure be extrapolated or predicted from short-term exposure studies?
12. How should exposure be assessed in practice? Consider measuring and modelling
13. Does analysis of MNMs life cycle differ compared to 'regular' chemicals? Do we need to be concerned about recycling? Is there evidence that waste needed to be treated with special care?

14. To what extend is the dosimetry for MNMs (e.g. deposition pattern upon inhalation, biodistribution) different from the bulk material and what are the options to extrapolate information on these aspects from bulk material or different sizes of the same chemical to the NM range? Will MNMs have different exposure patterns in the body compared to bulk material and what are the main reasons for this different biodistribution pattern? To what extend can biokinetics play a role for extrapolation purposes (for both exposure durations as well as interspecies extrapolation)?
Hazard assessment:
15. Can MNMs be grouped according their mode of action in relation to specific physical and chemical properties and what are the common denominators (e.g. asbestos like fibres (HARN), hydrophobic, redox activity related to surface)?
16. For which (groups of) MNMs can threshold (no-adverse-effect) levels be derived for human health and the environment based on existing data?
17. What are the no-adverse-effect levels of long-term (low dose) exposures and can these be derived from short-term (acute and sub-acute)? If not, what kind of information should be generated?
18. Which (additional) nano-specific testing and endpoints identified so far in OECD, RIPoNs and other projects are indeed relevant and necessary for adequate hazard assessment of MNMs in a regulatory context?
19. 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". How does this facilitate read-across, grouping/clustering, development and validation of QSARs, use of historical data, ranking etc. in order to reduce costs and animal testing? What data are lacking to perform such an assessment
20. What new testing guidelines and testing strategies (including decision tree approaches) for toxicity testing for MNMs can be suggested? How can these be validated and in what regulatory settings can these be applied?
21. How should surface modifications of MNMs be considered in safety assessment? How does surface modification change the intrinsic toxic properties and biodistribution?
Risk assessment for risk management options:
22. What can be a long term, new/novel (?) testing strategy to support environmental and health impact considering the rapidly growing number of MNMs and the desire to bring a product fast to the market?
a) For reducing hazards by MNMs and (safer) product design
c) For minimising/eliminating exposure for MNMs with no/low hazard thresholds or when hazards and risks are uncertain or unknown
23. Is there is a need for a new approach to deal efficiently with coated MNMs or nanocomposites, how will this differ from existing approaches?
24. What are critical characteristics of MNMs that need to be considered to develop safer MNMs?

2.4 Consultation (virtual workshop)

A letter was prepared and addressed to the stakeholders (via the National Coordinators) and regulators (available in NANoREG files) requesting them to provide feedback on the questions/issues to be addressed by NANoREG by:

a) Reviewing the list of key questions in Table 1 (initial set of questions) and identifying whether any additional critical issues were not addressed,

b) Rating all the questions from 5 = very important to 1 = nice to know, to get some feeling for prioritization,

c) Examining the extended list (Table 2),

d) Where relevant, suggesting additional missing questions and issues to Table 1.

All partners involved in Task 1.1 activated their corresponding contacts network asking for feed-back on these requests. The targeted letters were sent to the members of CASG Nano, as well as to the NANoREG project National Coordinators, in the latter case via the responsible partner in WP7. The deadline for responding was 17 June 2013, while indicating that possibilities for commenting at later stages would also be possible. Further opinion was sought through the EC's ISG Nano in October 2013 and received from several services by 15 November 2013.

2.5 Received feed-back and Discussion

Responses were received from twenty four stakeholders or regulators (see 2.7 for a list of respondents). The answers varied in comprehensiveness and detail: a simple score allocation without any further details, commented ones, some with requests for clarification, and long very detailed comprehensive review tables. Some respondents provided no indication of priority for some items or optional priorities depending on different interpretations of the questions. Others provided no prioritisation for any issue/question. All the responses were compiled, reviewed and taken into consideration for the following description and discussion.

2.5.1 Responses to the initial set of questions

Table 3 shows averaged results of the priorities assigned by the respondents. These results are averages of all respondents combined, independently of the country of origin, status or representativeness of the respondent or of its EU Member State. The scoring method used for priority setting was not very discriminating. All questions are in the high end of the priority scale. This may indicate that a good selection was made by the NANoREG team (only one respondent indicated some doubt about the appropriateness of the complete set of questions without providing a full alternative set).

Hence, only a very generic trend could be distinguished and the results do not provide enough discrimination to assign real priorities. Rounding to the integer number shows that question 1 seems to be the major perceived priority, then questions 2 to 8 form a cluster around 4 points, where question 2 seems to be slightly less interesting.

In addition to the possibility of a good initial selection of question/issues and the scoring method used, other explanations are possible for the flatness of the overall result, which can also be e.g. due to the general scarcity of definitive answers to many important questions. The outcome confirms that the always stated high priority of thorough and accurate characterisation of MNM is also currently perceived as one, if not *the*, bottleneck for MNM assessment. Additional explanations can be inferred from the comments that accompany some of the responses. The close interlink of the different issues from a perspective of RA and RM seems to emerge as an additional priority levelling factor, although some lack of clarity or poor formulation of the questions from a regulatory language perspective appears to be relevant as well. Indeed e.g. some respondents attempted to give some indications on how to answer the questions presented instead of trying to improve or comment the question itself, in other cases, it appears that the questions were simply not understood or their interpretation was ambiguous for the respondent. Reformulation of the questions or adding guidance seems important (see sections 2.5.4 and 2.6).

Table 3: Averaged results of the priority setting provided by respondents regarding the initial set of issues/questions to be addressed by NANoREG (scale: 5= very important to 1=nice to know)

Nr	Key Issues or questions	Priority
1	***Measurement and characterization:*** How can MNMs be identified for the purpose of risk assessment as well as according to the EU definition of MNMs?	4.5
2	***Identification:*** Is a MNM (particles, fibres) always a MNM? Or are there circumstances that result in MNMs being transferred into something which does	3.5

	not fit into the EU definition of MNMs?	
3	***Metrology and dose metrics:*** Which metrics (metrology) should be used for MNMs in regulatory toxicology?	4.3
4	***Extrapolation***: 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'?	3.7
5	***Persistence and long-term effects:*** Will MNMs accumulate in man, the environment and environmental species and what are the driving forces?	4.0
6	***Kinetics and fate:*** To what extend is the dosimetry for MNMs (e.g. deposition, biodistribution) different from the bulk material?	4.0
7	***Kinetics and fate:*** What are the options to extrapolate information on these aspects from bulk material or different sizes of the same chemical to the NM range?	3.8
8	***Mode of action:*** What are critical characteristics of MNMs that need to be considered to develop safer MNMs?	4.0

Note: no weighing was applied to the scores given, independently of the status or representativeness of the respondent or of its EU Member State. Some responses contained no indication of priority for some issues/questions. Where the response contained optional priorities for a question, a judgement was made on whether to use an average of these options or the most relevant one according to NANoREG interpretation.

2.5.2 Responses to the extended list of questions

Due to the broadness and heterogeneity of the received responses, it is not possible in this report to describe and comment in detail each and every comment received. Instead, a general view and collation of the opinions expressed by the respondents is presented.

Some respondents attempted a similar simple and numerical prioritisation as done for the previous set, while others discussed the relevance of some questions and/or their relationship internally to the list and with the initial set of questions/issues.

As for the initial set of questions (Table 1), the simple scoring system was used by a very limited number of respondents, thus reducing its significance. In some cases the aim of the consultation was misunderstood and misinterpretation or lack of understanding of the questions themselves was apparent. Reformulation of some of these additional questions and/or adding some of them to the initial set seemed necessary, as observed in section 2.5.4 and concluded in section 2.6.

2.5.3 Proposals for additional questions

Only a small number of respondents provided additional questions or attempted better reformulations of the proposed ones. This input, as indicated later was also used in reformulating the questions or developing new ones.

2.5.4 Interaction with T1.2 - D1.2 Gap Analysis

T1.1 interacted with Task 1.2 / D1.2 "Gap Analysis" during the preparation of this report. Table 4 is taken from the report on D1.2. It clearly shows that the initially set of questions actually addresses most of the main questions relevant to regulators, but not all of them. Indeed, as D1.2 highlights, questions on e.g. exposure are missing. As the wording used in the initial set of questions (see the literature references in D1.2) did not fully reflect the current policy issues in a regulatory language, but rather used a scientific language, some respondents missed the link between the questions and real regulatory needs. Actually, the initial set of questions has to be regarded as a first translation from questions relevant to regulators towards questions relevant to scientists.

In addition, as several of the respondents to the consultation of Task 1.1 have also indicated, none of the questions of the initial set specifically addresses exposure and risk assessment. Scientific knowledge on this topic is especially useful for the last five policy issues. The link between the policy or regulatory issues and the essential scientific knowledge and data needs to be clearer and needs continuous attention throughout the whole project duration.

Table 4: Policy issues addressed by the initial set of questions

Initial set of regulatory questions → **Policy issues* ↓**	How can nanomaterials be **identified** for the purpose of risk assessment as well as according to the EU definition of nanomaterials?	Is a nanomaterial (particles, fibers) always a nanomaterial? Or are there circumstances that result in nanomaterials being **transferred** into something which does not fit into the EU definition of nanomaterials?	Which **metrics** (metrology) should be used for nanomaterials in regulatory toxicology?	What guidance can be provided on how to decide when **information** from different forms of nanomaterials (or from the bulk material) can be **'re-used'**?	Will nanomaterials **accumulate** in man, the environment and environmental species and what are the driving forces?	To what extent is the dosimetry for nanomaterials (e.g. deposition, **biodistribution**) different from the bulk material? What are the options to **extrapolate** information on these aspects?	What are **critical characteristics** of nanomaterials that need to be considered to develop safer nanomaterials?
Implementation of a harmonized definition within all regulatory frameworks	✓	✓	✓				
Timely evaluation of both existing and new nanomaterial				✓			
Tonnage level/threshold for registration within REACH			✓				
Registration of nanomaterials and products for market surveillance	✓						
Labelling of nanomaterials and products for consumer transparency	✓						
Testing protocols and dossier requirements				✓	✓	✓	✓
Lack of information on workers protection		✓		✓	✓	✓	✓
Risk governance approaches to deal with uncertain and complex risks	✓						✓

* These policy issues are derived from several recent policy related documents (Azoulay, Buonsante, Cameron, & Vengels, 2012; Bosman, 2013a, 2013b; Christensen, 2012; Christensen & Larsen, 2013; EC, 2012; Fleischer, Jahnel, & Seitz, 2012; KEMI, 2013; UBA, 2013). Annex 2 gives more insight in which NANoREG work package the regulatory questions will be addressed. [See full literature references in D1.2]

The gap analysis (NANoREG D1.2) concludes that:

- Most importantly the key characteristics or properties that influence the release, exposure, behaviour (fate and kinetics), effects (hazards) and thus the subsequent risks of nanomaterials need to be identified.
- Knowing which characteristics determine the release, exposure, behaviour and effects of nanomaterials in the environment and humans, will provide information on when nano-specific risk assessment is necessary and which information is needed to allow such risk assessment.
- In addition, standardized methods to determine the key characteristics are needed.
- Finally, knowledge on these characteristics needs to be implemented in nano-specific risk assessment strategies and approaches, including extrapolation, read across and grouping approaches. These strategies and approaches need to be verified by experimental data obtained from standardized exposure measurements, kinetics and toxicity studies

2.5.5 Analysis of the received feed-back

All the comments and suggestions for priorities received were compiled and grouped according to the issue/question they addressed. A non-weighted assessment of the assigned priorities and accompanying comments was performed using expert judgement and taking into account the information presented in the previous sections. This was attempted for each issue/question independently and, as well, in combination for the cross linked questions indicated by the respondents. The aim was to be as comprehensive as possible and to find wording that accommodates most of the respondents' comments. Input from other sources was also considered, as for the conclusions of the NANoREG UK Launch 26 June 2013. The European Chemicals Agency (ECHA) was also informally consulted during the preparation of this deliverable. This assessment resulted in an updated set of questions which is presented in the next section (Table 5). Based on the information received, the relevant policy issues could be expanded resulting in the preparation of a new table of policy issues vs. NANoREG questions, also presented in the next section (Table 6).

2.6 Conclusions and recommendations

The scoring system used for priority setting is rather general and for future exercises a different system should be used. The actual usefulness of a scoring system still needs to be debated and, if needed, the system shall be re-designed and agreed upon by WP1.

The wording used in the initial set of issues was not optimal for the targeted readers, as it did not fully reflect the current policy issues in a regulatory language so some respondents missed the link between the questions and real regulatory needs. Actually, the initial set of questions has to be regarded as a first translation from questions relevant to regulators towards questions relevant to scientists. Furthermore, this limited set contained components of prioritisation and condensation of the extended set, making them not fully understandable from their formulation. The questions should have been better explained to the consulted stakeholders and this needs to be improved in future consultative exercises.

It would be useful to add some explanatory text or expand the questions to better show the relationship with regulatory needs. In addition, some additional clarifying text or guidance on what is expected to be taken into account or included in the answer might be useful.

The most outstanding issue identified was the apparent lack of exposure-related questions in a context of risk assessment.

The resulting proposed *refined set of questions* is shown in Table 5. In addition to providing supplementary explanations on what is intended for each question, Table 5 includes additional questions and issues and, as such, constitutes an expansion of the initial set of questions. It may not be possible to address such an extended set within the NANoREG timeframe and with its resources. There is a need to re-assess the feasibility of answering these questions by the project to evaluate whether some of them should be addressed in a possible NANoREG II.

Based on the input received a new table illustrating the relationship between (additional) policy issues and (additional) questions has been made (Table 6). The actual policy discussions are also based on factors that are not in the scope of the project. In this sense, the set of questions proposed in Tables 5 and 6 is an element in these policy discussions and it will not, by itself, lead to definitive answers or replace the political debate.

Most of the key questions relate to the original nanomaterial and its intrinsic properties. This is also the approach under REACH that has the broader intent to cover all downstream uses and hence also products. The NANoREG project should keep in mind actual product safety issues which are addressed in the value chain case studies and are also relevant for consumer exposure, recycling and waste treatment (key question 13, Table 5). The consumer safety approach and socio-economic questions are relevant for the project, too.

Table 5: Proposed refined set of key questions from a regulatory perspective to be addressed in NANoREG (substituting the questions/issues listed in both Tables 1 and 2).

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No	Key questions from a regulatory perspective
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? These questions (closely related to Q1) refer to developing cost effective standard methods, detailed protocols and reference materials both for calibration and analysis of both pristine materials and materials in relevant media or complex matrices throughout the complete life cycle of the nanomaterial. they also refer to whether different categories of characterisation methods (varying e.g. in precision and accuracy) can be defined: Could an "intelligent characterisation strategy" be defined?
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? As recommended by several committees and guidance, notwithstanding e.g. the OECD GSPD, NANoREG should use mass, particle numbers and surface area (as far as possible) to characterise dose. The data generated within the project will contribute to the development of a body of comparative data (e.g. shape and aspect ratio should be examined when appropriate for the MNM). Using this comparative data, NANoREG should examine which metrics are the most appropriate depending on the different types of materials and media involved, as well as the (eco)toxicological effects and exposure to be assessed in the Risk Assessment process.
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? Take into account the relation with the following questions.
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? Relate the information with, for instance, the following objectives: • To perform more accurate risk assessment, • To decrease uncertainty (safety factors), • To select, if needed, a second route for acute toxicity testing, • To design additional tests – that are 'affordable' – or to relate to studies that involve exposed workers, such as in the silica industry, • To decide on a strategy for further testing (carcinogenicity, reproductive toxicity, etc.).
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)? Consider both measuring and specific modelling for nanomaterials and evaluate the needs for standardisation and validation.
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? How to minimise and structure LCA to avoid ending up with a '1:1 model of the world'? In other words: what is the exposure probability throughout the different life cycle stages of the MNM: production process of the NM itself, releases during the production process of products in which MNM are used, waste treatment, consumer articles, wearing, abrasion,

	etc.? Do waste treatment / recycling processes lead to exposure to NMs that can be hazardous to health and environment? If so, are additional risk management measures required? Do the recycled product / residues loose some value /usefulness due to undesired characteristics?
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 sub-acute)? If not, what kind of information should be generated?
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?

Table 6: Policy issues addressed by the refined set of questions.

QUESTIONS / POLICY ISSUES	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Harmonised definition within all regulatory frameworks and appropriate testing/measurement instruments for implementation	√	√		√	√											
Timely evaluation of both existing and new nanomaterials	√	√	√	√	√	√	√	√	√	√	√	√	√	√		
Tonnage level/threshold for registration within REACH				√				√	√			√	√	√	√	
Registration of nanomaterials and products for market surveillance	√	√	√	√				√		√	√	√	√	√		
Labelling of nanomaterials and products for consumer transparency	√	√	√	√				√		√		√	√	√		
Testing protocols and dossier requirements		√	√		√	√	√	√	√	√	√		√	√	√	
Lack of information on workers protection					~~√~~		√	√	√	√	√	√	√	√	√	
A more coherent and transparent regulatory landscape across Europe and possibly worldwide	√	√	√	√	√	√	√		√	√	√	√		√		
Risk governance approaches to deal with uncertain and complex risks	√								√							
Lack of impartial, well balanced and authoritative communication of the knowledge on safety of MNMs specifically addressed to different stakeholders															√	√

2.7 List of respondents

1. AT BioNanoNet. See http://cms.bionanonet.at/content/view/2/3/lang,english/
2. AT BMVIT: Bundesministerium für Verkehr, Innovation und Technologie
3. BE MILIEU: Leefmilieu - Risicobeheersing
4. CH TEMAS: Erfahrung und Expertise aus Wissenschaft, Technologie und Management (on behalf of the Swiss NC),
5. DE BAuA: Bundesanstalt für Arbeitsschutz und Arbeitsmedizin
6. DE UBA: Umweltbundesamt
7. DE BfR: Bundesinstitut für Risikobewertung
8. DE BNN: Bundesverband Naturkost Naturwaren

9. DE: Bundesministerium für Wirtschaft und Technologie
10. DK HMA: Sundhedsstyrelsen, Danish Health and Medicines Authority,
11. DK EPA: Miljøstryrelsen, Danish Environment Protection Agency
12. DK NRCWE: National Research Centre for the Working Environment,
13. FI TUKES: Turvallisuus- ja kemikaalivirasto, Finnish Safety and Chemicals Agency (Finnish NC)
14. IE TCD: Trinity College Dublin
15. IT VN: Veneto Nanotech
16. NL Min I&M: Ministerie van Infrastructuur en Milieu
17. PT ISQ: Instituto de Soldadura e Qualidade
18. SE KEMI: Kemikalieninspektionen, Swedish Chemicals Agency
19. UK CEH: Centre for Ecology and Hydrology
20. UK HSE: Health and Safety Executive
21. UK NPL: National Physical Laboratory
22. UK NanoKTN: Nanotechnologies Knowledge Transfer Network,
23. UK IOM: Institute for Occupational Medicine
24. UEAPME: Union Européenne de l'Artisanat et des Petites et Moyennes Entreprises

Services of the European Commission that provided comments in November 2013: Directorates-General for Enterprise and Industry (ENTR), for the Environment (ENV) and for Health and Consumers (SANCO).

3 Deviations from the work plan

The initial plan of the project foresaw that the consultation with stakeholders would take place in a dedicated workshop at M4 (D1.1). However, given the complexity, variety of issues, the short time available and the huge increase of involved stakeholders, it was agreed with the Management Committee to organise a virtual workshop in which the involved partners would report on the inputs from their national coordinators and other stakeholders contacts and this information would be consolidated and be the basis of a report on an updated set of issues/questions to be addressed by the WPs 2-6. As Task 1.1 will run throughout the project, there will be further occasions for consultations at later stages, supplemented by the workshops organised by WP7 and the feed-back workshop due at M22 (D1.5). Moreover, it seemed more appropriate to consider the present report of a (virtual) workshop as D1.1, rather than the workshop itself. It is clear that the report of a workshop – either face-to-face or virtual, as in this case – can only be prepared and delivered after the workshop took place. One month after the workshop seemed a reasonable time scale and consequently the D1.1 title and the corresponding delivery date have been changed. Thus, D1.1 has been renamed "*Report on a Virtual Workshop to identify, formulate and prioritize issues/questions*", with and updated delivery date of 31 July 2013 (end M5).

4 Performance of the partners

All partners fulfilled their tasks in satisfactory time and quality.