ProSafe White Paper – Recommendations elaborated and Questions on actions, initiatives and ideas to achieve future-proof regulation of nanomaterials

The Dutch Ministry of Infrastructure and Water Management will host the Policy Conference **A Future-proof approach to Nanomaterials**, on 17 and 18 April 2018 in Rotterdam. During the conference participants will discuss initiatives and proposals for collaboration whilst creating alliances for joint actions. The objective of the conference is to enhance further cooperation on nanosafety and regulation. A major outcome would be to facilitate / stimulate policy proposal preparation at European and national levels.

As time is limited, we have prepared two key questions in order to enable an efficient and structured discussion, listed at the end of this document. The questions follow the White Paper recommendations, drafted following the NANoREG and ProSafe projects, which draw on the current state of the art in terms of research and national and European nano-policies developed over the last decade.

A summary of each recommendation with a short explanation of the context and relevance is given below.

1. **Accelerate adapting the existing OECD chemicals test guidelines for applicability to nanomaterials**.
   The OECD Working Party on Nanomaterials (WPNM) needs to consider adapting their existing working programme and undertake an ambitious schedule to adopt and implement the harmonisation recommendations laid out in the ProSafe Joint Document and various NANoREG deliverables. EC Member States should commit themselves to contribute to the achievement of such an ambitious programme. The "Malta project" has become a focus for modifying the TGs in line with the proposed REACH annex revision in 2020. However many more TGs and missing guidelines have been identified, meaning that increased collaboration between EU members of the OECD is desirable.
   Scientific relevance: Using OECD test guidelines will standardise testing procedures worldwide and would ensure results that are relevant to determine hazard.
   Policy relevance: Relevant, validated and globally endorsed test guidelines contribute to the availability of data for efficient and adequate risk assessment. Acceptance of data under the OECD MAD treaty rules harmonizes data requirements whilst removing secondary trade hindrances. Adapting existing guidelines can be done relatively quickly (1-5 years). This is a short-term perspective, and can be considered work in progress.

2. **Identify which data sets and descriptive test guidelines are lacking, specifically for nanomaterials, and develop these guidelines.**
   Information on various endpoints is needed for the purpose of grouping and read-across, some of which might be specific for the hazard properties of nanomaterials. The Nano Safety Cluster (or a novel EU "Regulatory Nano Safety Cluster" to be established with support of the MS) should indicate what novel tests can be developed to generate reliable data to enable grouping and read-across, in addition to currently required datasets.
   Scientific relevance: with time grouping will depend on big data which can only be derived from new data sets.

Policy relevance: Using relevant, validated and globally endorsed test guidelines will ensure that high quality, reproducible data is generated and made available for efficient and reliable risk assessment. Developing new guidelines will take more time, but is equally necessary. This is a Mid-term perspective.

3. **Implement a project in which properly characterized nanomaterial(s) is tested using approved testing methods evaluating all relevant types of toxicological effects**.
   The European Commission (RTD) should initiate (at least one) major demand-driven project to generate nanoEHS data for modelling purposes. Such a project should include adequately characterized materials with different properties (homologue and analogue series) including appropriate assays for examining the interactions of endpoints. Materials that should be included in such a project are (1) industrial, manufactured materials, (2) well-characterized reference materials of various size, shape, aspect ratio, surface charge, and surface functionality and (3) standard materials for calibrating different assays and measurement tools.
   Scientific relevance: Combining material characterization, adequate testing and all endpoints provides a reality check and opportunity for learning. The problem with most assays is the lack of well-structured, high quality datasets. Most research project data sets originate as the result of hypothesis driven approaches, lacking the rigorous methodology which data driven (QSAR) approaches have leading to regulatory relevant data.
   Policy relevance: Model development and insight in the "Mode of Action" is crucial for read-across and grouping, and depends on data quality and availability. A specific project generating quality data for modelling purposes would provide legitimacy for the methodology of applying such a new, systematic approach, and will identify what research direction is needed from a regulatory point of view. Short-term perspective. (1-5y)

4. **Enforce open access to all relevant characterization and toxicological information**.
   The European Commission and Member States (MS) should introduce and enforce an obligation to share the results of their EU or nationally-funded nanosafety research as a condition for funding project partners. Such an obligation goes beyond the rules on Open Access to Scientific Publications and Open Access to Research Data in Horizon 2020. The obligation should include uploading experimental nanoEHS data in a standardised format (e.g. ISA-TAB-Nano). The only valid exemption to this rule would be nanosafety information generated for or by industry with a clearly competitive character. The EC Standard Grant Agreement and the Consortium Agreement should be modified with respect to Intellectual Property Rights (IPR) and confidentiality. MS will have to adjust their procurement rules as well, since 65% of nano-safety expenditure in the EU is spent by individual MS.
   Scientific relevance: More testing results of well-characterised nano-materials enables quality control and reduces the need for testing specific nano-materials if comparable characteristics are to be expected. One major benefit is that the so-called 0-effect test study results will become available for regulatory purposes.
   Policy relevance: More data increases the possibilities of better quality control, avoidance of animal testing, improved risk modelling, grouping approaches, QSARs, and can eventually lead to better risk management, and lower costs for governments, producers and society. It also contributes to more transparency. Data sharing and utilisation in models is a "conditio sine qua non" for Safe by Design policy approaches Mid-term perspective. (5-10 y).

5. **Guarantee the long term storage, free access, quality assessment and comparability of research data on nano materials.**
   The European Commission supported by MS should be responsible for allocating resources for the development and maintenance of a sustainable system for advanced nanoEHS data management, including providing or organising structural funding. This advanced system should include the further development and management of ontology, data entry provisions, facilities for storing and

querying data, and providing an expert check on data quality (data curation). This latter facilitates and provides quality control on the weight of evidence and the regulatory appropriateness of experimental data (test design).
Scientific relevance: Improved availability of an increasingly large body of relevant, quality assessed data.
Policy relevance: The need to repeat solid research that has been done in the past will increasingly be reduced, so the available funding can be directed at new data creation. Short-term perspective.

6. **Coordinate future publicly funded nanosafety research to produce results relevant for regulation.**
   Where possible, calls for nanosafety projects should be far more specific in giving clear instructions to ensure that data and results generated are of a type and form which allows their use in topics of regulatory relevance, such as choice of materials, test methods to be applied, SOPs and data management. The yet to be formed Regulatory Nano Safety Cluster is foreseen to play a role in defining such conditions.
   Policy relevance: The responsibility of public administration is to create the regulatory conditions so that nano materials can be safely managed. Government spending should assist it in its mandate, and well directed funding will increase its efficiency. Mid-term perspective.

7. **Set Occupational Exposure Levels for which applicable standardised derivation method exists**.
   The European Commission (DG-EMPL) should initiate a concerted EU - MS effort in setting occupational exposure levels (OELs) for which standardised methods on how to derive these OELs exist. This should include guidelines for studies to be employed, both for conducting risk assessment determinations as well as for setting OELs. The Scientific Committee on Occupational Exposure Limits (SCOEL), operating under DG-EMPL is the designated authority for this task.
   Policy relevance: Occupational exposure generally is much higher than other exposure pathways, but since measures to reduce occupational exposure are more effective, setting and enforcing EOLs is a very efficient way to reduce total risk and reduce societal concerns on nano material use. Mid-term perspective.

8. **Legally define the term nano material**.
   The European Commission and Member States should include a legal definition of nanomaterials in REACH, and should provide a more robust legal basis for additional nano-specific requirements. REACH Annexes and guidance documents should give clarity on the method(s) that can be applied for determining whether a material meets this definition.
   Policy relevance: Creates clarity when additional nano-specific information can be requested for assessment proposes avoiding legal debate and the cost of unforeseen requirements. Short-term perspective, work in progress.

9. **Harmonize groupings and principles for grouping across different institutional settings**.
   The schemes for substance identification and substance specific profiles, irrespective of whether it is a manufactured nanomaterial or not, should be modified as suggested in NANoREG deliverable 2.12. The morphological categorization under REACH should be modified and aligned with the already developed (ISO) schemes and the OECD Guidance on grouping.
   Policy relevance: Harmonized grouping avoids inconsistency, confusion, and increases efficiency. The EU might be an effective arena to develop guidance on grouping. Mid-term perspective.

10. **Add physical characteristics and surface chemistry to the information requirements**.
    Information on particle size distribution, shape, porosity, and surface chemistry should be added to the information requirements. The recommendations given in REACH Guidance Documents on physico-chemical characterization endpoints should be adjusted according to the findings

presented in NANoREG Deliverable 2.12 and underlying deliverables.
Scientific relevance: The physical characterization, including the coating, provides information on whether a toxicologically different behaviour is to be expected and if it is necessary to request information on the results of toxicological tests.
Policy relevance: Nanomaterials undergo changes during their production, incorporation into a product and product use, with resultant changes to their hazard and exposure potential. To describe all characteristics of a nanomaterial during its life cycle would result in very large and expensive dossiers while the relevance for risk management would be very limited. Testing must be restricted to aspects where there is reason for concern (concern based testing). Short-term perspective, work in progress.

11. **Exempt nano materials from general information requirements that are not relevant for their risk assessment, but add those requirements that are of specific relevance**.

    The possibility for waiving information requirements as laid down in Annex XI of REACH for aquatic toxicity testing of non-soluble manufactured nanomaterials should be introduced as a general rule in the REACH guidance document(s). Testing accumulation in aquatic systems should focus on benthic organisms.
    Scientific relevance: Several of the standard REACH information requirements are not relevant for nanomaterials or cannot be applied due to the absence of adequate test methods for nanomaterials. On the other hand, some relevant endpoints are missing in the list of required information.
    Policy relevance: Well-tailored (nanospecific) information requirements contribute to adequate risk assessment whilst the resulting efficiency improvement reduces opposition from industry. Short-term perspective.

12. **Ensure that tests are designed to produce information that is fully relevant for risk assessment purposes**.
    Regulatory Agencies should develop (or update) guidance documents on test methods generating experimental data to ensure that the data used for risk assessment, always has regulatory relevance.
    Scientific relevance: Currently, tests are often performed with a dose range that does not allow the construction of a dose-effect relationship. Toxicity testing should be done according to OECD guidelines and should include relevant species, relevant exposure routes, standardized exposure periods, and relevant environmental compartments.
    Policy relevance: Test results that can be used for valid risk assessment purposes contribute to adequate risk management. They also reduce the number of tests which have to be performed by industry and risk assessors. Considerable societal benefits are expected to result from this, as trust seems to be the ingredient lacking in current regulatory efforts concerning nano-materials. Mid-term perspective.

13. **Determine Mode-of-Action and Adverse-Outcome-Pathways specifically for nano forms which are representative for large groups of chemical substances**.
    The European Commission and Member States should consider initiating a project aimed at determining the Mode of Action and Adverse Outcome Pathways for a number of nanomaterials that are representative for specific groups of nanomaterials. As a bonus, this approach reduces the need for animal testing. Such an initiative could benefit from the experience of the Eurat-1 Project for nanomaterials in cosmetics that was also aimed at getting a better understanding of mechanisms causing potential adverse effects, while developing methods to reduce animal testing.
    Scientific relevance: Will give a better understanding of the mechanisms by which toxicological effects occur, will improve the quality of risk assessment, and will help to avoid misrepresenting models based on animal testing as applied to humans.

Policy relevance: A better understanding of the mechanisms can lead to a reduction in some animal testing, while better risk assessment leads to improved protection of health and the environment. Long-term perspective. (+10 y)

14. **Design, test and implement an approach that allows for the appropriate risk assessment for advanced materials, especially those produced in low volumes**.
Member States and the EC should initiate a (further) exploration and development of possible options for a "future proof approach to risk assessment" which is also applicable to next generation (nano)materials. Possible options that could be considered are concern-based testing on the basis of risk potential as developed in the NANoREG project and the Safe-by-Design approach as developed in NANoREG and ProSafe, and now further explored in NanoReg2.
Policy relevance: The development of small niche products (less than 1 ton/y) of increasingly more complex, advanced nano-materials renders current legislation more and more inadequate. To safeguard health and the environment, the governance of the risks posed by advanced materials must be based on a robust but flexible regulatory framework able to deal with all possible future developments. This also includes a review of the current legislative framework, to make sure that future legislation will adequately regulate complex materials that transcend current legislative categories. It will have to be applied to smaller volumes of individual materials, or to groups based on their mode of action, while allowing for information requirements that take into account concern and existing knowledge. This would lead to considerable societal benefits. Long-term perspective.

Questions for participants

- Are there any actions, initiatives and ideas in your country (nationally or in international cooperation) that are linked to one or more of the recommendations listed above?

- Are there any ongoing national initiatives to address nanomaterials that are <u>not</u> directly linked to one of the recommendations?