Promoting the Implementation of Safe by Design

The ProSafe White Paper

Towards a more effective and efficient governance and regulation of nanomaterials

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ProSafe Project Office

Foreword

The title of this document, “Towards a more effective and efficient governance and regulation of nanomaterials”, summarises in a nutshell the aims, efforts and results of the FP7 project NANoREG and the H2020 project ProSafe, jointly referred to N1P. Both projects were driven by the need to reduce uncertainty in the regulatory assessment of the Environmental Health and Safety aspects of nanomaterials, in order to support a climate where the innovative potential of nanotechnology can be fully exploited.

The results of both projects have led to a document that provides recommendations (the White Paper elements) for policymakers and regulators aimed at a more effective and cost-efficient assessment of nanomaterials in a regulatory context. Amongst others, the recommendations include proposals for what is called “no regret measures” such as further harmonisation of test methods by the OECD, and proposals for a more efficient use of the results of nanosafety projects by improving the data management infrastructure. Other recommendations are aimed at making REACH more applicable for nanomaterials. For the long term, some possibilities for innovation in risk assessment are presented. They are aimed at speeding up the process of risk assessment, reducing costs and reducing animal testing. Finally, the White Paper introduces a recommendation to start thinking and working on more future proof approaches to secure the safety of nanomaterials. Approaches that would also fit next generation nanomaterials.

The recommendations are based on the efforts and achievements of a great number of parties. The almost 90 NANoREG partners from 17 EU Member States and Associated States, Brazil and the Republic of Korea, together with the 11 ProSafe partners provided the scientific and policy related input. The members of the ProSafe Task Force that evaluated over 1000 peer reviewed publications produced the valuable Joint Document that is one of the corner stones of the White Paper. The members of the NANoREG Scientific Advisory Board, together with representatives of Member States and industry, supported both of these projects with critical observations and advice during their set up and implementation. A warm thanks to all of them!

A draft version of the White Paper was distributed in a consultation stage to policymakers, regulators and industry, and the resulting responses were taken into account when finalising the White Paper. The members of the Management Committees of both projects, together with the chair and co-chair of the ProSafe Task Force were consulted at an earlier stage.

The White Paper will be presented to the National Coordinators of the Member States that funded the NANoREG project, the European Commission, and other international bodies. How the recommendations will be used or implemented by these organisations will become apparent over the coming years. An international policy conference to discuss the White Paper would be a logical next step in this context.

The White Paper does not necessarily reflect the opinion of all NANoREG and ProSafe partners, nor of all members of the Management Committees of the respective projects.

To keep the size of this document within reasonable limits, the text often refers to NANoREG and ProSafe documents. Links to these documents (deliverables, factsheets) which are available in the NANoREG and ProSafe Results Repository are given in Annex I of the White Paper.

The ProSafe Project Office

Abstract

The uncertainty regarding the effects and risks of nanomaterials on human health and the environment, and how they should be tested and assessed in the context of current regulations, is clearly holding back the full exploitation of the innovative potential of nanomaterials. To reduce this uncertainty the FP7 NANoREG project and H2020 ProSafe project (jointly referred to as N1P) have made a critical evaluation of methods to test and assess these risks in the context of the current REACH regulation. Where essential methods were lacking, new ones have been developed. For several existing methods, adjustments have been proposed. Possible improvements to the REACH regulation have also been identified in these projects.

The results of both projects have been translated in this White Paper into recommendations for European policy makers and regulators. Part of them have a “no regret” character, meaning that the proposed actions can be considered as necessary, feasible, effective and cost efficient. Examples of such recommendations are the implementation of the test methods developed or adjusted in NANoREG to use at the OECD level, by establishing Technical Guidelines or modifying existing ones. Another recommendation is the introduction of a compulsory requirement that all public funded nanosafety projects must open up and share their all their data and results. The NANoREG project has proven for the first time that this is possible. Concrete recommendations to make REACH better suited for assessing the risk potential of nanomaterials are also given.

The recommended measures proposed for data quality and data management will create a more solid information basis for risk assessment of nanomaterials. When implemented, the recommendations regarding REACH will improve the application of REACH in both a legal and scientific sense. In practical terms however, the application of REACH will remain complex, time-consuming and costly. Besides that, adapting and specifying the information requirements and test methods in REACH for nanomaterials that are now on the market, will not solve the regulatory hurdles for next generation (nano)materials. For this reason, the White Paper also recommends exploring the possibilities of a more future proof approach for securing the safety of (nano)materials. Possible options that are mentioned and to some extent developed in NANoREG and ProSafe are the “Safe-by-Design approach” and a more “Concern-based testing approach” of risk assessment.

It is for the Member States to decide what follow up they will give to the recommendations presented in the White Paper.

Executive Summary

Results of nanosafety research so far

Over the past 15 years there has been a significant global investment in nanosafety research. It has led to a better understanding of the effects of nanomaterials and the mechanisms which cause them. However, it still is difficult, if not impossible to come to unambiguous conclusions regarding the risks of most of the nanomaterials and nano-enabled products in the context of the current regulations.

The main reason for this rather disappointing conclusion is that the research was predominantly "science-oriented" and not "regulatory-oriented". Science-oriented research often results in experimental data that cannot be used in a regulatory context where data have to be well defined, standardised, reliable, reproducible and exchangeable. In this context it is important to note that not all traditional, standardised test methods are fit or relevant for nanomaterials. Additionally, methods specifically designed or adapted for testing nanomaterials are sometimes missing or not yet fully evaluated and harmonised.

A complicating factor why research in the past has not led to unambiguous results is the fact that the potential risks of nanomaterials may vary strongly during their life cycle, as a result of the nanomaterial undergoing major transformations. The hazard potential of pristine nanomaterials created during the production process differs from the effects of e.g. nanomaterials embedded in a coating or nanomaterials absorbed onto organic material in an aquatic environment. The presence of (sometimes high levels of) unintentionally produced nanomaterials (caused for example by abrasion or combustion processes) and naturally occurring nanomaterials (caused for example by volcanoes, rock weathering, etc.) further complicates both the distinction and judgement of exposure-related effects linked exclusively to manufactured nanomaterials. On top of this, a variety of analytical problems linked to aggregation, agglomeration and precipitation of nanomaterials in test media can lead to erratic or non-reproducible results.

Limitations of current regulation

Equally important, experience shows that the current legislation is not sufficiently robust to assess the risks of nanomaterials in an efficient and effective way. The absence of a robust, legal definition of nanomaterials in REACH leads to disputes as to whether specific information should be provided or not. The entry point for the REACH legislation (chemical identity) currently does not sufficiently cover the specific character of nanomaterials for which size, shape, coating and functionality are dominant factors determining hazard properties. Issues mentioned before like the absence of standardised test methods, and differences in hazard potential during the life cycle of nanomaterials lead to the current situation where it is impossible to come to unambiguous conclusions regarding the risk of most of the nanomaterials in a regulatory context.

To a more effective and efficient governance and regulation of nanomaterials

The White Paper proposes recommendations for policy makers and regulators to solve or work around the problems and limitations mentioned above ("the White Paper elements"). The most important ones are summarised below:

No regret measures

√ *Improving data quality and data management*

The availability of harmonised and validated test methods for nanomaterials is a condition *sine qua non* for risk assessment in a regulatory context. They are needed to generate data that are reliable and comparable, and thus can be used and re-used for risk assessment and modelling the effects of nanomaterials. The NANoREG project has developed a great number of test

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methods varying in status from proof of concept to validated, and that now can be made operational for use in a regulatory context.

1. The OECD Working Party on Nanomaterials (WPNM) should consider adapting their existing working programme and undertake an ambitious schedule to adopt and implement the harmonisation recommendations laid down in the ProSafe Joint Document and various NANoREG deliverables. EC Member States should commit themselves to contribute to the execution of such an ambitious programme.
2. The NanoSafety Cluster should take the initiative to select test methods that future nanosafety projects should focus on for further development and application.

In order to establish correlations between nanomaterial properties and the key interactions or endpoints in humans and the environment, sufficient well-defined experimental data on environmental, health and safety effects of nanomaterials (nanoEHS) are needed. Such data can serve as the basis for Quantitative Structure-Activity Relationships (QSARs), models, Adverse Outcome Pathways AOP and read-across. These methods and tools can make risk assessment less time consuming and less costly, and are essential for implementing Safe by Design.

Now, based on the results of the NANoREG project and the Joint Document, it becomes possible to define what intrinsic characteristics of materials are most relevant to determine potential adverse effects. Since reliable test methods have now been developed, it is time to generate these experimental data.

3. The European Commission should initiate (at least one) demand-driven project to generate experimental nanoEHS data. Such a project should include adequately characterized materials that have different properties and include appropriate assays for examining interactions or endpoints. Materials that should be included in such a project are (1) “real-world” materials, (2) well-characterized reference materials of varied size, shape, aspect ratio, surface charge, and surface functionality and (3) standard materials for calibrating various assays and measurement tools.

Apart from the need to improve the quality and comparability of experimental nanoEHS data, the possibilities to use nanoEHS data outside and beyond a project need to be improved. Currently H2020 requires that only data used for peer reviewed publications should be shared. The NANoREG, ProSafe and eNanoMapper projects have created and implemented a system of data management. This includes an agreement on opening up data, standards for data logging, ontology for nanosafety research and a database. This system can be expanded to a data management arrangement that should be used by the whole nanosafety community.

4. The European Commission and Member States (MS) should introduce and enforce an obligation to share the results of 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 (ISA-TAB-Nano logic) way. A 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.
5. 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 a check on data quality (data curation). This last should be aimed at avoiding or repairing reporting errors as well as judging the regulatory appropriateness of experimental data (test design).

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The NANoREG and ProSafe projects have taught us that nanosafety research has to be better linked to the policy and regulatory needs of the EU. Many of the finalised and current nanosafety projects are the result of national or international “Calls” that defined their goals in rather general terms. They often are not specific with respect to research topics that are relevant for using the results in a regulatory context, such as materials to be used, test methods to be applied and data logging. This limits the use of the projects’ results and experimental data for regulatory purposes like grouping and read-across, and for the development of QSARs. A more “top-down” approach, by precisely defining a call with respect to the basic conditions for proposals, or by tendering a well-defined project, would increase the impact of the results of nanosafety projects. Recommendations 2 (NanoSafety Cluster), 3 (generation of quality data) and 4 (advanced data management) are all relevant in this context.

Not only a top-down approach can help in a better alignment to regulatory needs, but more interaction with/involvement of regulatory bodies (i.e. ECHA, EFSA, SCCS, SCOEL) can also facilitate here. These regulatory bodies also need to clearly indicate where they need scientific knowledge or input.

6. 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 NanoSafety Cluster could play a role in defining such conditions.

√ *Harmonised occupational exposure limits*

Bearing in mind that many nano-innovators are SME businesses, as are their downstream users, the most effective and efficient way to manage occupational exposure is by establishing Occupational Exposure Limits (OELs). Several EU Member States are developing or have developed OELs. However, a concerted action between EU Member States coordinated through the Directorate-General for Employment, Social Affairs and Inclusion (DG-EMPL) and using the Scientific Committee on Occupational Exposure Limits (SCOEL) would be quicker, more targeted, and more cost-effective, while keeping the playing field level throughout the EU.

A joint project in setting occupational exposure levels for which standardised methods exist (see Joint Document), with guidelines for studies to be employed for conducting risk assessment determinations as well as for setting occupational exposure levels is strongly recommended.

7. 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.

A realistic REACH for nanomaterials

The present dispute between ECHA and groups of REACH registrants with respect to the information requirements for nanomaterials illustrates that there is a need to create a more solid and unambiguous legal basis for requirements that are specific for nanomaterials. The White Paper recommended modifications partially overlap with already ongoing adaptations of REACH Annexes and guidance documents by the EC and ECHA.

8. 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.

To make REACH more applicable to nanomaterials from a scientific point of view, and to support possibilities for read-across and grouping, the information requirements in the Annexes and related guidance documents should be updated. Grouping and read-across of hazard and

potential exposure data for nanomaterials should be further facilitated in order to increase the efficiency of risk assessment.

9. 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 categorisation should be modified and aligned with the already developed (ISO) schemes and the OECD Guidance on grouping.
10. 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 Deliverables 2.12 and underlying deliverables.
11. 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.
12. ECHA should develop (or update) guidance documents for the use of experimental data to ensure that data used for risk assessment, have a regulatory relevance.

Innovation in Risk Assessment

There is a great discrepancy between the time to market of new (applications of) NMs and the time currently needed for risk assessment to comply with REACH (such as chronic exposure studies). Apart from that, the costs of such tests are also high. Both constraints can be partially reduced by creating a more fundamental understanding of the mechanisms causing adverse effects (Mode of Action; Adverse Outcome Pathways). This makes it possible to predict the effect of nanomaterials on the basis of a more limited set of toxicity data, and to reduce animal testing.

Development of cheaper and faster test methods like *in vitro* High Throughput Screening (HTS) and *in silico* methods can also contribute to reducing the lead time for risk assessment and to reducing costs. It also contributes to the long-term aim to reduce animal testing. With respect to High Throughput Screening the NANoREG project has clearly shown the great potential of this technique (Deliverable 5.7).

13. 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 while at the same time reducing 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.

Exploring a more future proof approach

Implementation of the recommended measures outlined above with regard to data quality and data management will create a more solid “information basis” for risk assessment of nanomaterials. The recommendations regarding REACH will improve the application of this regulation in both a legal and scientific sense. In practice, the application of the regulation will remain complex, time-consuming and costly. Nevertheless adapting and specifying the information requirements and test methods in REACH for nanomaterials that are now on the market, will not solve the regulatory hurdles for the next generation of (nano)materials. In the actual regulatory context, every new generation material will necessitate adjusting test methods, information requirements and legislation. A process that, as the nanomaterial file illustrates, takes at least ten years. Possible improvements mentioned under Innovation of Risk Assessment will only partially solve this issue.

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To better align the dynamic character of developing new materials and the static character of regulations, the possibilities of a more future proof approach for securing the safety of new (nano)materials must be explored. Some possible options are mentioned in this White Paper and to some extent have been developed in the NANoREG Framework, such as the “nano-specific risk assessment approach” and the “safe-by-design approach”. The first option is aligned with a more “concern-based testing approach” based on risk potentials that serve as indicators for potential hazards. It may include the application of functional assays, recommended in the Joint Document, as promising techniques for determining the potential hazard. The safe-by-design approach looks at ways to identify, and thus avoid, possible adverse effects of nanomaterials from the earliest stages of the innovation process onwards.

14. 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 potentials as developed in the NANoREG project and the safe-by-design approach as developed in NANoREG and ProSafe, and now further explored in NanoReg^2.

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1 Introduction

Investments in nanosafety research over the past fifteen years have significantly increased our knowledge on the potential adverse effects of nanomaterials. The translation and application of this knowledge into a regulatory context however remains problematic. Test methods developed in research oriented projects and the data generated by such tests, are often not fit to be applied in a regulatory context since the relevance, reliability and reproducibility of these methods may be uncertain or poorly established. The guidance, schemes, and supporting modes currently available for the REACH Regulation are found to be inadequate when it comes to the registration and risk assessment of nanomaterials. Despite some improvements that have been made up to mid-2017, serious issues with respect to the implementation of scientific knowledge still remain, as will be explained later in this document. The resulting uncertainty on how to assess potential exposure and adverse effects of nanomaterials on human health and the environment causes a negative impact on the investment climate for nanotechnology.

These observations were sufficient reason to develop and carry out the FP7 NANoREG project. The aim of that project was to develop reliable, reproducible and relevant methods for testing and assessing the effects of nanomaterials in a regulatory context. The project, involving some 90 partners from EU Member and Associated States, Brazil and the Republic of Korea, has resulted in a large number of scientific as well as policy and regulatory-oriented deliverables. About 70 standard operating procedures (SOPs) with a status ranging from “proof of concept” to “validated”, together with a large set of well-defined experimental data were also generated. All project results are publicly available in the NANoREG Results Repository.

Results of the project have been integrated in the NANoREG Framework for the Safety Assessment of Nanomaterials[i]. It provides an overview on how REACH currently assesses nanomaterials. It also proposes forward-looking strategies aimed at making the safety assessment of nanomaterials in the context of REACH more practical and economically viable. The NANoREG Toolbox supports the implementation of the Framework by listing methods, datasets, models, guidance documents, decision trees, etc., from within and beyond NANoREG.

The H2020 ProSafe project synthesizes the results of the NANoREG project as well as the results of numerous other nanosafety projects. Building on this, the White Paper provides recommendations for policy makers and regulators to help them achieve a more effective and efficient risk assessment and management of nanomaterials. It also provides the background information that forms the basis of these recommendations. The ProSafe project was carried out to link scientists, regulators and policy makers in order to support evidence based policy for the governance of manufactured nanomaterials and nano-enabled products at an EU level.

The White Paper focuses on the application of REACH to nanomaterials, since this regulation is the most important and far reaching in terms of impact on developing European industrial capabilities in the key enabling technology of nanotechnology. With its wide coverage, the impact of REACH cannot be underestimated.

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2 Scientific and societal context of nanotechnology

2.1 Importance/impact of nanotechnology

Nanotechnology is one of the six "Key Enabling Technologies" (KETs) defined by the European Commission in its 2012 Communication.

These technologies are considered by EU experts to be the driver for the development of new goods and services and the restructuring of industrial processes, needed to modernize EU industry. Given sufficient resources and support they should play a central role in enabling an efficient, knowledge-based and low carbon economy in the EU and beyond. KETs are regarded by the Commission as crucial for ensuring the competitiveness of European industries in the knowledge-based economy.

KETs feed into many different industrial value chains and sectors. They create value along the whole chain – from materials through equipment and devices, to products and services. Due to this transverse nature and systemic relevance to European industries, KETs catalyse the strengthening and modernising of the industrial base as well as driving the development of entirely new industries in the coming years.

Nanotechnology in batteries

The use of nanotechnology in the manufacture of batteries offers several (potential) benefits.

- Reducing the possibility of batteries catching fire by providing less flammable electrode material.
- Increasing the available power from a battery and decreasing the time required to recharge a battery.
- Increasing the shelf life of a battery dramatically by using nanomaterials to separate liquids in the battery from the solid electrodes when there is no draw on the battery.

The transverse role of KETs generates a broad regulatory challenge. With our ability to create new and increasingly complex (bio)nanomaterials (Figure 1[ii]), we need to become more sophisticated in understanding how these materials interact with biological and geochemical systems, and how we can anticipate and avoid harmful effects. Actually, we are already at stage 4 in Figure 1. Nanobuds and peapods were already entering into market use in 2006 - 2008[iii].

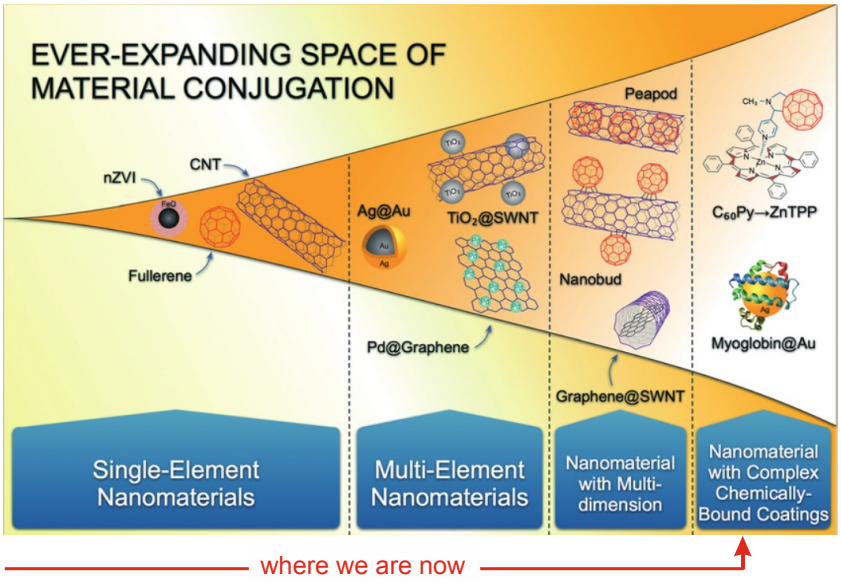

Figure 1: Increasing complexity of nanomaterials requires an adaptable testing strategy for assessing nanomaterial fate and toxicity – note that the figure does not include nanomedicine, or other routes of innovations in nanomaterials.

The global nanotechnology industry is expected to grow to some US$ 76 billion by 2020. The estimated Compound Annual Growth Rate (CAGR) of the global nanotechnology market is expected to be around 18% over 2016-2022[iv]. In the latest research study economic analysts have conducted research into the nanotechnology industry. In 2015, the global nanotechnology market showed impressive growth supported by certain prominent factors, like obtaining significant amounts of public and private investment in R&D, partnerships and strategic alliances between countries. At present, the biomedical industry is one of the largest sectors in which nano-enabled

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products have made major contributions, mainly in the healthcare industry. Significant developments are also being achieved in other sectors like electronics and energy.

The global nanotechnology market in environmental applications reached US$ 23.4 billion in 2014. This market is expected to reach about US$ 25.7 billion by 2015 and US$ 41.8 billion by 2020, registering a CAGR of 10.2% from 2015 to 2020[v].

The regulatory framework must be optimised in order to take full advantage of the innovative and economic potential of nanomaterials. This includes their positive economic impact on environmental technologies and their environmental footprint-reducing effect when included in products[vi]. Positive effects include improved quality of life. The issue that society is facing seems to be predominantly a matter of uncertainty regarding the safety aspects of nanomaterials. In addition, manufacturing industry needs clarity on how nanosafety is and will be regulated, and what its obligations are to meet regulatory requirements.

As the sophistication and complexity of nanotechnology increases with the upcoming products likely to be released into the market, the matter of acceptance and public perception means there is a policy need to be addressed. Nevertheless there will always be uncertainty about future assessment needs, since innovative manufacturing methods and products are continuously under development, so policy makers must be aware of what the general public perceives to be the risks associated with nanomaterials and related products[vii]. Public perception cannot form policy, but there is a responsibility for policy makers to assuage the concerns of the public at large. There is a potential for dissociation between the views of informed stakeholders and public reaction. Several examples are known from the history of environmental and health risk assessment where a failure to understand or align with public opinion has fed a public backlash, resulting in reactive policy, overregulation and/or an erosion of trust in the government.

In particular SMEs need to know exactly what is required from them to ensure efficient use of limited resources. They do not want to be involved in the process of deciding what tests should be carried out, but would simply like to know what tests are required. Additionally, society needs to be assured that the potential risks of nanomaterials will be properly dealt with. Also, insurance and venture capital require that these issues are addressed, thereby reducing the hurdles which can demotivate and hinder industrial development. To this end it is necessary to develop a common, science-based quantification of potential risks and associated assessment of the subsequent environmental, health and safety (EHS) effects of manufactured nanomaterials on man and the environment during their lifecycle. Liability always remains with industry, who is strongly motivated to minimise risks.

Questions like “what tests are suitable and reliable for identifying the EHS effects” or “how to assess the validity of test methods and relevant nano-specific aspects in risk assessment” must be answered. It is clear that any answer must fit the regulatory context and has to be accepted by all involved actors. Answers have to lead to regulatory requirements that are also palatable for innovative SMEs who often possess insufficient resources for expensive testing and validation of their products. A key issue here is the discrepancy between regulatory requirements for chemicals and the information needs formulated by regulatory risk assessors to address the nano-specific aspects of manufactured nanomaterials. For example, when conducting experiments or tests with nanomaterials, the results may correlate not only with new physicochemical parameters but also with how the surface chemistry of the particle is altered. Characteristics, fate and effects may change from nanoform to nanoform and throughout the life cycle. Hazard and fate are influenced not only by the chemical composition but also by functionality.

2.2 Selected results of 15 years of nanosafety research

Over the last 15 years there has been a significant global investment in nanosafety research. The EU contribution to this field of research over the past 12 years, through funding via research programmes, has been about € 400 million[viii]. Member States have also invested a similar amount in funding research into nanoEHS assessment. Closely linked to this and other funding initiatives from the US, is a sharp increase in the number of publications on nanosafety (Figure 2[ix]), though the majority of these, while of scientific interest, are mostly not of regulatory relevance.

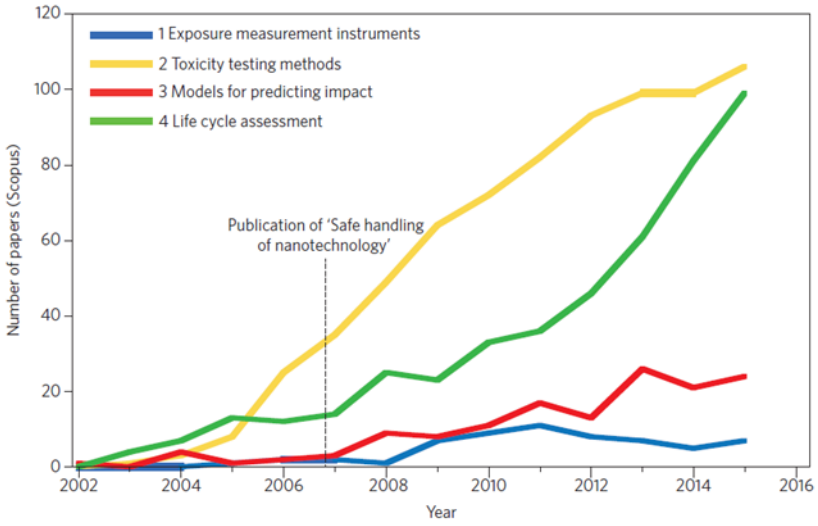

Figure 2: Estimated numbers of academic publications on nanosafety topics

This investment has led to a better understanding of the effects of nanomaterials on health and the environment[x] and nanosafety related mechanisms, but still many uncertainties remain. Clearly there are nanomaterials that, just as some conventional substances, have an adverse effect on human health and/or the environment, including any soluble nanomaterial, e.g. nanomaterials containing silver and zinc[xi].

We know that in the production phase of nanomaterials the occupational exposure is potentially high. We also know that when using protective measures with high efficiency, occupational exposure can be limited and controlled to an acceptable level as was concluded in NANoREG Deliverable 3.09 For many other stages of the life cycle of nanomaterials, our knowledge on the human exposure levels and their risks is less clear. The reasons for this are explained below.

√ *Research aimed at innovation differs from research in a regulatory context*

Most nanosafety projects are unique in the sense that they have selected their own nanomaterials to be tested, their own methods for testing, their own exposure dose, and their own dose metrics.

Due to this "let a thousand flowers bloom" approach, the experimental results are not always properly constrained, reliable, or comparable with the results of other investigations. In many cases they cannot be directly used for regulatory purposes, since the use of harmonised and reliable methods is not always followed. Academic research laboratories conducting analysis and experiments on nanomaterials do not necessarily have the same priorities as regulators, due to widely differing aims. Data coming out of an academic laboratory investigation has to be seen in the context in which it was generated, i.e. results published by academia on a specific nanomaterial might not always be relevant for a regulatory purpose.

√ *Bias in toxicity data on nanomaterials*

Academic research versus regulatory oriented research

Academic research labs aren't conducting studies for regulatory compliance, and do not have the same impetus to follow good laboratory practice and other established methods. The plus side of this is that academics have the flexibility to develop novel practices that may be more appropriate.

Harald F. Krug (2014) Nanosafety Research - Are We on the Right Track? Angew. Chem. Int. Ed. 53, 12304 – 12319

The apparent lack of reproducibility of scientific results between different laboratories has led the general public, scientists, some funding agencies and industries to question the validity and certainty of scientific findings. There is growing concern amongst professionals about scientific results that cannot be reproduced. Explanations include increased levels of scrutiny, complexity of experiments and statistics, and pressures on researchers. Journals, scientists, institutions and funders all have a part to play in tackling reproducibility (There is growing alarm about results that cannot be reproduced[xii]).

Many factors have been cited as contributing to imperfect reproducibility of experimental results. These include insufficient training in experimental design, poor data management and analysis,

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and inadequate instances of statistical inference. On a wider socio-economic scale, the academic business model is blamed for its misaligned incentives for publication. Others point to the lack of full transparency of methods used and data-user restrictions. Questions about the reproducibility of scientific research have been raised in numerous settings and have gained visibility through several high-profile journals and popular press articles[xiii] For nanotoxicology these issues have been highlighted in several review publications[xiv], [xv] that focussed on the reliability and reproducibility of results of *in vitro* nanotoxicity studies, which in many cases have been shown to have limited value for regulatory purposes

√ *Changes during the lifecycle of a nanomaterial*

A complicating issue when assessing the risk of manufactured nanomaterials (MNMs) is their transformation during their life cycle from particle production to their end of life. While regulators focus on what is generally referred to as the pristine MNM, the reality is that it will generally transform or undergo modifications during the life cycle. This may happen at the production site, and almost certainly when the MNM is incorporated into a specific product, perhaps through use of the product, and to the end of life which includes degradation and disposal of the product in the geological environment. In most instances, there is a lack of data about the physico-chemical properties and transformations along the various phases of the life cycle. In other words, we need to know whether an MNM is or will be transformed into a new form which requires special or specific safety testing. Where no other information exists, then we fall back on data from the pristine particles. It is evident that, in general, pristine materials are more hazardous than their transformed counterparts, so assessing pristine materials is generally playing safe. At the same time, the result is an overestimation of the risk that can (unnecessarily) delay the application of nanomaterial.

The large amount of nanoEHS data on MNMs from the production phase stands in stark contrast to the information available during its lifetime in a product. The changes that can occur to MNMs in products during their lifetime are only partially understood (Figure 3[xvi]). There are few studies which document the transformations and release, if any, of MNMs.

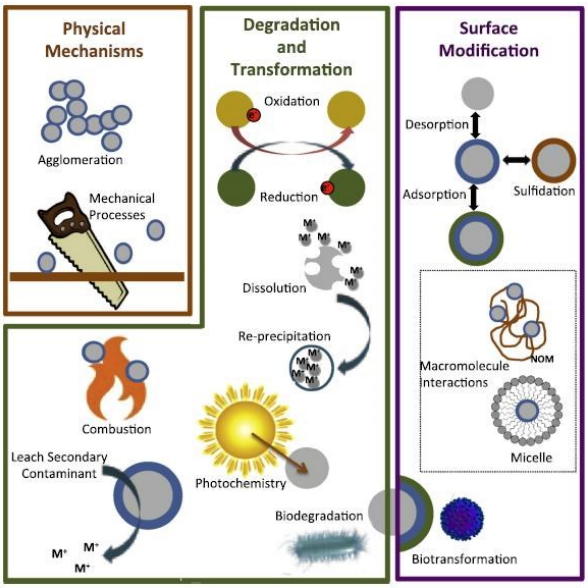

Figure 3: Sketch illustrating the possible transformations, mechanical weathering and chemical, as well as changes to the particle surface and physical mechanisms acting on the MNM which can affect a nanoparticle

Many transformations are not isolated events, but rather interconnected steps in a chain of changes as an MNM ages through a product life cycle, and after it is released into the environment. Key MNM transformations include mechanical degradation and chemical transformation both causing changes to the particle surface, its physico-chemical properties, and so determine its fate. The fate of MNMs during recycling of products, as well as in the environment, and the scale of any risk posed by the MNMs is currently a topic of much speculation. We conclude that exposure during the life cycle is highly relevant, but still largely unknown.

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√ *Information on background exposure is limited*

Aside from intentionally produced nanomaterials, people and the environment also are exposed to unintentionally produced nanomaterials, in the workplace, at home, as well as outdoors. Examples are:

- Fumes from hot processes (e.g. smelting, refining, and welding),
- Fumes from (incomplete) combustion processes (e.g., transportation, fireplaces, barbeques, even burning candles).

This makes it difficult to judge the actual contribution of MNMs to total human exposure from all nanomaterials or their estimated risk.

√ *Broadening the perspective: naturally occurring nanoparticles*

Naturally occurring nanoparticles are also a factor to be taken into account when judging the exposure of man and the environment to nanomaterials. Figure 4[xvii] gives an estimate of the total annual flux of nanomaterials from natural origin. An impression of the global budget (the amount entering or retained in different compartments in the global system) is also presented in Figure 4.

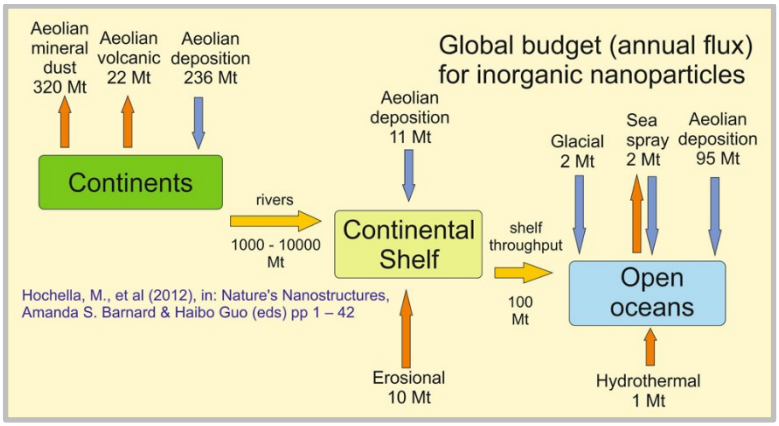

Figure 4: showing annual global budget for naturally occurring inorganic nano-particles

For the purposes of this compilation, geo-compartments are divided into the continents, the continental shelves with overlying ocean margins, the open oceans, and the atmosphere. The primary global movers of nanoparticles are rivers, glaciers, wind, and ocean currents. The primary major sources include soils and sediments, deep-sea hydrothermal venting, volcanic ash plumes, and sea spray. The geological long-term sinks are the continental shelves and the deep oceans.

Due to aggregation and sedimentation, about 90% of the nanoparticles are retained in estuaries and/or just offshore, where they are immobilised by sedimentary processes and 85% of the amount which passes into the seas and oceans is lost into the continental shelves. The airborne and waterborne inputs of mineral nanoparticles to the open oceans are very similar, both roughly 100 Mt.

A comparison can be made between naturally occurring nanoparticles and manufactured nanomaterials in terms of impact and effects. There is an annual flux of about 640 Mt of nanoparticles transported by rivers to the continental shelf. This is less than 10% of the global flux. If we consider the production of MNMs, we are looking at about 100,000 tons produced annually, excluding carbon black[xviii], which is a tiny fraction of naturally occurring nanoparticles. The market for carbon black is about 12 Mt annually and is mainly used in car tyres and rubber products (these two accounting for 90% of the global carbon black market).

Obviously, we cannot equate the potential risks formed by naturally occurring nanoparticles with the potential risks from manufactured ones along the life cycle from manufacture to end of life. However, once the MNMs enter the environmental or geological compartment, they will generally behave as natural nanoparticles, and they will be adsorbed onto clays and other particles and not pose any risk. The question, so far unanswered, is whether there are any MNMs which do not behave like natural nanoparticles in the environment.

Risk assessment exists to evaluate risks for MNMs in environmental settings, but there are strong indications that risks from MNMs in the environment will be minimal. The highest environmental

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risk from the group of metallic nanomaterials that undergo dissolution, can be dealt with due to their ionic release and not their particle behaviour. Risks need to be managed but it is recommended to focus on potential hotspots due to regional production concentration or accidental release.

2.3 Methodological uncertainty within experimental studies

In vitro research on nanomaterials over the past ten years has resulted in limited information that is of immediate use to regulators. In brief, the problems are: missing comparability of results, dose-metrics, quality control/dosing issues and deficiencies regarding significance.

One of the biggest uncertainties with experiments undertaken before 2005 is the instability of the nanomaterial dispersion, the lack of characterisation of the material, and a lack of understanding of transformational issues during experimentation.

Another important question is whether different responses are the result of cell line variability, culture conditions or due to differences in the nanomaterial itself. For permanent cell lines the problem is that these cells are not real analogues of cells in the living body, e.g. they are immortalized, and have different metabolic properties, etc. There are currently very few datasets available that allow an adequate resolution of this issue. The scientific and analytical challenges for *in vitro* approaches of nanotoxicology are presented in NANoREG deliverables D5.03 and D5.06.

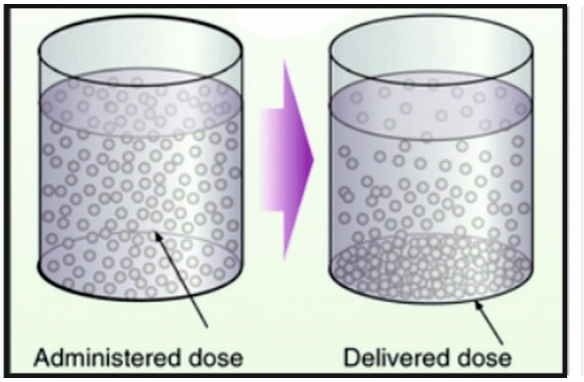

Figure 5: sketch showing the difference between the administered and the actual delivered dose in in vitro experiments

One of the challenges for scientists has been to understand the relationship between the dose administered during an *in vitro* experiment, and the actual amount of MNM that comes into contact with the cells (Figure 5; modified from[xix]). These can be widely differing amounts. In some cases only a small percentage of nanoparticles introduced into the experiment actually comes into contact with the cell, while the rest remains in suspension. In other cases nearly all MNMs have sedimented within a few hours[xx]. Prior to about 2010 there was no accurate data on the delivered, and therefore relevant, dose of nanoparticles reaching the cell surface. Adoption of recently developed dosimetric methodologies will facilitate determination of effective dose delivered to cell surfaces *in vitro*, thereby improving the accuracy and reliability of *in vitro* screening data, validation of *in vitro* with *in vivo* data, and comparisons across multiple datasets for the large variety of nanomaterials currently in the market[xxi]. We need also to be aware that in real-life situations the MNMs being ingested are not pristine particles, so experimentalists need to use relevant MNMs. In the Joint Document of ProSafe[xxii] seventeen specific recommendations are presented, related to how to conduct mammalian *in vitro* tests in order to make them more acceptable to both the scientific and regulatory communities.

2.4 Access to quality nanoEHS data

To make progress in nanosafety research it is important to build on the results of previous work (and avoid reinventing the wheel). It is disappointing to notice that apart from publications in scientific papers, results of nanosafety projects (deliverables and experimental data) often are not available to researchers or the general public. Although the awareness that access to nanosafety information is key, there still are serious obstacles to practical data sharing.

Formal hurdles like confidentiality provisions (e.g. the EU Framework Programme Grant Agreements and Consortium Agreements) are difficult to circumvent. Since there is currently no structural provision for storage of, and access to, information of projects that have been finalised, a great part of the results from publicly funded EU projects are not accessible once a project has ended. Importantly the quality of data (discussed in the next section of this chapter and a lack of standardisation of terms (ontology) or working data exchange strategy is a limiting factor for the re-use of already available information. This is an issue that needs solving since good quality data is essential for developing reliable grouping strategies.

> H2020 Annotated Model Grant Agreement
>
> ARTICLE 36 — CONFIDENTIALITY
>
> 36.1 General obligation to maintain confidentiality
> During implementation of the action and for four years after the period set out in Article 3, the parties must keep confidential any data, documents or other material (in any form) that is identified as confidential at the time it is disclosed ('confidential information').

3 Regulation of nanomaterials

3.1 Current regulation frameworks

The production, use and waste stages of nanomaterials are subject to several regulations at EU as well as at national level. While some regulations cover the whole life cycle of a chemical (e.g. the EU REACH Regulation), others only cover specific stages in the life cycle (e.g. national regulations on occupational exposure). Some of these regulatory systems have a generic character, e.g. REACH that applies to all "chemical substances" and articles containing chemical substances, while others set rules for a specific group of products, e.g. cosmetics (Regulation (EC) No 1223/2009), food (Regulation (EU) No 2015/2283), medical devices (Regulation (EU) 2017/745) and biocides (Regulation (EU) No 528/2012).

Classification, Labelling and Packaging (CLP) of hazardous chemicals is governed by Regulation (EC) No 1272/2008. The hazard information used for classification comes to a large extent from REACH.

General requirements in relation to occupational safety and health of workers at workplaces are presented in the Council Directive 89/391/EC. The aim of this framework directive is to ensure a high level of protection of workers at work. The Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work describes the minimum requirements for the protection of workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents (although not specifically mentioned these include MNMs), that are present at the workplace. Directive 2004/37/EC applies to nanomaterials that are carcinogens or mutagens, but does not apply to all nanomaterials by default.

Some of the regulations listed above do not specifically mention nanomaterials while others use the term nanomaterials without further specification. The regulations on biocides, medical devices, cosmetics and novel food have implemented a definition on nanomaterials in a legally binding way. Only in the first two of these regulations does the definition fully resemble the EC definition on nanomaterials mentioned below.

In October 2011, the European Commission (EC) published a Recommendation on the definition of a nanomaterial (2011/696/EU). The purpose of this definition was to determine when a material should be considered a nanomaterial for regulatory purposes in the European Union. The definition covers natural, incidental and manufactured materials and is based solely on the size of the constituent particles of a material, without regard to specific functional or hazard properties, or risks. This Recommendation is currently under review by the European Commission, with the aim to update the text of the definition in the light of 6 years of experience.

In addition, the definition was recommended by the Commission for use by EU agencies such as EFSA and ECHA. So, although not legally binding, the EC definition is gaining traction. REACH is in the process of including the text of the EC definition in the annexes.

In some Member States (e.g. DK, BE, FR, NO, SE) the production and use of nanomaterials has to be registered at a national level. This is not to be confused with the registration under REACH, or

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inclusion of information in the EU Observatory on Nanomaterials that has been recently launched by ECHA[xxiii]. In addition, Sweden has notified the EU of a proposal to register the manufacture in Sweden, or the transfer or import into Sweden, of nanomaterials.

Despite the range of legislation that (potentially) covers nanomaterials (the list above is not exhaustive), this White Paper focuses only on the application of REACH to nanomaterials, since this regulation has the broadest coverage and potentially greatest impact.

3.2 REACH and nanomaterials

3.2.1 Core principles of REACH

REACH stands for Registration, Evaluation, Authorisation and Restriction of Chemicals[xxiv]. It entered into force on the 1st June 2007. It is a regulation aimed at improving the protection of human health and the environment from the risks that can be posed by chemical substances, while seeking to enhance the competitiveness of the EU chemicals industry. It was developed based on detailed considerations of what was and what was not working under previous legislation. It was designed to meet a set of seemingly competing political goals. The three most important insights that influenced the structure of REACH were:

1. The notion that the generation of information on the intrinsic properties of a chemical substance is the most important contribution to risk management,
2. The idea that the concepts of reversal of the burden of proof and industrial responsibility render risk management effective, and
3. The observation that prior superficial knowledge of a chemical is insufficient to predict the outcome of a risk assessment.

Companies must identify and manage the risks linked to the substances they manufacture and market in the EU. They have to demonstrate how the substance can be safely used, and they must communicate the risk management measures to the users. If the risks cannot be managed, authorities can restrict the use of substances.

SIEF

The substance information exchange forum (SIEF) is a specific cooperation for REACH registration, organised by the co-registrants. SIEF partners are encouraged to share the data on a substance with co-registrants (in particular on vertebrate studies), share the costs for that data and prepare the joint registration.

Companies need to register their substances, and it is the tonnage of substance produced (in this case nanomaterials) which determines if registration is actually required, and what the information requirements are. The information which must be provided increases with increasing tonnage of the substance produced. If they are involved in animal testing they are obliged to collaborate with other companies who are registering the same substance in order to limit vertebrate animal testing. The European Chemicals Agency (ECHA) receives and evaluates individual registrations for their compliance. The EU Member States thoroughly evaluate selected substances to clarify initial concerns for human health or for the environment. Authorities and ECHA's scientific committees assess whether the risks of substances can be managed.

3.2.2 The limitations of REACH for nanomaterials

The application of REACH to nanomaterials has been extensively described in the NANoREG – "Definitive framework" (Chapter 3; safety assessment of nanomaterials under REACH), and NANoREG Deliverable 2.12, “Framework and procedures for characterization of MNM for regulatory needs”. These documents describe several “challenging limitations” of REACH and the current guidance for registration, testing, and exposure assessment.

To a great extent the limitations identified overlap with the conclusions on the nano-specific issues of REACH drawn up by ECHA and the Competent Authorities Subgroup on Nanomaterials (CASG-nano) in 2015 and 2016. These problems boil down to: a sufficiently robust legal basis for nanomaterials is missing, difficulties regarding the full characterisation of the nanomaterial in terms of its risk potential, and insufficient (quality of) data used to document safe use. These problems are discussed in the section below and supplemented with additional, more recently identified

ones. Possible measures to cope with these limitations, as well as already ongoing modifications of REACH Annexes and guidance documents, are mentioned in the next chapter (White Paper elements; section 4.3).

√ *Chemical identifier not suitable for nanomaterials*

The starting point for the registration of a substance in REACH is its chemical identity. This is a logical identifier since, for the majority of substances, their chemical composition is considered to be the main factor that determines the hazard properties. For nanomaterials however, this is not the case where both physical and chemical characterisation of the nanomaterials are of equal importance. Factors like the size, shape, charge, or functionalisations/coatings of particles can be of much more relevance than just the chemical composition of the nanomaterials.

This applies even more for coated nanomaterials where the relative chemical mass-based composition of the core would be the entry point for REACH, based on substance identification, while with respect to the hazard properties the coating can be more relevant. In fact, this may equally be true for materials with sizes exceeding the nanoscale, but has not been seriously addressed during the establishment of REACH. This should be dealt with in the revisions of the Annexes.

Coated nanomaterials in REACH

In REACH substances are identified by the main component (>80% on weight basis) and not on the basis of the components that determine functionality. For example: Is nanoscale silica that is APES (3-aminopropyltriethoxysilane) functionalised and further coated with 5 wt% Fe_2O_3 to be identified (classified) as nanosilica?

It is to be expected that the EHS effects of this material will predominantly be determined by the coating and not by its core.

Unless REACH identifies it as an issue, registrations due to coatings are only considered when the coating is chemically bound. Physical coatings are not included and are not described in the guidance! If the coating determines the toxicity of a substance, then in fact it would need to be evaluated separately, since REACH should be applicable for substances put on the market. When the (toxicological) behaviour of a coated particle cannot be estimated on the basis of (toxicological) information of the individual components (similar to mixture toxicity for 'normal' chemicals), a different approach is needed. This major limitation must be considered in conjunction with the next limitation of REACH.

√ *Robust legal basis for nano-specific approach missing*

As mentioned before, the current REACH regulation does not define a nanomaterial. It also does not offer the possibility, through its Annexes, of making exemptions, extensions, or other variations for nanomaterials with regards to the information requirements and the way to assess the risks of these materials. REACH requires that the hazards posed by all possible forms of the substance covered by a registration, including nanoforms, must be addressed by the toxicological and ecotoxicological information provided in the registration dossier[xxv]. Nevertheless, in practice it is questionable if and to what extent registrants of nanomaterials can be asked to provide additional information on physicochemical properties of MNMs.

MNMs in REACH dossiers

A group of 35 EU-based companies have asked ECHA's Board of Appeal to overrule the Agency's decision to make synthetic amorphous silica subject to substance evaluation under REACH citing initial grounds for concern, related to "the substance characterisation, nanoparticles and toxicity of different forms of the substance". The companies' argument is that none of these grounds are criteria for inclusion of a substance on the Community Rolling Action Plan (CORAP) of substances for evaluation. The same stance has been taken by the registrants of titanium dioxide; they also consider it as a breach of the REACH Regulation (Article 44).

In its ruling on these cases, the Board of Appeal makes clear that in the light of the context and purpose of REACH a registrant should provide information covering all (nano) forms of a registered substance. However, given the clear and precise wording of section 2 of Annex VI (information requirements on identification of the substance), there is no legal basis for ECHA to require more information to characterise a nanomaterial than required on the basis of this Annex VI.

√ *Information requirements for risk assessment*

Proper characterisation and classification is a cornerstone of the legal examination and assessment of nanomaterials. The REACH annexes VI-XI set rules for registrants to provide information on physico-chemical properties, on exposure, and hazard properties. The extent of the information requirements depends mainly on the total substance production volume in tonnes, in ranges from 1, 10, 100 and 1000 tonnes annual production thresholds.

Annex XI provides the possibility for a registrant to adapt the standard testing regime when testing does not appear scientifically necessary, when it is not technically feasible or when there are reasons for a substance-tailored exposure driven testing. The guidance which has been given so far on how to apply this Annex XI to nanomaterials is limited. It does not provide the possibility to make more generic exemptions to waive exposure testing.

A number of reasons can be put forward why a deviation from the “standard testing regime” would contribute to a more effective and efficient risk assessment for nanomaterials.

- As explained in chapter 3 of the NANoREG D1.11 "Definitive framework", 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. Examples of the first category are the octanol-water partitioning coefficient (irrelevant). For the second category dissolution can be mentioned as example, although it’s not currently a REACH requirement. On the other hand, some relevant endpoints are missing in the list of required information like for example atomic substitution, doping, porosity-filling, physical coating and chemical functionalisation (see NANoREG Del 2.12).
- Furthermore, nanomaterials need exponentially more data points than standard chemical substances. This is due to their intrinsic and extrinsic (test-medium dependent) properties and possible transformations during their lifecycle. Especially for relatively small production volumes it is hardly possible (and in fact not very efficient) to fulfil all information requirements in advance.

√ *Intellectual Property Rights (IPR) issues hamper substance information exchange*

Nanomaterials derive their value from specific characteristics like size, shape, porosity, coating, etc. Registering a nanomaterial in combination with the earlier mentioned substance information exchange forum (SIEF) may often lead to a disclosure of particle functionality of a MNM to competitors, although an opt-out option exists for confidential business information. It sometimes seems as if industrial partners make use of all legal options to avoid registration, and thus avoid revealing key characteristics of their nanomaterial.

So, the principle of REACH to share data (SIEF) can create a nano-specific hurdle to industry to register individual nanomaterials which are grouped by chemical identity and specific ranges in accepted Substance Identity Profiles (SIPs).

√ *Worst case scenario exposure*

A complicating issue when assessing the risk of MNMs is their transformation during their life cycle from particle production to end of life. While regulators focus on what is generally referred to as the pristine MNM, the reality is that MNMs will generally transform or undergo modifications during the life cycle. This may happen at the production site, and almost certainly when the MNM is incorporated into a specific product and through use of the product to the end of life which includes degradation and disposal of the product in the geological environment.

In most instances, there is a lack of data about the physico-chemical properties and transformations along the various phases of the life cycle. In other words, we need to know whether an MNM is or will be transformed into a new form which requires special or specific safety testing. Where no other information exists, then we fall back on data from the pristine particles. It is evident that, in general, pristine materials are more hazardous than their transformed counterparts, so assessing pristine materials is generally playing safe. At the same time this can result in an overestimation of the risk that can (unnecessarily) hamper the application of nanomaterials.

√ *Risk assessment – data quality*

Risk assessment in the context of REACH makes use of experimental data generated by the registrant and experimental data published in peer reviewed journals. Such an approach has limitations with respect to reliability and relevance of the data as explained in section 2.2.

- One of the main limitations is that a lot of the scientific nanomaterial-related research that is used to support regulatory decisions may not be up to standard for this purpose and that in some cases it cannot be replicated by new experiments.
- The urge to publish has led to what is called "data-dredging"[xxvi], a bias whereby, without regard to reproducibility of results, statistically significant results are collected in order to justify a publication. This means that opinion is weighted by published, high impact results[xxvii,xxviii].
- A third limitation is that this approach could lead to cherry picking: selectively collecting results depending on the interests of the party involved (collect bad cherries or paint a rosy picture).

We should point out that these last two points are not nano-specific.

3.2.3 Conclusions regarding the applicability of REACH for nanomaterials

As explained above, the REACH regulation is not fully equipped to deal with the specific character of nanomaterials. The most important shortcomings are the lack of a sufficient legal basis for the definition of a nanomaterial and specific requirements for nanomaterials, the chemical identifier as only point of entry in REACH, and the fact that the information requirements do not completely cover the relevant characteristics of nanoscale substances. Furthermore, the prescribed test methods are not always suited for this category of materials.

Since REACH does not (or only in a very limited manner) provide the possibility for concern-based testing, the regulatory requirements are very demanding with respect to information on characteristics, exposure and hazard of a substance. This information can, in general, not be retrieved from literature, modelling or read-across. Generating all the required information by the registrant is time-consuming and very costly. It does not fit the short "time to market" scenario of newly developed MNMs and their applications, or the limited capabilities of SMEs to fulfil all information requirements. Gaps in information are considered as uncertainties and translated into a cumulative uncertainty factor resulting in a relatively high negative ranking of nanomaterials.

It appears that this *de facto* results in a tendency not to register nanomaterials. An indication for this conclusion is the fact that the Europe-wide number of 18 (voluntarily) registered nanomaterials is far behind what could be expected on the basis of registration of products as seen in the French (mandatory) product registry. This registry has about 400 registered nanoforms, though clearly this number may include several different nanoforms of the same nanomaterial. The upcoming 2018 deadline for registration will either confirm this tendency (no registration of nanomaterials) or see registration of low tonnage nanomaterials.

The European Commission, Member States and ECHA are currently working on several improvements of REACH. Progress until now however seems slow and the foreseen modifications will only solve part of the problems mentioned above. To really make a meaningful step forward, more effective and efficient regulations and governance of nanomaterials, and more far reaching modifications are needed. In the next chapter of this White Paper such proposals will be presented.

4 The White Paper elements

The previous chapters described the factors hampering an efficient and effective assessment of the risks for human health and the environment related to production, use and fate of nanomaterials. This chapter presents a way forward to deal with these factors in order to achieve a more effective and efficient governance and regulation of nanomaterials. The first section encompasses proposals for “no regret measures”: measures and actions that are generally considered as necessary, feasible, effective, and cost-efficient. Other sections cover adapting REACH, innovation of risk assessment, and finally, a more future proof approach to the risk assessment of (nano) materials.

4.1 No regret measures: Improving data quality and data management

There is a lack of adequate, reproducible data to validate risk assessment strategies for manufactured nanomaterials (MNMs) and to develop a science-based understanding of how to quantify and predict the potential risks of many nanomaterials. Experimental data for nanomaterials found in literature are often contradictory or inconclusive. This is due to the fact that when dealing with manufactured nanomaterials there are particular problems related to sample preparation, quantification, characterisation, dosimetry and the stability of test solutions.

NANoREG and ProSafe have provided a wealth of information that now can be used to improve data quality and data management. The recommendations presented and explained in this section are aimed at implementing these findings.

4.1.1 Harmonised test methods

A Task Force of nine international experts was established within ProSafe to carry out a study to evaluate the reliability, and regulatory relevance of the outcomes from selected nanosafety projects.

OECD harmonisation programme

The OECD Council established the OECD Working Party on Manufactured Nanomaterials (WPMN) as a subsidiary body of the OECD Chemicals Committee in September 2006. This programme concentrates on human health and environmental safety implications of manufactured nanomaterials (limited mainly to the chemicals sector), and aims to ensure that the approach to hazard, exposure and risk assessment is of a high, science-based, and internationally harmonised standard.

The two key criteria used for the evaluation were reliability and relevance, as defined by the OECD. The nine areas of concern studied in this report were: (1) physicochemical characterisation, (2) exposures through the life cycle, (3) fate, persistence and bioaccumulation, (4) exposure modelling, (5) ecological effects and biokinetics, (6) human health effects and biokinetics *in vivo*, (7) human health effects and biokinetics *in vitro*, (8) (Q)SAR modelling of nanomaterials, and (9) risk assessment.

The evaluation was guided by an earlier ProSafe document referred to as the Road Map (Annex 1 to the Joint Document). This Road Map sums up the regulatory questions on which the evaluation was focussed as formulated in NANoREG deliverable 1.01 and defined the key topics the evaluation should focus on.

The ProSafe Task Force reviewed a selection of approximately 1000 published articles and research reports, which were specifically selected and sorted into a database based on key topics. Key findings were reported in the draft Joint Document that has been discussed by a wide group of invited international experts during a 3-day scientific conference organised by ProSafe and the OECD. The results of this conference are included in the Final Joint Document and will be published by the OECD.

The ProSafe Joint Document clearly shows that reliable methods and approaches are already available for many parameters and endpoints, which are either validated to be used for regulatory decisions, or at least have been demonstrated repeatedly, and are promising for immediate regulatory use after further development and validation. For each of the nine areas mentioned before, the document describes available methods including their relevance in a regulatory context.

Categories of Physical Chemical Property Metrics	Key/Preferred Measurement Methods	Strengths / Limitations/ Knowledge Gaps
Intrinsic Properties:		
Particle size distribution (number average)	1. Electron Microscopy (for equivalent diameter) 2. DLS/FFF/centrifuge (for hydrodynamic diameter	While all methods noted in Chapter 5.1 are generally useful in research, the following comments on 3 methods are particularly relevant to the EU definition, and determination of "Intrinsic" PSD: 1. EM is the only method that can distinguish primary particles in aggregates. This is likely the best measurement of PSD to fit with current EU definition. But sample preparation can skew results. Quantitative estimates of PSD can be achieved with automated EM image processing; method is partially validated. 2. DLS has data interpretation problems, especially for polydispersit[illegible] and oddly-shaped structures, but could serve as a first [illegible]
Particle shape (e.g. aspect ratio)	Electron Microscop[illegible]	

Figure 6: Cut out from Joint Document showing a typical overview of parameters, methods and comments.

Figure 6 gives an impression of the overviews provided in the Document. The figure only shows some physicochemical characteristics, but similar overviews are included in the ProSafe Joint Document for other endpoints.

Regarding the way forward, the Joint Document concludes that, given the current political and legal uncertainty on the applicability of REACH on nanoforms, an effective route to follow would be to improve the data quality requirements for MNMs by improving the harmonised methodologies as quickly as possible. The rationale is that when quality data becomes available in the regulatory process through detailed and approved data requirements there will be no need for battles around the validity of the requested information.

The current activities of OECD on adaptations of TGs and GDs for MNMs are to be encouraged, and it is to be recommended that the OECD should extend its respective activities, while the member countries and the EU should (financially) support an intensified harmonisation programme.

White Paper Recommendation 1: Harmonised test methods

The OECD Working Party on Nanomaterials (WPMN) should consider adapting their existing working programme and undertake an ambitious schedule to adopt and implement the harmonisation-recommendations laid down in the ProSafe Joint Document and various NANoREG deliverables.

EC Member States should commit themselves to contribute to the execution of such an ambitious programme.

4.1.2 NanoSafety Cluster

Partners in the NanoSafety Cluster (NSC) share a common desire to provide and share data and methodology within the nanomaterials community.

The NSC was established as a mechanism for on-going (European) research projects to benefit from each other, as well as from recently finished projects, through information sharing, as well as being a mechanism to collectively define strategic agendas for research, regulation and commercialisation. The eight Working Groups of the NSC address different aspects of the nanosafety challenge, from materials, through hazard, exposure and risk assessment, with crosscutting themes that include databases, dissemination and systems biology. The Working Groups will provide feedback on the execution and implementation of projects and define structural needs to the EC's High Level Group on nanosciences & technologies and its programming committee. The cluster should earn its place as a stakeholder in the research strategy discussion and its subsequent budget allocation.

At present, there is some communication and information exchange among NSC projects, however, these are rather non-committal activities, and include little exchange with stakeholders that are not automatically partners in the NSC.

One of the topics to be addressed urgently in the NSC is the sharing and consolidation of Standard Operating Procedures (SOPs) developed in the projects. Too many SOPs have been developed

whilst no time and budget has been made available to consolidate this knowledge. This leads to a divergence in results and lack of comparability. NANoREG has delivered approximately 70 SOPs that should be discussed and compared with other SOPs derived from the NSC projects. Consolidation and subsequent prioritization of SOPs is a strategic task for the NSC and its outcome should be shared with the WPMN of the OECD where most EU Member States, as well as the EC, are represented (e.g. Romania, Bulgaria and Cyprus are not). By such a mechanism the results of the EU research effort will be shared where it matters most, in terms of regulatory methodology development and harmonisation.

> White Paper Recommendation 2: NanoSafety Cluster
>
> *The NanoSafety Cluster should take the initiative to select test methods that future nanosafety projects should focus on for further development and application*.

4.1.3 Generating Quality Data; Standard and Benchmark materials

To enable to establish correlations between nanomaterial properties and the key interactions or endpoints in humans and the environment, well-defined experimental nanoEHS data, that can serve as a basis for QSARs, models, AOP and read-across, should be made freely available. Now, on the basis of the NANoREG project and the Joint Document, it has become possible to define what intrinsic characteristics of materials are relevant to determine potential adverse effects. Now that reliable test methods have been developed, it is time to generate experimental data for these characteristics.

To generate such experimental data a set of standard or benchmark materials must be established in order to enable comparisons between studies, and to increase the use of data collected for informatics. Three general categories of standard and benchmark materials should be developed:

- Development of well-characterized, reproducible, but not necessarily uniform, “real-world” materials for testing.
- Development of libraries of uniform, well-characterized reference materials of varied size, shape, aspect ratio, surface charge, and surface functionality.
- Development of standard materials for calibrating various assays and measurement tools.

A second step should be to define and execute a project to generate a large set of experimental nanoEHS data that enables the identification of correlations between nanomaterial properties and the key interactions or endpoints in humans and the environment. It should focus on adequately characterized materials (as mentioned before) that have different properties, appropriate assays for examining interactions or endpoints and be of sufficient breadth and depth for assessing correlations between nanomaterial properties and the behaviour of the materials. Each type must be characterized sufficiently for test results to be reproducible, and for correlations between observed effects and material structure and composition to be established that can ultimately be used to predict the effects of new materials, based on knowledge of their structure and composition.

Data from the new alternative test methods should be used in conjunction with *in vivo* data from currently accepted OECD or other protocols in a tiered testing framework that leverages the data from the new methods by relying on correlations with data from already accepted methods.

Both initiatives should be organised as demand-driven, and managed like the NANoREG project, in order to guarantee relevancy and focus. Given the relevance of these initiatives to develop a more innovative risk assessment and safe by design, the investment in such a project would be highly profitable. The NANoREG project has proved that a joint action between MS and the European Commission can be very effective for this purpose.

White Paper Recommendation 3: Quality data

The European Commission should initiate (at least one) demand-driven project to generate experimental nanoEHS data. Such a project should include adequately characterized materials that have different properties and include appropriate assays for examining interactions or endpoints.

Materials that should be included in such a project are (1) "real-world" materials, (2) well-characterized reference materials of varied size, shape, aspect ratio, surface charge, and surface functionality and (3) standard materials for calibrating various assays and measurement tools.

4.1.4 Data management

Apart from the need to improve the quality and comparability of experimental nanoEHS data and to generate experimental data, the possibilities for use of nanoEHS data outside and beyond a project need to be improved. The European Commission encourages data sharing, and it is compulsory for data used in peer reviewed publications. However, so far there is no protocol for compulsory sharing of nanoEHS information generated in EC- and national projects.

The NANoREG, ProSafe and eNanoMapper projects have created and implemented a system of advanced data management. This includes an agreement on opening up data, standards for data logging, ontology for nanosafety research and a database. In this context NANoREG created a NANoREG Results Repository which gives open access to all deliverables, SOPs and experimental data generated under the umbrella of this project.

To expand this system of advanced data management to all (publicly funded) nanosafety projects and to make it sustainable for the long term, several measures are necessary. Sharing of data and information related to nanoEHS must become an essential condition for participation in any project funded at EU or national level, with provisions for industry who need to protect intellectual property. For instance, a special clause in Grant Agreements would be the correct method to achieve this, and should be applied by all EU funding agencies for the forthcoming funding programmes. A sustainable structure for long-term curation, ontology work and data storage is also badly needed.

In order for parties other than the generator of the data to exploit nanoEHS data, it is crucial to have a harmonised use of terms (ontology), the assurance that the quality of data meets a certain minimum standard (data curation) and the accessibility of the data after a project has ended. Several curation actions are currently underway. The Swiss EMPA institute leads this action. Data curation has been defined as the active and on-going management of data. Curation activities enable data discovery and retrieval, maintain quality, add value, and provide for re-use over time[xxix]. Ideally such a curation effort should be a continuous EU action. DaNa v2 (Data and knowledge on Nanomaterials) contains a well-known curated literature database. This could be an example for – or be expanded to – a trusted database for nanoEHS data for assessment purposes. It could simultaneously serve as a pool of data to utilize in QSAR approaches. The recently launched EU observatory for nanomaterials also could be a logical place to host nanoEHS data, although that is not currently its purpose.

A long-term nanoEHS data management vision and related organisational system are crucial to achieve this. They cannot be provided by projects with a limited duration nor by partnerships on a voluntary basis like the EU NanoSafety Cluster. Tasks to implement this vision can only be assigned to and executed by an organisation that has or gets guaranteed long-term funding.

White Paper Recommendation 4 + 5: data management

The European Commission and Member States (MS) should introduce and enforce an obligation to share the results of 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 (ISA-TAB-Nano logic) way. A 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.

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 a check on data quality (data curation). This last should be aimed at avoiding or repairing reporting errors as well as judging the regulatory appropriateness of experimental data (test design).

4.1.5 Top-down approach

The NANoREG and ProSafe projects have taught us that nanosafety research has to be better linked to the policy and regulatory needs of the EU. Many of the finalised and current nanosafety projects are the result of national or international “calls” that defined their goals in terms that are not specific with respect to research topics that are relevant for using the results in a regulatory context, such as materials to be used, test methods to be applied and data logging. This limits the use of the projects’ results and experimental data for regulatory purposes like grouping and read-across, and for the development of QSARs. A more “top-down” approach, by precisely defining a call with respect to the basic conditions for proposals, or by tendering a well-defined project, would increase the impact of the results of nanosafety projects.

The recommendations mentioned in 4.1.2 (NanoSafety Cluster), 4.1.3 (Generation of quality data) and 4.1.4 (Advanced data management) are all relevant in this context.

White Paper Recommendation 6: Top-down approach

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 NanoSafety Cluster could play a role in defining such conditions.

4.2 No regret measures: Harmonised occupational exposure limits

Workers may be exposed to nanomaterials and their products which could lead to adverse health effects. These effects have not yet been fully explored. Research shows that the most important uptake route of nanoparticles is inhalation.

A precautionary approach is recommended, where most of the control measures and recommendations will be similar to those applied for dusts or aerosols. Exposure research over the last decade has been focussed on developing competing mitigation systems, while research partners work to develop a future market. This competition has led to delays in consolidating the state of the art and developing standards. The evaluation of the performance of control measures in view of exposure and risk reduction is hampered by the absence of exposure limits. To bridge this knowledge gap, safe practices for production and use should be defined, based on state-of-the-art knowledge and expertise.

Recently, data on the protection effectiveness of filter (materials), clothing and glove materials against nano-aerosols has been published[xxx]. The results indicate a very good performance for filter materials and non-permeable materials. This has been supported by the outcome of NANoREG deliverable 3.09 on the effectiveness of personal protective equipment (PPE). A review analysis of the efficacy of technical solutions (e.g. measures, tools, protective clothing, etc.) and PPE was also conducted as part of the European SUN project, which showed generally similar to slightly lower protection factors for MNMs when compared to particles coarser than MNMs. The effectiveness of engineering controls on manufacturing equipment should also be noted, along with limited exposures from newer equipment such as spray applicators used for nanomaterial applications such as coatings.

National and EC regulation

In addition to national regulations, the provisions of Framework Directive 89/391/EEC and the Chemical Agents Directive 98/24/EEC (CAD), Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work apply whenever exposure to MNMs or use of nanotechnology in a professional capacity is known or likely to take place, with the aim of ensuring adequate protection of workers' health and safety.

The risks posed by 'nanoparticles and ultrafine particles' are by far the greatest, as agreed by experts in the expert forecast by EU-OSHA (OSHA 2009). In particular new asbestos-like acting chemicals (including nano-sized) cause major concern.

Setting Occupational Exposure Limits (OELs) is the best way forward, bearing in mind that many nano-innovators are SME businesses, as are their downstream users, who generally follow this precautionary approach. Several EU Member States are developing or have developed OELs. However, a concerted action between EU Member States coordinated through DG-EMPL and using the Scientific Committee on Occupational Exposure Limits (SCOEL) would be quicker and more cost-effective, while keeping the playing field level throughout the EU. A joint project in setting occupational exposure levels for which standardized methods exist (see Joint Document), with guidelines for studies to be employed for conducting risk assessment determinations, as well as for setting occupational exposure levels is strongly recommended.

White Paper Recommendation 7: harmonisation of exposure limits

The European Commission (DG-EMPL) should initiate a concerted EU - MS effort in setting occupational exposure levels (OELs) for which standardized 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.

4.3 A realistic REACH for nanomaterials

Evaluating the applicability of REACH for nanomaterials, the conclusion can only be that REACH, until amended, is not optimised to deal with nanoforms of substances. Summarising, the key issues are:

- The lack of a definition of nanomaterials in the REACH legislation hampers demanding specific information for nanomaterials
- The chemistry of a substance as entry point for REACH hampers taking into account the functionality (characterised by physico chemical properties) of nanomaterials
- The commercial implications of a mandatory exchange of information that reveals the functionality of a nanomaterial (SIEF) reduces the willingness to register individual nanomaterials/nanoforms
- Information requirements and related test methods as laid down in REACH Annexes are not always relevant or fit for nanomaterials
- The possibilities for a tiered – concern based – testing approach are absent.

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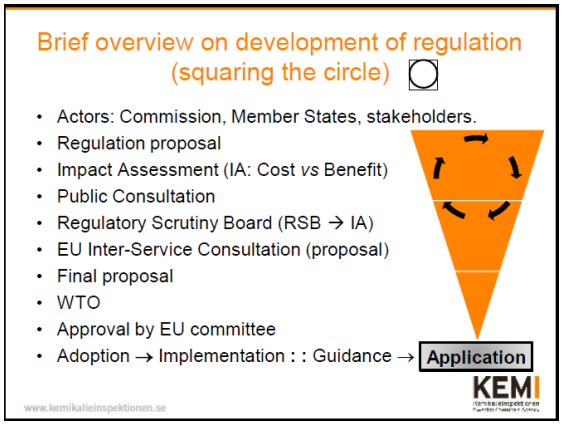
To solve these issues, adjustment of REACH is necessary at several levels: modification of the text of REACH itself, modification of its Annexes and modification of Guidance Documents, each of them with specific procedures and timelines.

Regarding the first level , this will have to wait for the overall evaluation of REACH to be completed.



The box illustrates the steps leading to the development or modification of European legislation such as REACH, which may include reiteration of some of the steps. Resolving the issues outlined above by amending the REACH Annexes only is a similar long and winding road. After almost 5 years into the process, agreement has been reached on the outcome of the Impact Assessment for adapting the Annexes. While this is hardly encouraging, it is the reality of the development process. Given the current political outlook of the EU, it would be unrealistic to expect a speedier process. Although it is encouraging that discussions have moved to the REACH Committee, a formal proposal for adjustment has not yet been presented by the EC and approval and especially adoption and entry into force are likely to take some years more. This must be seen in the light of the contrasting pace in which new materials/new forms are being developed.

Amending Guidance Documents is – in general - less time consuming and for several of the issues noted above, already ongoing.

In the following paragraphs, the necessary adjustments are presented and explained. Part of them have already been taken on board of still running or just finalised ECHA projects to make REACH better fit for nanomaterials. In this context, it can be mentioned that ECHA recently published five documents that will help registrants preparing dossiers that cover nanoforms ahead of the 2018 registration deadline. The documents include two new publications as well as recommendations and updates of the existing guidance on nanomaterials. The new publications are:

- Nano-specific Appendix to Chapter R.6 of the Guidance on Information Requirements and Chemical Safety Assessment (QSARs and grouping of chemicals): It advises registrants on how to justify the use of hazard data between nanoforms (and the non-nanoforms) and within groups of nanoforms of the same substance.
- How to prepare registration dossiers that cover nanoforms - best practices: This document gives recommendations for distinguishing between different nanoforms of a substance, and how to report information on nanoforms consistently in the dossiers.

4.3.1 Legal basis for the definition of a nanomaterial

To clarify to the registrant when specific data requirements for the nanoform would be required, and to ensure that nano-specific information can be assessed independently from non-nanomaterial (bulk) data, the definition of a nanomaterial must be given a legal basis by including it in the main text of the REACH regulation or at the level of Annexes.

Linked to a definition, clarity should be provided with respect to the method(s) that can be used to determine the size distribution of a material and thus identify whether the material is a nanomaterial or not. NANoREG deliverable 2.10 provides such a method. The European Commission is currently revising the REACH Annexes to include the EC definition of nanomaterial.

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White Paper Recommendation 8: REACH - legal basis for nanomaterials

The European Commission and Member States should include a legal definition of nano-materials 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.

4.3.2 Substance identification of nanomaterials

An analysis of the current guidance documents and Q&As on substance identification reveals that the guidance with respect to substance identification in the different documents is not consistent. The key parent document for substance identification (ECHA-16-B-37-EN) states that "the current state of development is not mature enough to include guidance on the identification of substances in the nanoform in this document". Several ECHA Appendices however express the need for specific information on nanomaterials, including size/size-range, shape and surface chemistry. It is recommended that the schemes for substance identification are harmonised, and substance specific profiles must be defined, irrespective of whether it is a manufactured nanomaterial or not (although it is realised that this may be hampered to some extent by the lack of a legal basis that defines nanomaterials).

NANoREG provides several concrete proposals for modification, such as reporting particle size distribution and adjustment of the scheme for morphological categorization. In this context schemes already developed for shape type classification by ISO are mentioned provide a more solid basis than the system laid down in the recently published ECHA document "How to prepare registration dossiers that cover nanoforms - best practices".

Reporting on surface-chemistry as described in this document is considered an important improvement. However, surface-chemistry (i.e. the chemical nature of the surface of a particle) is not the only chemical modification that should be included in the information requirements for NMs. Nanomaterials may be modified in many different ways in modern material design including atomic substitution, doping, porosity-filling, physical coating and chemical functionalization. They all should be mentioned since all these modifications potentially change the properties, reactivity, fate and hazard of the NM.

NANoREG presents a proposal for a modified categorization scheme that takes into account the results of an analysis of current REACH guidance on substance identification and morphological categorization (Figure 7[xxxi]). Note that this is not a grouping or read-across scheme for hazard data.

It was also suggested that the final identification and reporting should include characterisation of physicochemical properties including surface characteristics according to the (nano-) materials by sub-dividing them into:

1. Structure/chemical composition,
2. Shape/porosity, and
3. Specific physico-chemical properties.
4. Surface Characteristics

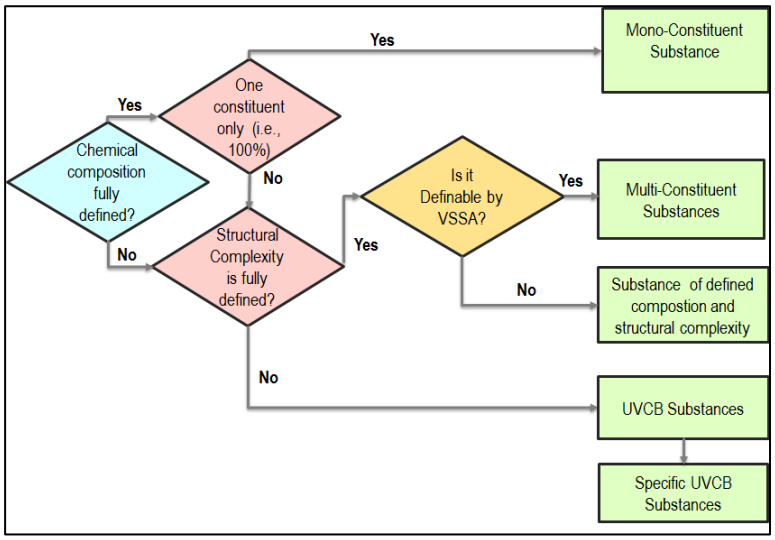

Figure 7. Possible routes for identifying various silica-based nanomaterials (NANoREG D2.05)

The number of characterization endpoints under "Specific physico-chemical properties" could vary from limited to rather extensive depending on the material type and information needs, but should at least include a characterization of the surface chemistry (including atomic substitution, doping, porosity-filling, physical coating and chemical functionalization, etc.).

The specific categorization of the materials should be done according to the principal nature of the first generation MNMs (solid, capsule/hollow, porous) and then subsequently according to the physical location and extent of structural and chemical modifications to achieve the second generation MNMs (modified internally or externally by either organic or inorganic compounds), or third generation MNMs with organic and inorganic chemical modifications. The proposed classification and proposed descriptive codes enable quick identification of various NMs by their complexity, which could also be an easy way to identify requirements for new risk assessments. Figure 7 shows an example of this structure considering nanostructured NMs of silica.

White Paper Recommendation 9: REACH – substance identification

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 should be modified and aligned with the already developed (ISO) schemes and the OECD Guidance on grouping. Information on particle size distribution, shape, porosity and surface chemistry (e.g. reactivity), should be added to the information requirements.

4.3.3 Information requirements

Information on a minimum of 13 physicochemical characterization endpoints is requested in the ECHA Guidance Documents. Recommendations on how to generate the data also are given. However, it is noted that the current analytical methods proposed in the OECD TGs needed for REACH registration are rarely fully applicable for the characterization of nanomaterials.

Revision of OECD Technical Guidelines

In NANoREG D2.03 important OECD guidelines relevant for particle characterisation were assessed for their applicability to nanomaterials. Some of the test guidelines were found not to be applicable for nanomaterials. Others needed modification to make them fit for testing nanomaterials.

Deliverable 2.09 presents proposals for adapting the Guidelines TG 105 (water solubility), TG 108 (complex formation in water), TG 109 (relative density), TG 110 (granulometry) and TG 112 (dissociation constant in water) to make them fit for testing nanomaterials. On top of this measurement of dispersibility, zeta potential and water dissolution rates have been addressed.

NANoREG developed and demonstrated SOPs for identification of nanomaterials by sizing, using electron microscopy and BET gas-adsorption and gas-desorption profiles (NANoREG D2.10 and D2.11). The established SOPs for sizing dispersed near-spherical particles

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and primary nano-objects in agglomerates and aggregates are documented by inter-laboratory testing in 9 laboratories (NANoREG D2.10).

Procedures were developed for several other endpoints of regulatory relevance, including identification and quantification of surface chemical modifications (NANoREG D2.04) as well as dissolution testing, and reactivity (NANoREG D2.08). Revisions of several OECD TGs were proposed or TGs were proposed to be replaced with alternative or new methods (NANoREG D2.09).

It is evident that further testing and/or acceptance of the other SOPs is needed in order to establish international guidelines and standard methods to support the regulatory process. A revision to clarify the guidance and recommended characterization methods in general would be of great benefit for the registrants of REACH. Recommendations in this field have been presented in section 4.1.1.

White Paper Recommendation 10: REACH – 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 Deliverables 2.12 and underlying deliverables.

4.3.4 Waiving

Apart from the proposed adjustment of the REACH Regulation with respect to requirements regarding endpoints that are not relevant, cannot be measured for nanomaterials or are missing, it is recommended that waiving should be permitted for some of the requirements.

Waiving currently may be applied on the basis of general exposure and fate knowledge, since Annex XI[xxxii] gives the possibility of exposure-based waving and this applies to any substance including nanomaterials. However, given the hetero-coagulation of nanoparticles and extreme nano-specific requirements of aquatic toxicity test protocols (unnatural conditions versus extremely low exposures) the relevancy of testing for aquatic toxicity of nanomaterials is highly questionable[xxxiii], [xxxiv] It has been shown that waste streams containing nanoparticles passing through aquatic routes will be sequestered at Waste Water Treatment Plants (WWTP) and retained in the sludge. Secondly, for MNMs passing through the WWTP into the effluent, the high level of natural coagulants (dissolved organic compounds) and natural NMs leads to hetero-coagulation of MNMs resulting in sequestering, transport, and finally sedimentation. Pelagic and benthos testing seems sufficient. Considering that the life cycles of many MNMs are determined by their application within products, it becomes clear that relevant exposure scenarios and particle aging or transformations of the MNMs are strongly dependent on the life cycle of the nano-enhanced products themselves[xxxv].

Hence waiving of aquatic toxicity testing of non-soluble MNMs[xxxvi] seems realistic on the basis of exposure and sedimentation.

White Paper Recommendations 11: REACH - Waiving

The possibility for waiving information requirements as laid down in Annex XI of REACH for aquatox testing of non-soluble MNMs should be introduced as a general rule in the REACH guidance document(s). Testing accumulation in aquatic systems should focus on benthic organisms.

4.3.5 Critical evaluation of nanoEHS data

As explained in section 3.2.2, a critical approach to data used for risk assessment is needed. Efforts to improve methods and their resulting data should not be undermined by comparing them with data that has not undergone the same scrutiny.

Given the limited reliability of data originating prior to 2010, predominantly due to unstable dispersions for *in vitro* and ecotoxicological studies, and poor characterisation of test items, it is clear that the data from peer reviewed sources needs to be curated before using it in the REACH (or other regulatory) assessment processes. As a rule of thumb, in particular data generated prior to 2010 needs to be carefully checked for relevance, robustness and reliability. Of course, data post-2010 must also be checked!

Annex 1 of the Joint Document ("ProSafe Roadmap for Members of Task Force when Reviewing Data, Protocols, Reports and Guidance notes for Regulatory Relevance") can be helpful to judge the regulatory relevance of data. Several nano-specific data curation criteria (not just general Klimisch criteria) have been developed by the Task Force generating the Joint Document and should be seriously considered[xxxvii].

> White Paper Recommendation 12: REACH – data quality
>
> *ECHA should develop (or update) guidance documents for the use of experimental data to ensure that data used for risk assessment, have a regulatory relevance.*

4.4 Innovation in Risk Assessment

The race is on; novel materials are developed in abundance while the time from R&D to market has been dramatically reduced during the last decade. As a result of this scientific/economic development, risk assessment needs to be accelerated too. The disparity between time to market in a matter of months rather than years, and contrasts with chronic exposure studies for assessment which take years from start to finish. Long-term inhalation exposure studies, like the BAUA/BASF study part of NANoREG (+4 years) are a clear example.

Current human health risk assessment procedures are challenged by societal, political and legal demands as well as by scientific and technological progress. As a result, visions and concepts have been launched that demand a paradigm shift in human risk assessment, of which the US National Research Council[xxxviii] is the most well-known example. According to these initiatives human health risk assessment should shift from hazard-driven animal-based approaches to frameworks that incorporate innovative human-relevant methods that are based on our understanding of mechanisms of toxicity, and apply the 3R principles (replacement, reduction, refinement of animal testing).

Our increased understanding of mechanisms of toxicity and progress made in the development of 3R test methods is not yet incorporated in human health risk assessment procedures. Safety assessment for repeated dose toxicity is one of the greatest challenges in the process of replacing animal testing. The EU policy to protect laboratory animals[xxxix] and the need for a new systemic toxicity testing arising from the complete ban on animal testing for cosmetic ingredients within the EU[xl] provides additional impetus for this large-scale collaborative effort. Also national policy developments like the Dutch policy intention passed by parliament to replace animal testing for chemical safety by the year 2025 contributes to this momentum.

Improvement of relevance is another objective. The potential advantage of using data from *in vitro* models is the opportunity of using human cells or human-derived cell lines, with higher human relevance than traditional *in vivo* animal data. However, as we have seen from the results of NANoREG there is still a lot of work to be done to solve the challenges of *in vitro* testing. The major flaw of *in vitro* testing is that only few tests are validated in a way that can avoid *in vivo* testing. This is still the bottleneck. We have to find ways to address the distribution of MNM in the living organism, which is essential for toxic effects and cannot be accurately mimicked by *in vitro* models for most exposure scenarios. We have to be aware that such a push for the improvement and acceptance of novel assessment techniques is a long-term objective that needs to be supported for at least the coming decade, since acceptability of *in vitro* results remains the main bottleneck for the utilization of novel techniques.

Clearly a real investment has to be made into both alternative testing methods, and equally important, the acceptance of these methods. Of course this can be said for all chemicals. Unfortunately, efforts made over decades have so far only validated a few *in vitro* tests in such a

way as to be able to completely avoid *in vivo* testing. Projects like SEURAT-1 should be the model for similar initiatives for chemical assessment. This would require a major effort and commitment, since SEURAT-1 did not need to look at the oral and inhalation routes with its focus only on cosmetics. The suggested strategy for chemical read-across is to show how a traditional read-across, based on structural similarities between source and target substance can be strengthened with additional evidence from data using new approaches. For example, information from *in vitro* molecular screening, "omics" assays and computational models could be integrated to get regulatory acceptance, though this is a medium- to long-term goal. It would serve several objectives, assessment keeping pace with innovation while elucidating the mode of action and its strengthening of categorization and grouping strategies.

The suggested strategy for chemical read-across is to show how a traditional read-across, based on structural similarities between source and target substance can be strengthened with additional evidence from new approach data (i.e. information from high-throughput screening (HTS)/high-content analysis (HCA) approaches[xli], *in vitro* molecular screening, "omics" assays and computational models) to get regulatory acceptance. Foreseen topics are[xlii]:

a) Theoretical descriptions of adverse outcome pathways (AOP) based on existing knowledge,

b) Hypothesis-based testing strategies employing alternative *in vitro* and *in silico* methods with a clearly defined toxicity prediction goal, and

c) Applying existing information (e.g., physical chemical properties, *in vivo* animal data, human data) and HTS/HCA approaches, with selected data generated from alternative methods, achieving a regulatory-accepted safety assessment, based on mode of action knowledge of the compound.

In an ideal world, nano-(Q)SAR models would be based on large data sets that are obtained by following a standardised protocol where possible using HTS methods, and assessed in terms of quality and suitability for modelling, prior to model construction (Figure 8).

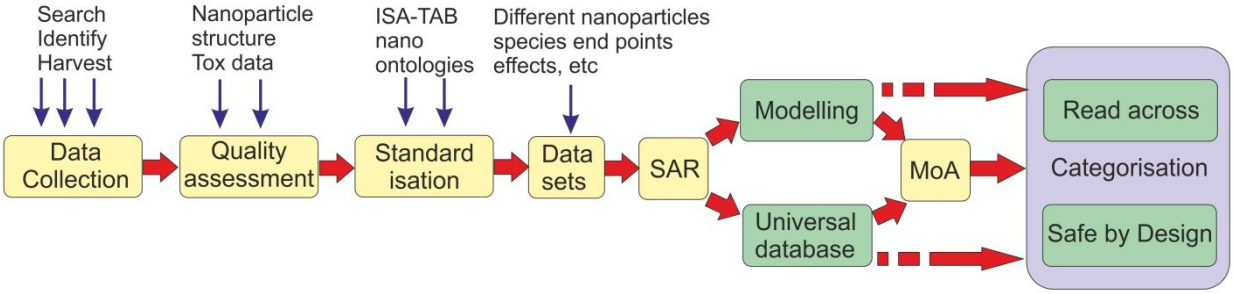

Figure 8: shows the general data collection framework for (Q)SAR studies, together with the issues that directly affect the reliability and suitability of the data collected for modelling purposes (modified from[xliii])

The sufficiency of the data for development and independent validation of modelling approaches, and the feasibility of developing nano-(Q)SAR models should be properly evaluated, with careful attention being given to (1) the reliability of the data source, (2) the quality and size of the dataset and (3) the suitability of the data for computational analysis, based on functionality and not on identity[xliv].

At the systems level, the intention is to demonstrate how test systems can be produced by integrating various *in vitro* and *in silico* tools coming from research projects, in order to assess the toxicological properties of chemicals using mode of action as an analytical basis.

A main message to take home from the NANoREG experience is that such a development cannot be expected to be generated through academic research alone. Demand-side management as executed in the NANoREG project is needed to steer towards this goal. This will mean allocation of dedicated (national and EU) budgets utilising the expertise of relevant institutes. At institutional level initiatives to establish Regulatory Research as a specific discipline in the academic world need be supported actively by regulatory policy makers.

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White Paper Recommendation 13: Innovation in Risk assessment

The EC and Member States should consider initiating a project aimed at determining the modes of action and adverse outcome pathways for a number of nanomaterials that are representative for specific groups of nanomaterials while at the same time reducing 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 at the same time developing methods to reduce animal testing.

4.5 Exploring a more future proof approach

Implementation of the recommended measures outlined above with regard to data quality and data management (section 4.1) will create a more solid "information basis" for risk assessment of nanomaterials. The recommendations regarding REACH (section 4.3) will improve the application of this regulation in both a legal and scientific sense. In practice the application of the regulation will remain complex, time-consuming and costly. In addition, adapting and specifying the information requirements and test methods in REACH for nanomaterials that are now on the market will not solve the regulatory hurdles for the next generation of (nano)materials. In the actual regulatory context, every new generation material will necessitate adjusting test methods, information requirements and legislation. A process that, as the nanomaterial file illustrates, takes at least ten years. Possible improvements mentioned under Innovation of Risk Assessment (section 4.4) will only partially solve this issue.

Next generation materials

Specialised material development and its application is what the future holds for us. An example of a material now on the drawing board is a Genetically Engineered Nanofiber-Like Virus For Tissue Regenerating Materials.

The ability to create such novel materials of biological or chemical origin and intermixing technologies will lead to a materials revolution that will shake up the economy and health care capabilities. Subsequently our assessment needs and capabilities have an ever more urgent need for technical innovation in order to speed up the assessment process and legislative reform to be able to effectively and efficiently regulate risks associated with novel materials.

To better align the dynamic character of developing new materials and the static character of regulations, the possibilities of a more future proof approach for securing the safety of new (nano)materials must be explored. Some possible options are mentioned in the White Paper and to some extent have been developed in the NANoREG Framework, such as the "nano-specific risk assessment approach" and the "safe-by-design approach".

The first option is aligned with a more "concern-based testing approach" based on risk potentials that serve as indicators for potential hazards. It may include the application of functional assays, as recommended in the Joint Document, being promising techniques for determining the potential hazard. The safe-by-design approach looks at ways to identify, and thus avoid, potential adverse effects of nanomaterials from the earliest stages of the innovation process onwards. Both options are explained in the sections below.

White Paper Recommendation 14: Future proof approach

Member States and the EC should initiate an (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 potentials as developed in the NANoREG project and the safe-by-design approach as developed in NANoREG and ProSafe and now further explored in NanoReg2.

4.5.1 nano-specific Risk Assessment approach

For the assessment of the risks of nanomaterials, REACH requires comprehensive data to judge hazard and exposure. Data that often are not available for nanomaterials and any applications that are newly developed. Generating these data is costly and very time-consuming and does not fit with the pace of developing and marketing such materials and applications. A tiered approach of testing, assessing and prioritization would undoubtedly reduce costs and loss of time, thus stimulating innovation, and at the same time obtain sufficient information for risk assessment.

NANoREG developed such a tiered approach: the nano-specific risk assessment approach. According to this approach, the nanomaterial is initially characterized for a limited set of physicochemical parameters, and then tested in a first tier. This concept includes six 'risk potentials' that serve as indicators for potential hazards namely, solubility/dissolution rate, stability of coating, accumulation, genotoxicity, inflammation and ecotoxicity. These six risk potentials have been developed based on overlapping approaches to risk assessment of nanomaterials such as those developed within MARINA, GUIDEnano, ITS NANO and NANoREG. If a reason for concern is proven, then this will be followed by the standard full description and characterization of the nanomaterial. This approach will also enable the registrants to build up the evidence base for establishing SIPs as a result of the recommended data for QSAR and grouping by ECHA (Nano-specific Appendix to Chapter R.6). Finally, this also provides a better fit with the SCENIHR recommendation to perform case by case evaluations, where this does not contradict the aims of reducing animal testing or use of resources.

Prioritizing on the basis of risk potentials, and based on relevant tests as a consequence, means that intellectual property issues in the SIEF process would be pushed back to a later stage in the process. This would be well received by industry and innovators.

This approach has been developed in NANoREG Deliverable 5.08 and Deliverable 1.11 (Part II; chapter 4), although cut-off values and decision criteria have not been proposed.

The most distinctive feature of a nano-specific Risk Assessment approach should be its focus on nano-specific issues, not only on hazard (e.g. as within the CLP), but also on exposure assessment, including an assessment of kinetic behaviour. The potential role of functional assays to trigger effects and fate should be highlighted (see chapter 5.1 of the Joint Document). Examples of such properties are dissolution rate and reactivity.

The approach described below supports further development of such insights by identifying:

Functional assays

Fundamental nanotoxicology studies require precise characterisation of the specificities of a given nano-element (size, chemical composition, detailed shape, level of aggregation, etc.) throughout an experiment. However, there is an urgent regulatory need for new methodologies to quickly assess the presence and reactivity of nanoparticles in commercial, environmental, and biological samples, since current detection techniques require expensive and complex analytical instrumentation. Rodent inhalation models to predict the toxicity and pathogenicity of nanomaterials are prohibitive in terms of time.

Such functional assays include cell culture assays for cytotoxicity (altered metabolism, decreased growth, lytic or apoptotic cell death), proliferation, genotoxicity, and altered gene expression. The choice of cell type for these assays may be dictated by the procedure or endpoint selected. Surface redox reactivity is a key emerging property related to potential toxicity of nanoparticles for living cells, and can be used as a key surrogate for determine for the presence of nanoparticles and a first tier analytical strategy toward assessing nanoparticle exposures.

- Those applications of nanomaterials that have the highest potential to cause adverse human health effects (due to high exposure and/or toxicity),
- Those aspects of exposure, kinetics or hazard that are most important to address in the human health risk assessment of nanomaterials,
- Those situations where the use of nano-specific grouping, read-across and QSARs is likely to become feasible and potentially become regulatory acceptable in the medium to long term, and
- The type of information needed for this regulatory acceptance.

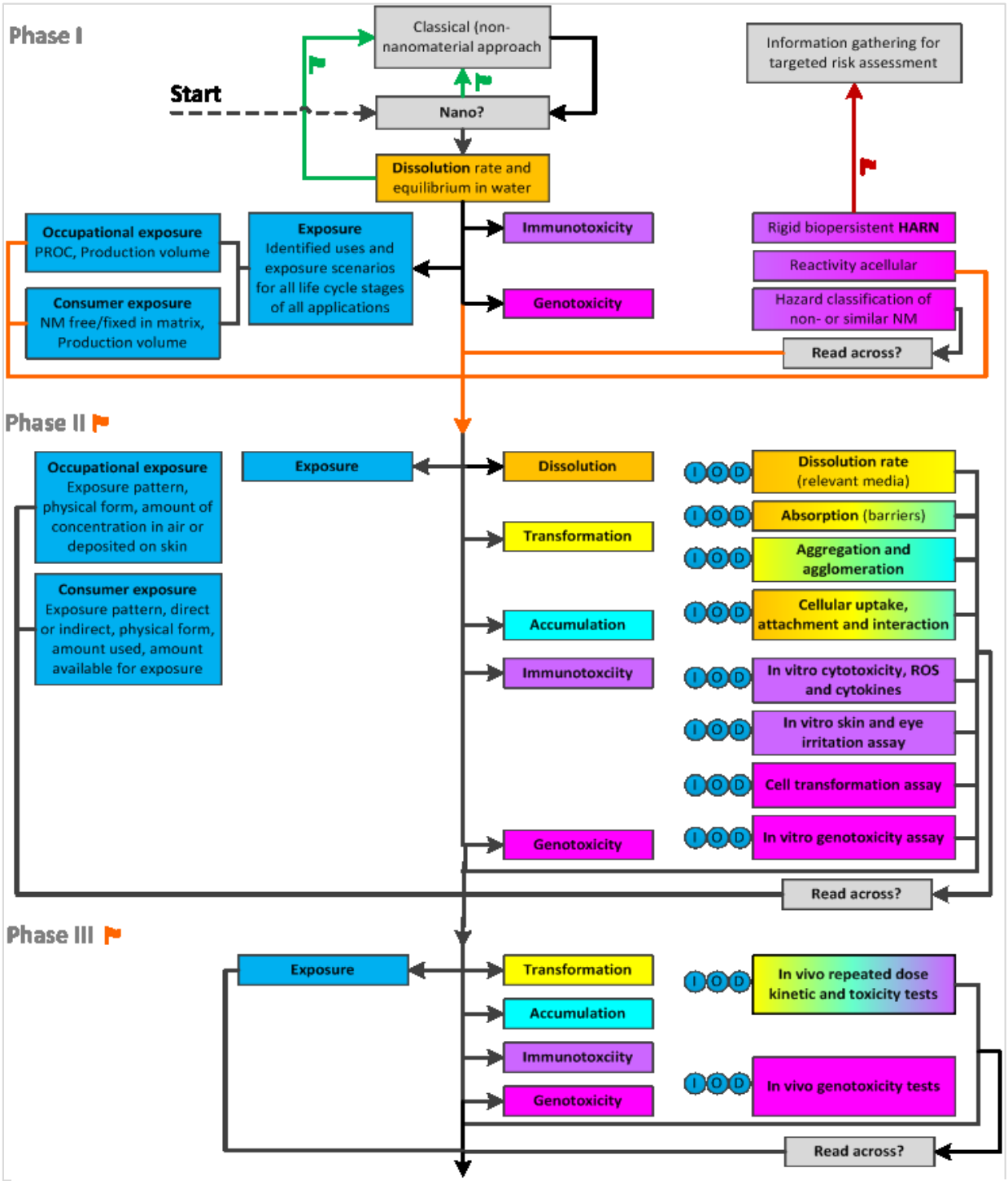

Figure 9: Flow chart showing the different phases of the proposed approach towards nano-specific prioritisation and risk assessment[1]. Black arrows: evaluation of the MNM following the elements related to kinetics, toxicity and exposure in phase I, II, III and further. Green arrows: the material is not a MNM or has such a high dissolution rate in water that it dissolves into its molecular or ionic form before it reaches its target → the classical (non-NM) risk assessment can be performed. Red arrows: the material is a "rigid and bio-persistent High Aspect Ratio Nanomaterial (HARN)" → substitution or information gathering for targeted risk assessment to evaluate the potential to cause mesothelioma is needed. Orange arrows: the material does not meet the criteria for classical (non-NM) risk assessment or targeted risk assessment to evaluate the potential to cause mesothelioma → use the information from phase I for prioritisation and/or further evaluation following the elements related to kinetics, toxicity and exposure in phase II, III and further. PROC = Process Category. I = Inhalation route of exposure. O = Oral route of exposure. D = Dermal route of exposure.

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The proposed approach is built on the extensive knowledge already developed in European research projects or through collaboration with other international organisations and committees. It aims to be applicable to nanomaterials that are already on the market. However, elements of this approach, such as the use of grouping and read-across methods, and of aspects most important to address the nano-specific issues within the risk assessment, will also be applicable to safe innovation approaches during the development of new nanomaterials in the research and development phase.

Further, the scientific knowledge on nanomaterials is not sufficient yet for defining decision criteria, cut-off values, validation and subsequent regulatory acceptance of nano-specific applications of (Q)SARs, grouping and read-across tools. Definition of such decision criteria is needed to develop an implementable approach, and would require international cooperation of policy makers, scientists and industry.

4.5.2 Safe by design

The safe-by-design (SbD) concept aims to reduce uncertainties associated with MNMs while they are still in development through market application to end of life and disposal. This has the potential to ensure that the risks of products launched in the market are known and managed, and where possible reduced, so that the predicted benefits outweigh any residual risks, and that industrial actors reach a situation of regulatory preparedness as their products develop. It can also support public opinion that innovators care about human health and environmental safety in addition to their profit margins. Through its implementation, it also holds the potential to create a closer collaboration between product developers and safety scientists as well as among scientists, innovators and regulators who all work together to further the common aims of technology development that will be safe for human health and the environment. By including a broader range of actors and issues for consideration, it aims to enhance the potential for safe, sustainable and responsible innovation using MNMs, as called for by the European Commission. Safe by Design is not only about design of MNMs at the concept stage, but also about the safety of MNMs from products during use, recycling or disposal, up to the stage of accumulation in environmental sinks. The SbD concept has been developed within NANoREG and ProSafe and awareness about the SbD concept has been promoted. NanoReg2 builds on these results by exploring the practical implementation of this concept.

Application of safe-by-design principles is considered to be crucial for a cost-effective risk management of MNMs. The application and implementation of safe-by-design supports the identification of uncertainties and risk potentials (hazard or exposure) as early as possible in an innovation process. Based on this information the uncertainties and risk potentials will be reduced or eliminated by using different management procedures such as; risk management, EHS management, regulatory management, and safety data management. All these measures will support the reduction and balance of costs (functionality-safety costs). There is also a significant potential to reduce the costs of developing regulatory dossiers as pointed out in chapter 5 of the NANoREG D1.11.

For the implementation of SbD there are two key issues at stake. First there is the challenge of making the innovator aware of the stage(s) of development of their material where relevant regulatory requirements come into play, namely for production, product and intended use. For this aspect, a web-based tool is currently being developed as part of the ProSafe actions.

The second big issue is the ability to apply design rules to make a material as safe as possible while satisfying functionality for its intended use. Since comprehensive data necessary to judge hazard and exposure are not available for most MNMs that are under development, the SbD concept initiated within NANoREG has also worked to expand the concept in relation to ‘risk potentials’. This currently includes six key issues that can serve as indicators for potential hazards, including bioaccumulation related potentials (solubility/dissolution rate, stability of coating, accumulation) and effect related potentials (genotoxicity, inflammation and ecotoxicity). These six risk potentials have been developed based on overlapping elements in several different approaches to risk assessment of nanomaterials such as those developed within MARINA, GUIDEnano, ITS NANO, NanoTest, and NANoREG. The suggested strategy for chemical read-across is to show how traditional read-across, based on structural similarities between source and

target substance can be strengthened with additional evidence from data using new approaches. Robust and reliable testing tools like “omics” and *in vitro* HTS approaches are of vital importance to keep the pace of safety testing in line with the design process. Eventually, this will all lead to a curated nanotoxicity database which provides the opportunity to do computational modelling to elucidate the structure activity relations (SAR) and eventually the mode of action. In an ideal world, this would than serve categorization and improve risk assessment in terms of cost, reliability and utilization early in the value chain.

At the moment SbD is best described as a developing concept. In the long term SbD has the potential to become a standard tool for governance of risk for novel materials. The Netherlands has stated that it will become standard policy to implement SbD in the future [xiv]. In the best case this could become an EU-wide, or even global practise. A still unresolved problem is how to sell the idea of safe-by-design to industry. While large industries already put this into practice, SMEs are unaware of SbD or do not have the resources to fund it. Food for thought in the nano-policy arena.

5 White Paper recommendations and the way forward

For clarity, this chapter reiterates the recommendations presented and explained in the previous chapter. Where relevant, links are provided to NANoREG or ProSafe documents which contain more detailed, supporting information with respect to these different recommendations. Furthermore, some ideas are presented on how to convert the recommendations into a concrete agenda for improving the regulation and governance of risk assessment of nanomaterials.

5.1 White Paper Recommendations

5.1.1 No regret measures

Part of the recommendation presented in this white paper have a “no regret” character, meaning that the proposed actions are commonly considered as necessary, feasible, effective and cost-efficient. Most of them are aimed at creating a solid information basis for the risk assessment of nanomaterials by improving the quality and accessibility of experimental data and other nanoEHS information.

Harmonised test methods

1. The OECD Working Party on Manufactured Nanomaterials (WPMN) should consider adapting their existing working programme and undertake an ambitious schedule to adopt and implement the harmonisation recommendations laid down in the ProSafe Joint Document and various NANoREG deliverables. EC and Member States should commit themselves to contribute to the execution of such an ambitious programme.

NanoSafety Cluster

2. The NanoSafety Cluster should take the initiative to select test methods that nanosafety projects should focus on for further development and application.

Generating quality data

3. The European Commission should initiate (at least one) demand-driven project to generate experimental nanoEHS data. Such a project should include adequately characterized materials that have different properties and include appropriate assays for examining interactions or endpoints. Materials that should be included in such a project are (1) “real-world” materials, (2) well-characterized reference materials of varied size, shape, aspect ratio, surface charge, and surface functionality and (3) standard materials for calibrating various assays and measurement tools.

Data management

4. The European Commission and Member States (MS) should introduce and enforce an obligation to share the results of 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 (ISA-TAB-Nano logic) way. A 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.

5. 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 a check on data quality (data curation). This last should be aimed at avoiding or repairing reporting errors as well as judging the regulatory appropriateness of experimental data (test design).

Top-down approach

6. 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 used and data management. The NanoSafety Cluster could play a role in defining such conditions.

Harmonisation of occupational exposure limits

7. 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.

5.1.2 A realistic REACH for nanomaterials

The recommendations in this category are aimed at making REACH more applicable to nanomaterials by taking away some of the legal and technical/scientific glitches. They will contribute to possibilities for grouping and read-across, and a scientifically sound risk assessment. However, the effects of the recommendations on the costs and the time needed for application of REACH will be limited.

Legal basis for nanomaterials

8. The European Commission and Member States should include a legal definition of nano-materials 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.

Information requirements

9. The schemes for substance identification and substance specific profiles, irrespective of whether it is a MNM or not, should be modified as suggested in NANoREG deliverable 2.12. The morphological categorisation should be modified and aligned with the already developed (ISO) schemes and the OECD. Information on particle size distribution, shape, porosity and surface chemistry (e.g. reactivity), should be added to the information requirements.

10. 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 Deliverables 2.12 and underlying deliverables.

11. The possibility for waiving information requirements as laid down in Annex XI of REACH for aquatic toxicity testing of non-soluble MNMs should be introduced as a general rule in the REACH guidance document(s). Testing accumulation in aquatic systems should focus on benthic organisms.

12. ECHA should develop (or update) guidance documents for the use of experimental data to ensure that data used for risk assessment have a regulatory relevance.

5.1.3 Innovation in risk assessment

The recommendations in this section are aimed at a more efficient (cheaper and less time consuming) risk assessment of (nano)materials.

13. The EC 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, while reducing 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 at the same time, reducing the need for animal testing.

5.1.4 Future-proof approaches

Implementation of the recommendations presented above will result in more efficient and effective regulation and governance of nanomaterials. However, it will not be the answer to the regulatory problems that will be faced for next generation materials. With the current regulatory approach new types of materials will require development and harmonisation of new test methods, adjustment of the legal provisions and generation of sufficient data for a more efficient risk assessment. As the nanomaterials file makes clear such a process may take ten to twenty years. A more future-proof approach is necessary to keep pace with innovation and to secure the safety of new materials. For this reason, this White Paper presents the following recommendation:

14. 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. Potential options that could be considered are concern-based testing on the basis of risk potentials as developed in the NANoREG project, and the safe-by-design approach as developed in NANoREG and ProSafe that is now further explored in NanoReg2.

5.2 The way forward

The recommendations presented above are the result of a detailed evaluation and analysis of the findings and results of NANoREG and ProSafe by the staff of the Project Office. They do not necessarily reflect the opinion of the partners or the management committee of either project, nor have they been approved by the EC or Member States that funded both projects.

The recommendations will only have a value when they have been debated and assessed by the organisations involved in, or responsible for, nanosafety research and the regulation of nanomaterials, including the EC, EU Member States, and the OECD. Ideally this would include the assignment of responsible organisations for a specific measure or recommendation, and allocation of the resources to fund the necessary measures.

15. The European Commission and or one of more Member States should initiate a policy conference for EU Member States to discuss and decide on implementing the recommendations laid down in the White Paper.

    Such a conference should ideally result in a set of agreed measures, the assignment of a responsible party for each specific measure, and arrangements on the funding of the specific measures. Based on the NANoREG experience, funded projects should be demand-driven (see recommendation 6 on the top-down approach).

Annex I: NANoREG and ProSafe documents relevant for the White Paper recommendations

Document	Fact-sheet	Name/*Content*	Linked to recommendation
ProSafe Final Report		ProSafe Final Report *Overview of the results and impact of the ProSafe project*	4, 5, 15
ProSafe D3.02		ISA-TAB-Nano database system established and adopted within the NanoSafety Cluster *- information on/links to ISA-TAB-Nano templates for standardised data logging as developed by eNanoMapper and the NANoREG project*	4, 5
ProSafe D3.03		Minimal ontology and naming convention for nanosafety data *- information on/links to the nanoEHS ontology as developed by eNanoMapper and applied by the NANoREG project*	4, 5
ProSafe SbD implementation concept		ProSafe SbD implementation concept *- Further elaborates NANoREG SbD concept with workflows, safety dossiers, safety profiles and harmonised SbD protocols, procedures and data*	13
ProSafe D5.08		ProSafe Joint Document *- overview of regulatory relevance of test/assessment methods on the field of Physico chemical characterization, exposure through the life cycle, fate – persistence – bioaccumulation/biomagnifications, exposure modelling, ecological effects and Biokinetics, human health effect and Biokinetics in vivo, health effects in vitro, (Q)SAR modelling of nanomaterials and risk assessment.* *- recommendations regarding harmonisation* *- Annex II ProSafe roadmap for members of Taskforce when reviewing data, protocols, reports and guidance notes for regulatory relevance*	1, 5,12,
NANoREG Final Report			2, 3, 4, 5, 12, 14
NANoREG D1.11	FS	Definitive Framework; *- Chapter 4: a new approach toward nano-specific prioritisation and risk assessment* *- chapter 5: Safe by design*	13, 14
NANoREG D2.04	FS	Protocol for quantitative analysis of inorganic and organic MNM surface coatings	9
NANoREG D2.05	FS	Protocol for characterisation and categorisation of MNM in powders and liquid dispersions *Advanced morphological categorisation scheme; it introduces relevant physicochemical properties of MNM by structuring them into: 1) Structure/Chemical composition, 2) Shape/Porosity, 3) Specific Physicochemical properties*	9, 10
NANoREG D2.06	FS	Validated SOPs for test item preparation for key in vitro and ecotoxicity studies	1, 12
NANoREG D2.08	FS	SOPs for exposure fate characterisation in ecotoxicity and in vitro studies	1, 12
NANoREG D2.03 D2.09:	FS FS	Experimental evaluation of OECD methods for analysis of physicochemical MNM properties (D2.03) Revised OECD methods for determination of physico-chemical MNM properties (D2.09)	1, 9, 10
NANoREG D2.10		Protocols for size distribution analysis of primary nanoparticles	1

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NANoREG D2.11	FS	Possibilities and limitations with respect to the use of VSSA for determining size distribution	8
NR Deliverable 2.12	FS	Framework and procedures for characterisation and reporting of manufactured nanomaterials for regulatory use - *Schemes for substance identification* - *methods to generate the minimum sets of physicochemical endpoints required for the substance identification, grouping, QSAR and read-across schemes for NMs in REACH.*	1, 9, 10
NANoREG D3.05	FS	Development of an aquatic Mesocosms Platform allowing the evaluation of kinetics of aggregation	11
NANoREG D3.09	FS	Data on the effectiveness of risk management measures	
NANoREG D4.12	FS	Accumulation potential and aquatic toxicity of relevant groups of nanomaterials and product formula *Proposals (SOPs) for revision of ISO and OECD standard methods for ecotoxicity testing including methods to prepare dispersions*	1
NANoREG D5.01	FS	Report on identification and setting of categorization, read-across, and extra/interpolation criteria	
NANoREG D5.02	FS	Report on the development of a solubility testing procedure	1, 13, 14
NANoREG D5.03	FS	In vitro screening methodology for absorption or crossing of other barriers	13
NANoREG D5.06	FS	Identification and optimization of the most suitable in vitro methodology	13
NANoREG D5.07	FS	Develop a rapid high throughput screening methodology to evaluate NM toxicity	13
NANoREG D5.08	FS	Decision tree for risk assessment of NMN - *Outline for a nano-specific approach of risk assessment*	13, 14
NANoREG D5.09		Summary report WP 5	13, 14
NANoREG D6.04	FS	Inventory of existing regulatory accepted toxicity tests applicable for safety screening of MNMs Selection of 6 risk potentials (as used in D5.08) and available test methods	13, 14
NANoREG SbD concept		Integrates currently used management processes for innovations, risks, EHS, regulatory affairs and data handling:	14

Annex II: Document history

Updated version 20170922	• Recommendation 13 on page 40 has been deleted. It was a copy of recommendation 14. The recommendations in chapter 5 now align with the recommendations in the executive summary and chapter 4. • Document history added • Chapter numbers annexes removed

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Annex III: List of References

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