Promoting the Implementation of Safe by Design

ProSafe Final Newsletter - Focus on project results

On 28 April 2017 the ProSafe project formally ended. Most of the work has been done and we can look back on two years of a pleasant and fruitful collaboration! As within the NANoREG project, a community has been developed with a network reaching out all over the world.

ProSafe was designed to coordinate and support EU Member States and Associated States in their effort to come to a well-grounded, effective and efficient way of managing the risks of nanomaterials. This by integrating and evaluating the results of numerous nanosafety projects from all over the world, by consulting experts in various fields of nanosafety-expertise and by involving policymakers, regulatory bodies and many others in the development of ideas and proposals regarding a more effective and efficient governance and regulation of nanomaterials. Did we succeed to make a change over the past two years?

In this final newsletter you can read more about the results achieved over the past years.
The Joint Document is to be considered a key result. It compiles the results of an extensive evaluation of the results of NANoREG and other nanosafety projects regarding their regulatory relevance. The work was carried out by a Task Force of senior experts chaired by Klaus Steinhäuser and Phil Sayre; we owe them many thanks for an impressive piece of work of high quality and - as I expect - of great impact. A draft of this document was discussed during the OECD-ProSafe Joint Scientific Conference in December 2016; this was a fruitful and inspiring event.

In addition to this, I mention the completion of the Delphi Poll and the Safe-by-Design approach and Safe-by-Design web tool. And finally (or is this only the beginning?) the ProSafe White Paper has been developed. Although not finalized yet, the current version is getting into shape for the next exercise: a discussion with regulators, policy makers and risk assessors on the recommendations in the White Paper with respect to, among others, REACH and its appendixes and Guidance documents, data management and future nanosafety research. Detailed information on all the ProSafe activities and results can be found in the ProSafe Final Report with hyperlinks to the public deliverables and other relevant documents. Just like for the NANoREG project, all documents will be made available as off the end of the project (ProSafe Results Repository). An achievement that hopefully inspires other nanosafety projects, since sharing of information is key to making progress.

I hope you will enjoy reading this newsletter and will have a look into the ProSafe Results Repository

Tom van Teunenbroek
Coordinator H2020-ProSafe

Content

I) Introduction: Project objectives and achievements

A serious threat to the capitalization of the innovative and economic potential of Nanotechnology is the limited understanding of the Environmental, Health and Safety (EHS) aspects of nanomaterials (NMs). This limited understanding leads to uncertainty on how to judge the EHS aspects of these materials in a regulatory context. This has a negative impact on the investment climate and on societal appreciation of products containing NMs.
Reducing and eliminating these uncertainties and developing ways to incorporate nanosafety in the design of nanomaterials is an objective of a great number of nanosafety projects funded by the EC or national authorities. The ProSafe project is aimed at coordinating and supporting part of these efforts by bringing together and where possible aligning the results of these projects. The main aims and resulting products of the ProSafe project are:

1. The Joint Document (JD): This document compiles the results of an extensive evaluation of the results of NANoREG and other nanosafety cluster (EU) projects and the results of the OECD sponsorship programme by a Task Force of independent senior experts. The document served as a reference document for the OECD-ProSafe Joint Scientific Conference in November 2016. The Joint Document also serves as the technical annex to the EU policy-oriented White Paper.
2. The White Paper: This document will provide building blocks for regulators and industry to cover EHS aspects of manufactured NMs (MNMs) including evaluated methods for testing and assessing risks of nanomaterials and including Safe by Design (SbD).
   Contributing aims and activities for the White Paper are:
   - Analysis and synthesise of what will come in the next 3-10 years for nanomaterial product development and its risk management (“foresight study").
   - Establishing standard approaches for (EHS) data management.
   - Acceptance and further elaboration of the NANoREG safe innovation and safe-by-design concept.

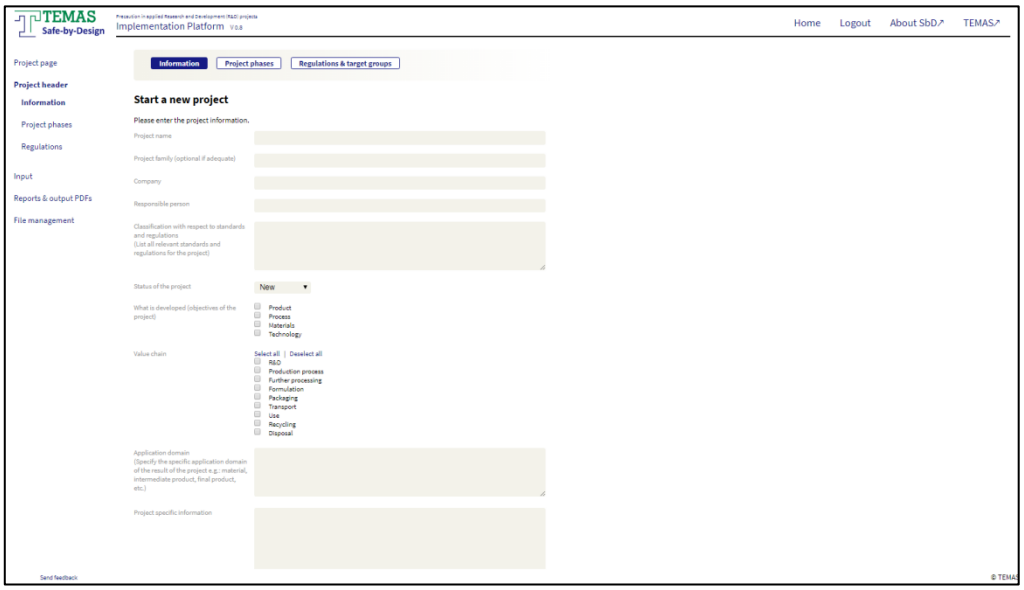
II) SbD Implementation Plan: tools, needs and gaps

The Safe-by-Design (SbD) concept as developed in the NANoREG project needed to be made concrete and applicable by companies to address safety of innovation. Taking into account the need for a consistent SbD application throughout the EU, the ProSafe activity focused on harmonization of tools and concepts. In particular, requirements and terms of the content to be harmonized have been identified, with an overview on fundamental and regulatory aspects, cross-cutting issues, as well as newly identified challenges and issues and future related activities. The nanosafety community was called to provide opinions and information on tools, processes, instruments, etc., covering the harmonization needs. The list of requirements for the implementation of SbD settled a basis of supporting items for further activities in the field of SbD, which were taken up by NanoReg[2] project, through the development of a working tool called the "Safety Dossier", and the subsequent TEMAS on-line SbD implementation platform (https://temas.taglab.ch/SbDimplementation/index.php?p=home).

One of the most obvious translations of SbD is to create safer, greener, and yet efficient nanomaterials, e.g. Green Chemistry. However, it is necessary to know how MNMs properties influence hazard and exposure. The - potential - ability to control properties by innovation processes is only helpful if it is known which properties are problematic and which are not. Also, predictive tools such as (Q)SAR models and MNMs grouping developed on the basis of MNMs toxic mechanism of action structured as Adverse Outcome Pathways are needed. Availability of reference and benchmark materials, appropriate assays, and large accessible experimental datasets is paramount to develop these models.

More needs were identified for each element of risk assessment, and details may be found in D4.4 in the ProSafe Results Repository.

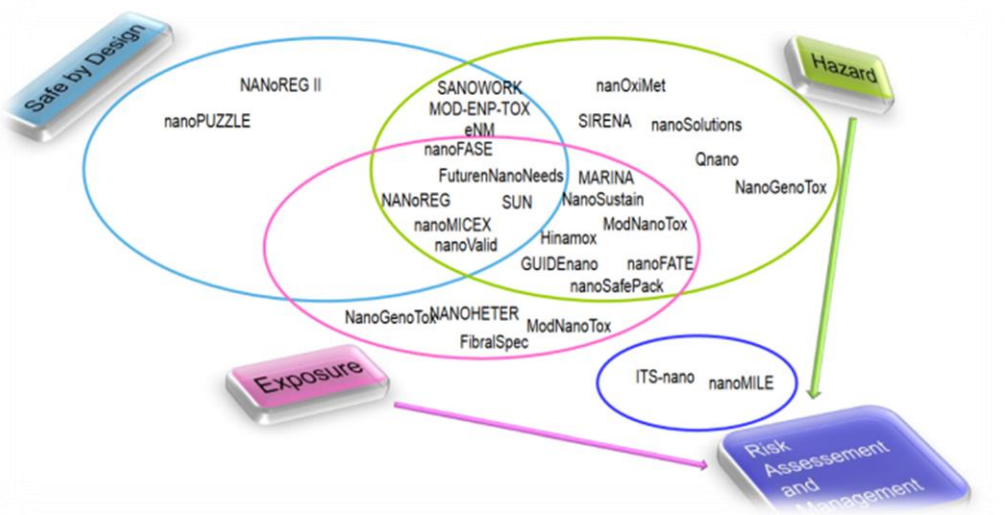
Finally, to improve efficiency of the SbD process, it would be relevant to have a way to prioritize MNMs safety in different moments of the innovation process. The three principles of Emergent risk, Plausibility, and Severity are suggested to be included in the SbD application along the entire life cycle. This approach supported by grouping and QSAR methods could allow the identification of MNMs to be avoided, and the identification of hot spots for which investments for risk and uncertainty reduction may give the largest advantage.



On-line Safe-by-Design Implementation Platform (TEMAS)

III) Harmonization of databases

Access to EHS database by the nanosafety community is hindered by several factors: i) the lack of knowledge of their existence, ii) different structure and management systems, iii) different ontologies. To build a consistent and useful database for the application of Safe-by-Design along the value chain and regulatory safety assessment, it is necessary to streamline the data acquisition, improve database management by using a common and agreed platform such as the ISA-TAB NANO templates, and link different databases through dedicated IT tools.



Map of R&D projects contribution to EHS Database

The first result achieved by ProSafe was the mapping of the existing databases generated by research projects included in the NanoSafety Cluster (NSC) Compendium 2014, NSC WG4 2014 Database Survey, and other relevant projects up to December 2015. More than 50 research projects were examined, reporting in an internal Access database information such as the scope of the project, the data domain (e.g. toxicology, exposure), type of tests carried out (e.g. in vitro), source of data, location of the database, the data curation, entry format, etc. The amount and quality of data available was very variable. The findings ranged from readily and complete accessible database to lack of any information, such as un-accessible web site, making those data and the investment to generate them effectively lost to the EHS community. The mapping resulted in the following databases: 34 on physicochemical properties, 30 on toxicology data, 20 on ecotoxicology, and 17 on exposure. Other potential sources of data evaluated by ProSafe, but not used in the Access database, included the US-EU Community of Research, the US-CEINT, the NANEX and NECID databases on exposure, and the MODENA-COST action.

The harmonization of EHS databases goes through the data entry format and an agreed ontology, allowing for a proper data management across different databases, and establishing the basis for a future common EU (and maybe global) data platform. While efforts to meet good data management needs have been duplicated across (many) different projects, for the time being it is positive to recognize that some attempts of standardisation is taking place across projects, primarily as result of data exchange and project build up, such as MARINA templates, and the ISA-TAB Nano logic. The latter is really important for ProSafe and the EHS landscape in general, since it represents a link between regulatory driven projects like NANoREG and NanoReg^2, with an established cooperation with the eNanoMapper project.

eNanoMapper and the further ISA-TAB Nano template and ontology development in other projects could represent the shared effort to reach the final goal of NanoEHS database harmonization, with easy to use data entering and end-user applications.

Until a unified data collection and management system is in place, the lack of interoperability of databases calls for exchange formats and IT "translation" tools. eNanoMapper developed a database set-up, including project instances, and a powerful IT capability to link existing data or datasets. eNanoMapper has also basically demonstrated the possibility to link vendor databases, extracting a minimum set of NM physicochemical characteristics, using a test case based on Sigma-Aldrich NMs. It is worth noting that preliminary bilateral agreements between NANoREG on the one side and NANOREG[2] and caLIBRAte on the other have been struck in early 2017 to transfer part of the NANoREG dataset, with the help of partners that were involved in eNanoMapper.

As a conclusion, to capitalize on these efforts, ProSafe recommends the European Commission to duly consider ways to further integrate the work promoted by ProSafe on data management, into upcoming strategic nanoEHS R&I funding, and to link this appropriately to the burning issue of data sustainability and curation. To achieve that, the buy-in of stakeholders is essential, to ensure the openness of access to those data. Unless funding authorities (in case of public funding) push for opening up the datasets of projects, even before (part of) those datasets are transferred to a suitable location for sustainable long-term curation, the positive effects on the nanoEHS community of stakeholders of actions geared towards sharing/linking clearly will remain quite limited.

IV) Equipment gaps and needs

Implementation of Safe-by-Design by industry requires the development of appropriate methods and tools for risk assessment and management in different industrial sectors. While some tools have been developed thanks to research projects and commercial endeavours, a lot of work still remains to be done to allow for a proper SbD application. The equipment need is an important piece of the puzzle of the White Paper; therefore, ProSafe realized a review and assessment of equipment needs considering all risk assessment parts. The main question was: "What types of equipment are needed to enable industry to effectively manage the risks of MNMs through the SbD process?"

The basis for the assessment was NANoREG regulatory questions and nanomaterials, with the final aim to address the question of where there are equipment road blocks specific to anticipated risk management decision needs and how these barriers could be resolved. Linked to the documents collection carried out to elaborate the Joint Document, relevant publications in addition to results from research projects were identified, leading to the assessment of the adequacy and fitness for purpose of the equipment for: i) physicochemical characterization, ii) exposure measurement, iii) toxicity, iv) kinetics, v) and other equipment.

Equipment needs for specific parameters

Measurement	Criticalities	Recommendations
Phys chem		
Size distribution	- Necessary a range of methods - Difficult application for polydisperse and aggregated materials - No methods for complex matrices	- Development of reasonably priced, accessible, standardized and validated methods to quickly identify and quantify MNMs in different media - Development of standardized and validated methods to determine MNMs most important characteristics in different media during life cycle
Volume specific surface area	- BET measurement not the one in the Recommendation - BET applicable only on powder materials - Other methods available, but not sufficiently developed	- Develop methods applicable to different forms of MNs in different media
Aspect ratio	- Sample preparation for Electron Mycroscopy (EM) - EM slow procedure for no HARN MNs	
Rigidity	- Lak of established methods	- Understanding role of rigidity in toxicology - Development of better equipment for the measurements
Dissolution rate	- Solubility is a dynamic process - Differentiating between dissolved species and particulate species - Taking into account speciation (e.g. insoluble salt particles)	- Need to define benchmarks of solubility for MNMs for regulatory purposes
Chemical composition	- Mixture of on-line and off-line methods needed - Mass spectrometry difficult below 30 nm	- Development of methods to assess composition of particles < 30 nm - Development of on-line methods to detect particles < 10 nm
Surface chemistry	- Complex chemical composition - Interactions with surrounding media	
Exposure	- Metrics - Maximum size to be measured - Spatial and Temporal variability - Discrimination from background - Predominantly non portable instruments	- Better integration of off-line and on-line methods - Increase use of portable instruments - Development of fibre air concentration measurement
Toxicity		
High Throughput/ High Content Screening	- Need of validation with *in vivo* pharmacology - Exposure-dose-response extrapolation for hazard assessment	- HTS/HCS necessary for fast and reliable screening of large numbers of MNMs - Carrying out validation studies on MNMs for which *in vivo* data are available
Organ on chip	- Need of validation and standardization - Need to address different regulatory framework	- Evaluate reliability vs. standard *in vitro* testing vs. *in vivo* testing on model MNMs
Systems Biology and Omics	- Need significant Data Management - Data meaningful if associated to a known Adverse Effect Pathway	- Work toward Omics as part of regulatory toolkit - Develop the AOP approach further - Work toward microarray technology standardization - Data storage, access, and management procedures need to be standardized

Major gaps were identified, where prospects for these to be filled relied, and where it seemed that work was not likely to fill these gaps. It was not possible to establish a prioritization between different equipment in terms of need, since specific methods are often specific to individual MNM types. Therefore, general prioritisation to answer the set of NANoREG regulatory questions across the highly diverse equipment needs was not pursued.

However, taking into account the number of regulatory questions that could have benefitted from an improvement in equipment, as well as the ability to support safety decisions on several MNMs, the two aspects that emerged mostly were High Throughput/High Content Screening Assessment, the particle size distribution and detection/characterization in general. Developing faster, cheaper and more effective equipment to address these two aspects would have a positive impact also for the SbD implementation, since being able to characterize nanomaterials along the life cycle, and evaluating in easier way the hazard associated to different MNM and associated transformation forms (i.e. so called MNM aging) would represent a necessary step to choose between alternatives. Other indications were specifically identified for some other parameters.

V) EHS experts' opinion: the ProSafe Delphi poll

As seen before, one of the main discussion themes is if the methods/tools platform is sufficiently robust to allow SbD application to MNMs in the research pipeline. To assess this, more than 250 EHS experts from Europe and North America were involved in a Delphi Forum. Experts were asked questions regarding readiness, relative importance, and development timelines of technical methods for measurement of exposure or toxicity for specific MNMs, use types, and life cycle release points. Data were characterized by stakeholder type, region, and level of experience. Outcomes from discussion have been used to develop the project White Paper proposing path forward risk management policies for nanomaterial uses. Publication of the Delphi forum results is planned in a peer-reviewed journal.

Important differences in perceptions of risk assessment and methodology development needs between MNM type, life cycle stage, and MNM use emerged from the data analysis. For example, consumer exposure through food and medical devices was considered more controllable than environmental exposure. Also, differences between regions were highlighted, while similar patterns of response were seen for some themes.

The differences recorded for MNM, their applications, and regional perception, may inform where methods development programs need to be accelerated and also may inform a better focus for policy discussion, harmonization, risk communication, and governance of international trade.

One of the main findings of the Delphi forum, which is mirrored in other reflections linked to SbD implementation, was that a better understanding of exposure is often needed before understanding of toxic effects. This discussion indicates an exposure-driven SbD approach, with a tiered assessment aimed at matching appropriate toxicity data to relevant exposure scenarios. It also expresses a need to prioritize development and standardization (but also application in SbD) of characterization and exposure methods over toxicity assays, probably because hazard assessment is perceived as a better populated field after 20 years of research. In conclusions, the main, but perhaps too simplistic, opinion seems to be that a SbD approach must consider appropriate matching of exposure to toxicity at all decision stages.

Concerning the level of control of risk, environmental exposure is seen as the least understood and less easily measurable. In addition, the opinion was that development of methods for environmental exposure assessment could be more than a decade away. For SbD this may mean that design options will be limited for uses that interact with the environment. However, a way around the current limitations was suggested as adopting methods to take decisions based on mass concentration or functional assays results following a "hot-spot" approach.

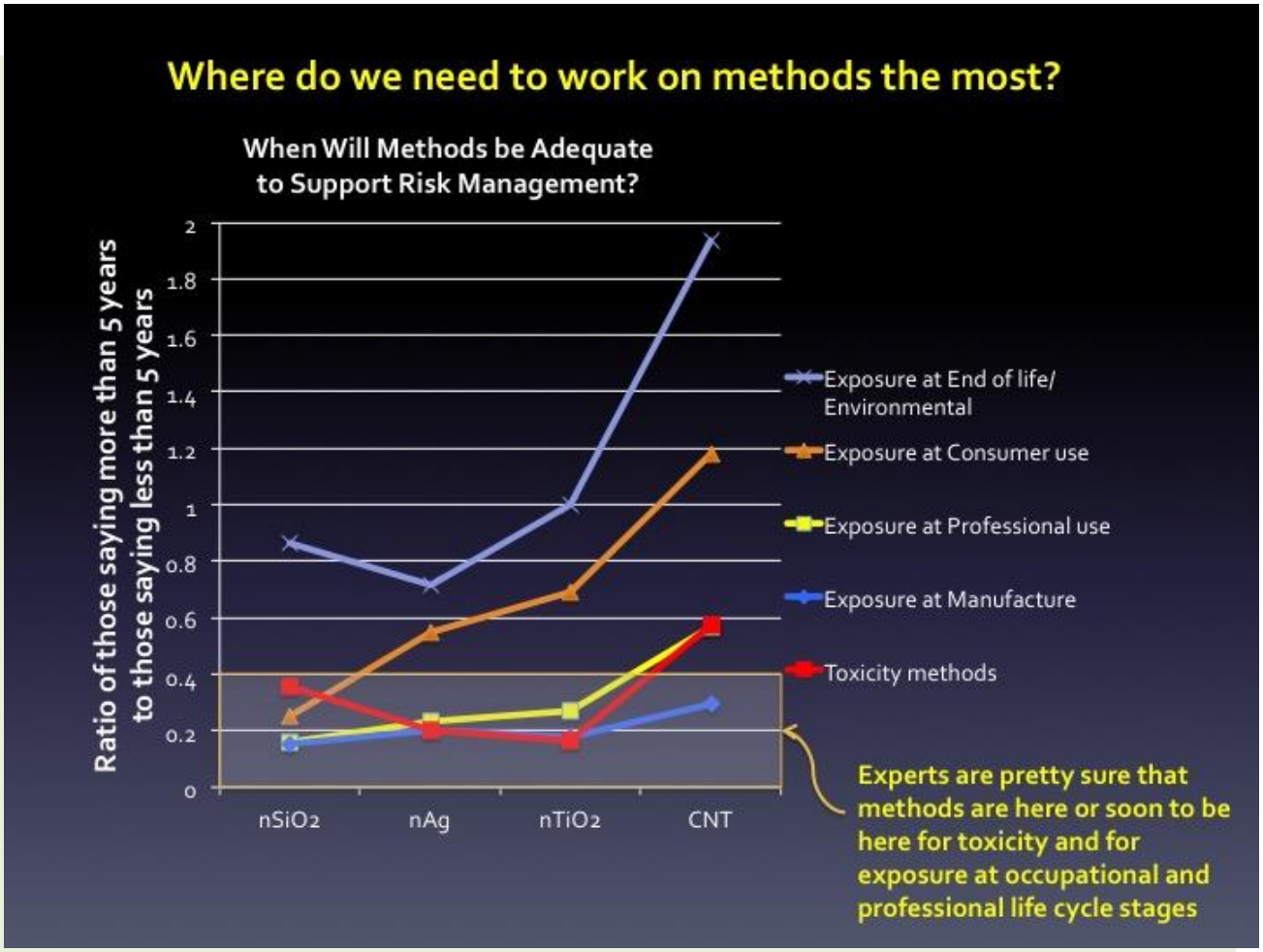
The main factor affecting the perception of risk control possibility was glimpsed in some comments as the existence of regulations and standards. However, geographical, technical, and sectorial differences in the application of regulations may pose another layer of complications to the whole concept of controlled risk, asking for harmonization efforts globally and cross-sectorial.

In conclusion, in order to implement Safe-by-Design (SbD), experts found that:

- There is the need to balance exposure and toxicity decision factors, starting to focus more on exposure;
- Where methods are in place to control risks, SbD support should be based on standard development and harmonization;
- Exposure methods for consumer and environmental exposures are years behind in development and should be accelerated;

As contribution on the White Paper, the recommendation coming from the Delphi poll is that the review of equipment needs expert view on available methods for risk management/SbD and that methods for consumer/environmental exposure assessment are a priority.

The assessment of the data collected to through the experts was done within the ProSafe constrains, with its framework of objectives and activities. Therefore, fresh eyes on the opinion data that were developed through the Delphi forum may further advance our understanding of prevailing opinion and thereby aid in sound policy development. The data will be publicly available in the ProSafe Results Repository.



VI) ProSafe-OECD Joint Scientific Conference

The joint scientific conference "Science based support for regulation of Manufactured Nanomaterials" took place on 29 November to 1 December 2016 at the OECD Headquarters - Conference Centre- in Paris. The conference was a joint initiative of the OECD and the H2020 ProSafe project, and also formed the final conference of the FP7 NANoREG project. This conference focused specifically on the regulatory relevance of new and state of the art research and initiatives in the field of nanosafety. This included EU FP7 as well as Horizon 2020 research projects, but also non-EU research and activities related to OECD and ECHA, as well as some relevant US research programs.

In the three day event, 180 international experts discussed the regulatory relevance and applicability of science-based results generated over the past 10 years. The conference was organized around interlinked themes, i.e. physical-chemical identification and characterization, human health and ecological effects, consumer, occupational and environmental exposure, tiered testing strategies, tools for risk assessment as well as computational methods. The basis for discussion of these themes was formed by a comprehensive review of regulatory relevance and evaluation of over 1000 peer reviewed publications and reports, called "ProSafe Joint Document".

The ProSafe Joint Document evaluation was carried out by a group of experts that covered the most relevant scientific fields of nanosafety on the basis of the "ProSafe roadmap for reviewing data, protocols, report and guidance notes for regulatory relevance". The Joint Document was finalised in March 2017. A summary will be published in a special issue of NanoImpact as peer reviewed article. It gives an impressive overview of the state of the art of methods and strategies to test and assess the risk of nanomaterials and their regulatory relevance. It is one of the building blocks for the ProSafe White Paper.

At the meeting it was highlighted that -inter alia- strategies for robust physical-chemical characterisation, tiered testing schemes, grouping frameworks, and modelling approaches can contribute to a more efficient and reliable safety assessment of nanomaterials. Several promising examples originating from current scientific projects were discussed. Furthermore, experts expressed the need for more specific guidance regarding the EHS data that should be generated to fulfil regulatory requirements. It was stressed that sharing of experimental data is key to making real progress in developing models to predict the effects of nanomaterials; a basic condition for safe by design, grouping and read across. Structural provisions regarding data management are needed, including harmonised data logging, data curation and sustainable data storage.

Detailed outcomes of the conference are presented in a conference report which summarizes the discussions at the conference and highlights the findings of the experts.

It also includes summaries of the lectures presented and a plenary panel discussion. It features a compilation of conclusions and recommendations for regulatory questions regarding assessing risk for human health and environment. This compilation will be considered in subsequent discussions between policy makers, regulators and industry on how to test and assess the effects and risks of nanomaterials. It may also serve as input for international programmes for the harmonisation of test methods, such as that of the OECD.

VII) White Paper: conclusions and recommendations

The overall result of the project is the White Paper. A draft version of this document has recently been distributed for consultation. The White Paper provides recommendations for European policy makers and regulators aimed at a more efficient and effective governance and regulation of nanomaterials. Important building blocks are the ProSafe Joint Document and the NANoREG Framework.

Nanosafety research so far

The White Paper starts with a description of the present situation regarding the scientific, societal and legal context of nanotechnology and nano safety. It states that after 15 years of research on Nano EHS, it still is difficult to come to a unambiguous conclusions about safety of nanomaterials. Main causes are mentioned and elaborated. Also it is concluded that the current regulatory framework is not adequate to address nanomaterials safety. The absence of a legal definition of nanomaterials in REACH leads to disputes as to whether nano-specific information should be provided or not. Also, the chemical identity as defined in REACH does not cover the specific characteristics of nanomaterials.

White Paper elements

On this premise, the draft White Paper comes with recommendations to achieve a more effective and efficient governance and regulation of nanomaterials (White Paper elements).

- No regret measures: Recommendations in the White Paper follow up on the Joint Document and several NANoREG deliverables with respect to harmonization of test methods and a more stringent evaluation of the quality of data to be used for risk assessment of nanomaterials. Other recommendations in this category are aimed at improving management of nanoEHS data on the basis of the experiences and results of eNanoMapper and NANoREG with respect to opening up data, accessibility, ontology and data curation.
- Adaptation of REACH and its annexes and Guidance Documents to make it better fit for nanomaterials with respect to information requirements, categorisation and methods for testing and assessing the risks of these materials.
- Innovation in Risk Assessment. Recommendations aimed at a more efficient process of Risk Assessment by getting a better understanding of the mechanisms that cause potential adverse effects of nanomaterials
- Future proof approach. Recommendations in this category are aimed at developing new approaches to secure the safety of materials. Approaches that also can be applied for next generation materials. As examples of options that can be further explored the White Paper mentions a “concern based” approach on the basis of risk potentials and Safe by Design. Both options have been elaborated in NANoREG

Most of the recommendations are formulated as a concrete action including the addressee for the action.

Follow up for the ProSafe White Paper

After processing the comments received during the consultation procedure the final White Paper will be published in September 2017. It is than up to the policymakers and regulators to make up their mind and decide regarding the implementation of the recommendations.

VIII) The final project meeting in Rome

At the end of the project, it is necessary to look back to evaluate the work done, and to look forward and discuss about how to exploit the results achieved in the project period. The ProSafe final project meeting and EC review meeting provided good feedbacks and ideas for the future.

Final ProSafe Consortium meeting

The final ProSafe Consortium meeting was held in Rome, the 1st and 2nd of March 2017, at the Istituto Superiore di Sanità (ISS).

Since the main result of ProSafe is the White Paper, its status and foreseen content was presented by the coordinator. Details of the final document are presented in the last item (item VIII) of the newsletter.

The second point of the agenda was the presentation of the results of the ProSafe-OECD Joint Scientific Conference, showing a summary of the Conference organization, participation and results (item VII of this newsletter). The basis for the Conference was the Joint Document, elaborated by the ProSafe Task Force. The content and conclusion of the document were presented, and some details of the document are in item III.

Several activities were already carried out in research project at European and national level, as well as at global level, that could support the SbD implementation. The results of a synergy scan to identify data, models, tools, and concepts, were shown in the 4th plenary session. This activity is also relevant for the database harmonization (item IV), since projects often generate data relevant for nanosafety. Harmonization of data generation, reporting and use is a pre-requisite for the exploitation of all available knowledge for regulatory safety purposes. On this sense, NanoSafety cluster could play an important role, supported by appropriate policies of the EC.

Results of a Delphi poll were presented as well, focusing on the second round findings, for which emphasis on real life exposure-driven safety prioritization was expressed by many experts. Item VII will give more details.

Concerning the exploitation of the project results, and engagement of stakeholders, some considerations were made concerning the fact that to attract interest from national bodies, and generate their participation, it is necessary to communicate concrete results as early as possible. Another discussion point was that while the joint call process was managed in the best possible way, the success rate was quite disappointing, with few countries willing to participate, and only one transnational initiative was funded.

Finally, the SbD implementation platform developed by TEMAS was presented (item III) as a strong contribution to the NANOREG^2 project, together with the mapping of available tools and methods, as well as needs and gaps to be filled.

The ProSafe Consortium in agreement with the General Assembly, agreed to make all ProSafe deliverables relevant for third parties publicly available. The users of the information have to comply to the conditions of the "Creative Commons Attribution-Non Commercial-Share Alike 4.0 International License" (http://rivm.nl/en/About_RIVM/International_Affairs/International_Projects/Completed/ProSafe).

The last part of the meeting was dedicated to the discussion of the meaning of both NANoREG and ProSafe projects results. The topics: i) Data management, ii) Concerted research actions, iii) Prioritizing harmonization activities, and iv) SbD were discussed. The following conclusions were drawn. Data management has to be defined as

early as possible in the project development, and based on agreed/compulsory unified ontology. This is only the first step toward data sharing between projects, for which examples are already available in other domains. The format conversion could be an issue, which has to be solved at the beginning of the project. Concerning concerted actions, the main finding is that it is necessary a stronger top-down approach in R&D calls, identifying the priorities in research-policy discussion groups, and opening deliverables and databases. Harmonization activities discussion focused much on SOPs, their promotion in different fora, and active use in the innovation process, as a way to reach OECD TG status. Other topics included the need to derive health reference values (e.g. DNEL, PNEC), and the need of global regulatory harmonization.

Finally, recommendations about the use of SbD were identified. SbD is probably more needed for small companies further away from market than for large companies. Also, it is important to develop SOPs and norms to implement SbD, with a stronger tie to regulations. Finally, to support SbD implementation the creation of networks sharing issues and best practices is a necessary step.