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1 Description of task

The Foresight report is described in the ProSafe Grant Agreement Description of the Action (DOA) as:

> *This document will provide expert opinion allowing foresight into the impact on risk management of trends in a) nanomaterial uses and b) risk analysis applied to expected future nanomaterial uses. The document is intended to serve as a tool for regulators considering priorities for policy and methods development and will provide input for the White Paper.*

The DOA also describes a process of gathering expert opinion that includes a Delphi forum and a Core Group of experts to advise the foresight process. The White Paper to which the Foresight report is aimed as input is in turn described in the DOA as:

> *A major aim of the project is to document and propose the changes which need to be effected in order to put new procedures and science based approaches for regulating EHS for nano materials into practise. The white paper, following on from the Joint Document (task 5.4) and final scientific conference (task 5.3), will contain a review of the regulatory relevance of the output from NANoREG and the OECD WPMN, divided into relevant topics. The White Paper, targeted at ECHA, the OECD, and Member States, will analyse this review and propose the steps needed to get support for establishing a legal basis by which science based recommendations can be used in the long term regulation of MNMs.*

2 Description of work & main achievements

2.1 Summary

Task 2.3 of the ProSafe project developed and evaluated expert opinion to generate foresight about whether technical methods will be ready to support Safe by Design (SbD) risk management approaches for uses of manufactured nanomaterials (MNM) in the R&D pipeline. The project used a Delphi forum process to develop and refine our understanding of opinion across multiple interaction and feedback points for hundreds of experts in Europe and North America and dozens of combinations of MNM types, uses, and life cycle exposure points. The forum process used a multi-stakeholder expert steering group, two web surveys, and a discussion panel workshop as interaction and feedback points. The overall process took 18 months and included detailed participation by over 250 experts in Europe and North America. This approach provided useful information about prevailing opinions of experts and it provided useful experience on what works to understand such a complex risk management challenge.

The complexity of the undertaking and the difficulty in navigating the combinations of physical and analysis factors to be considered was itself a lesson regarding the complexity of making judgements about SbD for nanomaterial uses in general. The expertise disciplines, application areas, and stakeholder perspectives alone were challenging to navigate. Adding a layer of foresight regarding markets and regulatory policies on top of this complexity is a further challenge. Therefore, a lesson learned regarding foresight for SbD application to MNM uses is that general principles applied to all future nanomaterial uses at any particular SbD decision step are probably rare. Approaches to address complexity as new materials and new understanding emerges appears to call for a stepwise decision process, like SbD, where each step considers the context for the use and the implications of alternative material and use choices. A further complication for risk managers assembling dossiers to support decisions is that a rapid pace of progress in methods and data development may mean that the utility of older data must be questioned more frequently than is current practice, as newer and more relevant data sets rapidly emerge.

Given the complexity of forms and exposure contexts for MNM risk management across life cycles and uses, new measurement methods will be needed to collect and relate data for MNM uses that cause multiple released MNM forms and environmental transformations for different use conditions and exposure contexts. The scales and kinds of data collection and collation approaches are huge, and speak to a need for “high throughput“ as well as for more complex relational structures than may be used for standard chemical risk management.

Discussion in the Delphi forum identified important similarities and differences in perceptions of risk assessment and methodology development needs between MNM type, life cycle stage, and MNM use. The opinions expressed in this executive summary are derived from the prevailing opinions observed among the experts. In reviewing the opinions expressed here it should be noted that the finding of „most experts“ may at times be more a reflection of prevailing perception and bias than it is an outcome of data-driven

evaluation. In some cases, the opinions of a few who are well aware of the data may be hidden behind general perceptions of those experts who are less familiar with specific methods and data.

A consistently expressed opinion was that a better understanding of exposure is often needed before understanding of toxic effects can proceed to support a SbD approach for a use. Addressing this need may require sequencing of data development within a decision support context so that appropriate matching of toxicity data to exposure data can occur. It may furthermore require sequencing of methods development and methods standardization for characterization and exposure measurement preceding dose estimation and toxicity testing. In some cases, the sequencing may in fact start with development of instrumentation for characterizing dose-related aspects of MNM, or for compiling large amounts of data on form and transformations of MNM particles in exposure pathways, prior to initiating data development on toxicity. Toxicity information may also drive decisions, so the overall discussion sequencing did not support a simple "exposure first" opinion by most experts. 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.

Adding to this sequencing challenge is the perception of experts that assessing exposure to MNM after release to environmental media is less well understood, less easily measurable, and may have the potential to be less well controlled than assessing exposure to MNM in most other settings (for example, occupational and direct consumer exposures to products during use). Methods to support exposure assessment for some MNM in the environment are not available now and their development 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, because assessment methods may not be available to assess variations in design for released MNM. However an exception to this distinction was pointed out in comments that simple decisions at high concentration effluent locations or hot spots (e.g., decisions based on mass concentration or functional assays) may be just as simple in environmental matrices as in occupational settings.

Some use type and life cycle stage combinations were generally believed to be more controllable than others. Consumer exposures through foods or medical products and occupational exposures, both in manufacturing and professional use, were generally discussed as being controllable. This may imply a shorter time horizon for implementation of SbD for those cases where these life cycle points are the only possible sources of exposure.

This greater ability to control risk was attributed by some to be due to established regulatory oversight or standard practice. However, the opinion was also expressed that implementation of control measures is variable across companies, regions, and MNM types. Therefore, more uniform enforcement of regulation or more widely adopted standard practices may be needed to support SbD in multiple regions and market sectors.

A shift in emphasis from MNM toxicity testing methods to exposure assessment methods is seen as necessary to support SbD decisions. Furthermore, in many cases SbD decision steps for particular places in the value chain will need to consider the effectiveness of regulatory enforcement or consistent risk management practice as products and uses reach different life cycle stages. In some cases, particularly for uses that interact with the environment, the SbD development pathway will also need to consider development timelines for new methods to support adequate risk management.

Further analysis of the Delphi forum data is recommended due to the depth and variety of the data collected and the effect of interpretation by different readers of the data, which is difficult to do in an unbiased way. Fresh eyes may further advance our understanding of prevailing opinion and thereby aid in sound policy development.

2.2 Background of the task

This document is intended to provide an evaluation of expert opinion regarding foresight into the impact on risk management of trends in a) nanomaterial uses and b) risk analysis applied to reasonably anticipated future nanomaterial uses. The document is intended to serve as input to the ProSafe White Paper, and generally as a tool for risk managers considering priorities for policy and methods development.

An underlying reason for the foresight report is concern that nano-enabled products may enter markets faster than the development of risk management capabilities suitable for them. Therefore, so that risk uncertainty does not impede innovation, regulators will need to understand the likelihoods for specific kinds of nanomaterial use in products as well as likelihoods that there will be methods to manage risks of those products arising from the added nanomaterials. Focus on Safe by Design SbD methods is particularly useful in this context of use of an emerging set of technologies (nanotechnologies).

2.2.1 *Scope*

The design and analysis of the Delphi forum feeding into foresight conclusions considers a time horizon of approximately 3-10 years. The overall purpose of the analysis is to inform SbD approaches for manufactured nanomaterial (MNM) uses, and so the document is not intended to address risk management

issues for products that are already in commerce. However, the insights gained may also inform existing MNM uses. It is anticipated that issues for the beginning of the 3-10 year time horizon would inform policy regarding MNM uses that are currently in end-stage development for manufacturing pipelines. The end of the 10-year horizon would inform research, policy, resource prioritization, and methods development to support risk management through SbD approaches.

The analysis in this report also considers the MNM uses in the context of possible exposures through the life cycle[1] of the MNM-use. Furthermore, because methods to measure exposure, hazard and risk are considered by some to be inadequate for some MNMs, the report also describes a) time horizons for development of instrumentation and methods/standards, and b) development of safe by design production practices for nanomaterials or other "prevention" risk management approaches.

The report primarily considers those MNMs being evaluated in the NanoReg and NanoReg II projects and their likely use in products in a near future (3-5 years) time frame. In contrast, consideration of the development of risk management technologies considers a longer time horizon, given that the development time needed for instrumentation and standard methods can be many years and, in some cases, it is anticipated that new instruments or new standard methods are needed.

Foresight for the entire nanomaterial domain (e.g., all MNMs and all uses) and further into the future is beyond scope; however, it is hoped that some findings may be generalizable to longer time horizons and other types of nanomaterials.

2.2.2 *Input from Other ProSafe Tasks and from NanoReg*

ProSafe Work Package 2 included two tasks (Task 2.1 and 2.2) that informed the structure and content of this report (Task 2.3). Task 2.1 provided a synergy scan of projects to consider sources of information and experts regarding measurement methods, risk assessment, and uses for nanomaterials. Task 2.2 provided a review of foresight literature for nanotechnology to determine whether other efforts had developed similar analyses to the one planned for Task 2.3 and to inform methods for developing foresight. Review of the Task 2.2 report with respect to Task 2.3 revealed that there were no similar foresight analyses to the one planned and that the methods needed for foresight would probably require expert elicitation methods. The need for expert elicitation methods was due to a lack of comprehensive or representative information about the kinds of products in development for nanotechnology and the consequent lack of information about methods needs.

Task 2.2 also provided a horizon scan of methods and instrumentation being used to support risk management of uses of nanotechnology. Here again, an outcome of reviewing the Task 2.2 report in the context of Task 2.3 was that it is difficult to generate comprehensive or representative information about relative importance of specific methods or instrumentation. This difficulty is partly due to the breadth of the scope of the project (effectively, all possible uses and a broad range of risk management contexts) and to the emerging nature of nanotechnology uses and measurement methods/instrumentation for nanotechnology uses. This emerging nature of the information made it again clear that foresight, and indeed horizon scanning, for methods readiness for risk management of future nanotechnology uses requires expert elicitation. As discussed in further detail in the description of Round 2 of the Delphi forum in this report, Task 2.2 also provided a basis for developing questions to elicit expert opinion about specific methods needs.

The input from Task 2.2 also involved information from the NanoReg project. In particular, Task 2.2 was structured so that it addressed instrumentation and methods needs to support a specific set of risk management questions developed by NanoReg. In addition to this input from NanoReg through Task 2.2, Round 1 of the Task 2.3 Delphi forum was limited to 6 MNM types that were the subject of NanoReg research and methods development.

2.2.3 *Definitions (nanotechnology, nanomaterials, and nanomaterial uses, etc)*

This report solicits and reviews expert opinion from multiple regions, stakeholders, uses, and life cycle stages. The breadth of variation in regulatory decision focus (e.g., consumer safety, environmental safety, occupational safety), innovation initiatives (e.g., composites, electronics, food, medicine), and discipline (e.g., engineering, chemistry, physics, biology) across these experts is quite broad. Because of this wide scope of discussion and decision frameworks, it is not possible to provide a single frame of reference for the meaning of nanotechnology or of a manufactured nanomaterial or of nanomaterial uses that would capture both the general needs for policy discussions and the specific needs for methodology discussions for particular classes of use and exposure routes.

[1] In this report, the term "life cycle" refers to consideration of each of the manufacture, use, and disposal or recycling stages of a product.

Some terms used in the questions of the Delphi Forum were defined so that discussions could be focused; however, it was not the intention of the report to limit discussions to a particular definition for nanomaterial. Therefore, a manufactured nanomaterial (MNM) is not defined in this report. Similarly, the specific form of the 6 MNMs used in Round 1 of the Delphi were not defined beyond simple listing of a general name (e.g., nano titanium dioxide, multiwalled carbon nanotube, nano silver).

2.3 Description of the work carried out

2.3.1 *General methodology*

A five-step Delphi forum process was used to develop understanding of foresight from experts active in the field of nanotechnology. This process was intended to permit an independent synthesis of information derived from leading experts. The steps were:

1) Core group formulation of initial questions

A Core Group of experts from US, Canada and Europe (government, academia, industry) were recruited by the project team. The Core Group was provided with a scope statement for the desired outcome of the Delphi forum and an initial set of possible questions. Through web conferencing and document revisions, the Core Group advised on the development of the questions used in the first round of the Delphi forum.

2) Delphi forum Round 1

With advice from the Core Group and using the expert contact lists from multiple sources involved in commerce, regulation, or study of nanotechnology uses, the project team assembled an invitation list of approximately 2500 experts worldwide. Efforts were made (through contacting trade associations and considering commodity manufacturers as well as product manufacturers) to ensure that the invitation list would reach the full range of the value chain for MNM use in products. The questions developed with the Core Group were coded into a web-survey instrument (www.scipinion.com) and sent to the expert invitation list. Round 1 was open for response for approximately 2 months in late 2015 (details discussed below). During this period the project team developed web and newsletter announcements. The project team also enlisted leading experts to stimulate participation as ambassadors using direct emails to their contact lists.

3) Expert review panel

A panel of experts was convened to evaluate the collected information including the first Delphi round results and to help define the aims of the second Delphi round in light of the foresight objectives. Advice was sought using specific questions regarding content and meaning of the first round. The evaluation occurred in an expert roundtable and a nanomaterial specialty section meeting of the 2015 Society for Risk Analysis (SRA) Annual Meeting in Washington DC (details below).

4) Core group-advised development of Delphi Round 2 questions

Round 2 questions were developed with guidance from the Core Group in consideration of their review of the Round 1 data, the expert panel reviews at the 2015 SRA meeting, and advice from ProSafe Partners. The resulting questions were intended to clarify issues raised in Round 1. The second round included more opportunities for “free text” explanation of responses to some questions. In addition, input from the literature review in Task 2.2 of ProSafe (horizon scan of instrumentation and methods) suggested that expert opinion was needed to aid in prioritizing methods-development needs for SbD. Therefore, Round 2 questions also sought information about the most needed development areas for methods for MNM characterization, exposure assessment, and toxicity assessment.

5) Delphi forum Round 2

The questions were coded into the same web survey instrument and the same ~2500 expert list for Round 1 was used to invite participation. Round 2 was open for approximately 2 months in summer 2016.

2.3.2 *Step 1: Core group formulation of initial questions*

The first interaction point (step) in the Delphi forum was the development of the initial questions for the first round, this was done by the project team (Richard Canady, Martie van Tongeren, Rob Aitken and Alice Davis) in collaboration with the Core Group (listed in Appendix 1).

2.3.2.1 Purpose

The questions for this first round were guided by the purpose, i.e. to gain expert opinion on the current status and trends in:

- Nanomaterial uses,
- Risk analysis capability for determining safety of those uses, and
- Pathways to implementation of SbD practices in assuring safety of those uses.

From initial development work based on the above purpose, the project team provided the Core Group with a scope statement and an initial draft set of questions. Following this, there were multiple web conferencing calls (June 2015, August 2015, and September 2015) and revisions to the question documents; the design and development are detailed below.

2.3.2.2 Design of the first Delphi round

Nanomaterial use is diverse and difficult to speak of in regulatory terms as one kind of material or use, therefore the structure of this first round was set up to explore variation in opinions of risk management adequacy when considering specific classes of material use and material types. During the discussions with the Core Group it was agreed that the first round would ask questions focussing on six MNMs that were considered in the NanoReg project; titanium dioxide, carbon nanotubes, silicon dioxide, barium sulphate, cerium oxide and silver.

From discussions, edits and feedback it was agreed that the first Delphi round survey would consist of the following 4 main sections:

1) General information

This section aimed to collect general information about participants in relation to the region and sector in which they work.

2) General risk assessment/management

The general risk assessment/management section asked participants more specifically about their knowledge of use and management for the six MNMs, where SbD is already in use and what actions would be most effective to improve ability for this.

3) Current uses and risk management for selected MNM

There were six subsections on current uses and risk management. Each of these subsections asked the same question set on exposure, toxicity and risk assessment/management; however each subsection focused on a different MNM.

4) Safety and innovation

The safety and innovation section of this Delphi round was focused towards industry participants, asking questions on innovation models and information needs along the innovation process so that priorities for supporting adaptive risk governance could be evaluated. These questions in the final section and the results from these were collected on behalf of NanoReg.

The structure and number of questions in each of these sections and subsections are presented in Table 1 and the full set of questions is available in Appendix 2.

Table 1 Round 1 Question Structure

Section	Number of Questions
General information	9
General risk assessment/management	4
Current uses and risk management for selected MNM	-
Titanium dioxide	13
Carbon nanotubes	13
Silicon dioxide	13
Barium sulphate	13
Cerium oxide	13
Silver	13
Safety and innovation	13

2.3.3 *Step 2: Delphi Forum Round 1*

2.3.3.1 Recruitment

The first Delphi round was launched on the 30th October 2015 and closed on the 31st January 2016. Between 3rd and 25th November 2015 contact was made with 101 colleagues (including the core group members) asking them to email and share the link and invitation to participate to their (relevant) contacts.

In addition to this, an expert list of individuals was collated by the project team and Core Group from personal contacts, related project participant lists and professional groups and associations. This group of over 2500 individuals was collated for the purpose of invitation to participate in the two Delphi rounds. In identifying these experts there was consideration for representation across the following:

- Value chain or life cycle (e.g., commodity materials, formulation, manufacturing, use, recycling). This will require understanding of the value chains for products identified in the horizon scan and evaluated in NanoReg.
- Stakeholder reference point (e.g., government, industry, NGO).
- Region (e.g., Europe, North America, SE Asia).
- Relevance to NanoReg WP's and outputs.
- Outreach (e.g., professional societies, granting agencies, trade associations, advocacy groups).

This variety of input into the expert list was needed because the complexity of material uses, value chain transitions, life cycle transitions, and risk management applications seemed too great for any individual group of authors to have access to. Each of the individuals on this list was emailed an invitation to participate in the first Delphi round between 20th and 23rd November 2015.

As well as this direct email contact, recruitment was also completed using other routes by the 101 colleagues identified above and the IOM project team. These routes included the invite being raised at meetings (e.g. Nanocommission preparation meeting, Society Board Meetings), shared through various LinkedIn groups (e.g. Nano Materials Society, Nanotechnology Global, Nanotechnology Zone, Nanotoxicology Research, Nanostrom, Nanotechnology World Association, Cefic), through Twitter accounts (e.g. IOM World, SafeNano, IOM Singapore), on websites (e.g. IOM World, SafeNano, IOM Singapore, ProSafe), as postings on online blogs, as well as within news items and newsletters (e.g. Sustainable Nanotechnology Organization). In addition to this the project team also advertised the first round of the Delphi through presenting at the following events:

- SRA Annual Meeting - Risk Governance New Initiative meeting
- SRA Annual Meeting - NanoSafety Cluster Roundtable
- SRA - Foresight Webinar
- Roundtable - From Nano Risk Management to Risk Governance: Methods and Tools.

On the 16th December after the first Delphi round had been open for just over two weeks a reminder was sent to the expert list of over 2500.

During recruitment and participation, an incentive offered to participants was being able to see specific analyses of responses across all participants once they had finished entering their data, and to comment on these using the debate and comment functions.

2.3.3.2 Content of questions

The data in Round 1 were collected by the following MNM types, life cycle stages, sector of uses, and stakeholder categories:

- NM type
    - Titanium dioxide
    - Carbon nanotubes
    - Silicon dioxide
    - Barium sulphate
    - Cerium oxide
    - Silver
- Life cycle stage

- Manufacture
- Professional use
- Consumer use
- End of life/environmental

- Use type
  - Food additives and packaging
  - Construction
  - Agriculture
  - Advanced composites
  - Electronics/optics
  - Medical
- Stakeholder information
  - Region
  - Employment sector
  - Category for the majority of work
  - Level of training and experience
  - Amount of career effort in the sectors of use considered in the Delphi

2.3.3.3 Format of the interaction

The two Delphi rounds were administered through SciPinion; “an online platform for scientists to voice their opinions anonymously to support science-based decision-making”. Through this platform a SciPi survey was developed, in this report the SciPi is referred to as a Delphi round.

The Delphi round was introduced with the page shown in the screenshot in Figure 1 below.

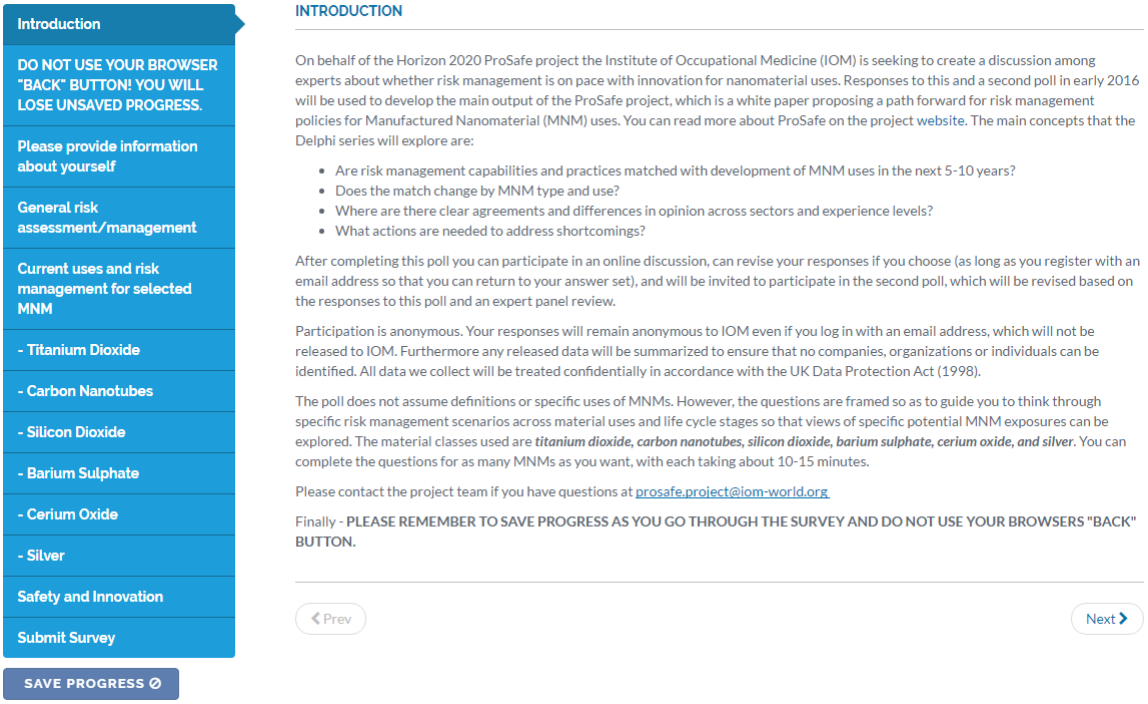


Figure 1 Screenshot of Round 1 Introduction Page

Within the different sections and subsections there were a mixture of question and response types depending on the questions being asked, these included; lists and tables of tick boxes, radio buttons and open text responses (Figure 2 and Figure 3). The question types (grids) and sectional design of the forum

was generated specifically for the ProSafe project so that the complexity of use type, life cycle stage, and MNM type could be captured in as little time as possible for the experts participating. This design work required new programming and substantial review and editing by SciPinion and the project team.

6) Level of training and experience in the following areas.

	None	1-4 years	5-10 years	>10 years
Material science/chemistry				
Toxicology				
Exposure science				
Risk Assessment				
Nanomaterial applications				
Product stewardship				
Public health				
Finance or insurance				
Other				

Figure 2 Screenshot of Tick Box Response Options

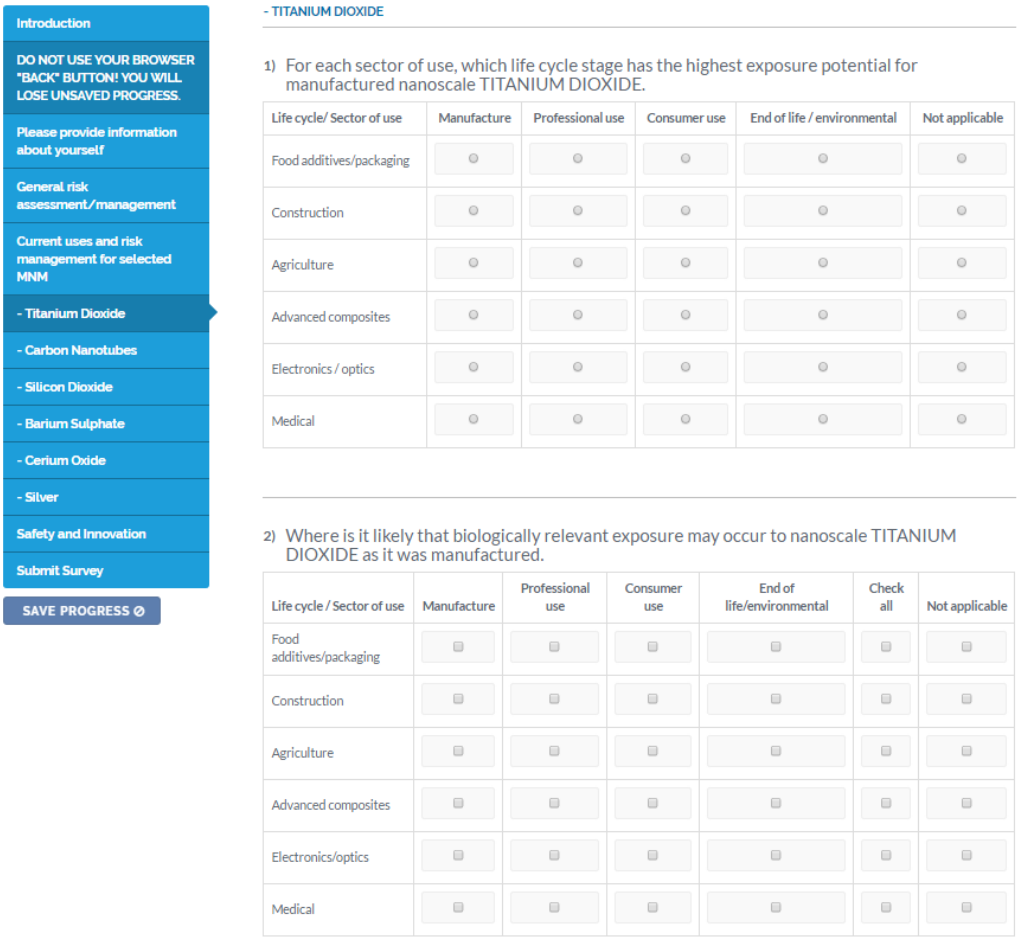


Figure 3 Screenshot of Round 1 Structure and Presentation of Questions

By using the SciPinion platform, the project team was able to use various functions applicable to the use of a Delphi method, such as the option for participants to view live results from all participants once they have completed and then to change their answers should they wish.

The platform also provided a debate function where participants could submit their anonymised opinions on the results and the topic area more widely (Figure 4). Within this feature, participants were able to insert comments, vote on other participant's comments to show whether they agree or disagree (thumbs up/thumbs down) and to flag where input was considered inappropriate.

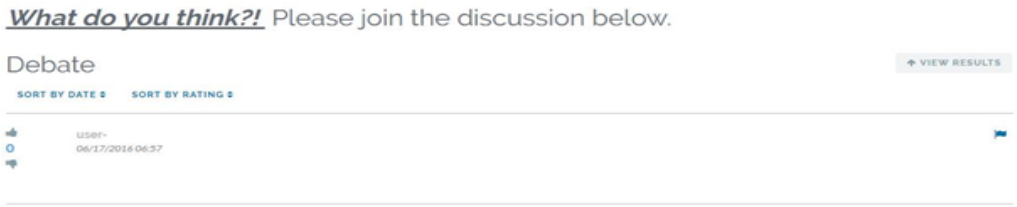


Figure 4 Screenshot of SciPinion Debate Function

2.3.3.4 First Delphi results

General results

Despite our extensive recruitment efforts, only 118 participants completed the first round of the Delphi, with the majority of participants being from Europe and North America, and working in the employment sectors of research and government (Table 2 and Table 3).

Table 2 Round 1 Region Results

Region	Count of Region
Asia	5
Europe	62
North America	44
Other	6
(blank)	1
Total	118

Table 3 Round 1 Employment Sector Results

Employment sector	Count of Employment sector
Government	29
Industry	13
NGO	8
Other	14
Research	52
(blank)	2
Total	118

Selected evaluations of the responses are provided below. The full list of questions and the default graphics for response from the SciPinion website are provided in the appendices.

2.3.3.5 First Delphi results: Where is Safe by Design already in practice?

In addition to the graphics provided by SciPinion (Appendix 3), additional analyses of the results were carried out with input from the Core Group. These are presented in Figure 6 to Figure 11. A "heat map" format was developed by the project team by first translating of the checkbox responses in SciPinion into an R-base file and then constructing percent of total responses per checkbox to differentiate among the use and life cycle combinations. The translation to R-base also allowed differentiation of response across stakeholder groupings. The heat maps generated for the question in Figure 5 "Where is Safe by Design already in practice for new use development for MNMs" provided a visual representation of the aggregate responses that greatly facilitated further discussion of this point in later steps of the forum. The heat map in Figure 6 (rows and columns are inverted compare to the question in Figure 5) shows that high percentages of experts felt that SbD is in practice for all use types during manufacturing stages (i.e., that addresses health risks for workers). In contrast, few experts indicated SbD is in practice when considering the end of life or environmental life cycle stage.

2) Where is Safe by Design already in practice for new use development for MNMs?

Life Cycle Stage / Sector of Use	Considering manufacturing	Considering professional use	Considering consumer use	Considering end of life / environmental	Check all
Food additives/packaging	☐	☐	☐	☐	☐
Construction	☐	☐	☐	☐	☐
Agriculture	☐	☐	☐	☐	☐
Advanced composites	☐	☐	☐	☐	☐
Electronics/optics	☐	☐	☐	☐	☐
Medical	☐	☐	☐	☐	☐

Figure 5 Question 2 in the first round of the Delphi Forum

Similarly, experts marked SbD as being in practice for professional use for all sectors of use to a degree, with most saying that we are already using SbD practices for construction, advanced composites and electronics/optics uses in the manufacturing life cycle stage, and for consumer use in the food and medical sectors.

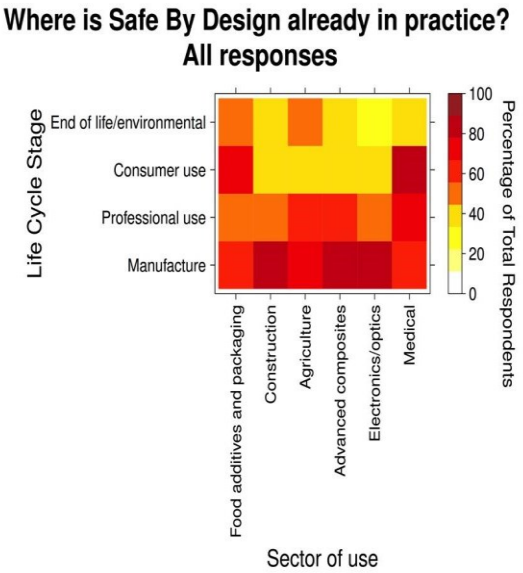


Figure 6 Heat Map of All Responses for 'Where is Safe by Design already in practice?'

Results in Figure 6 were divided into European responses and North America responses (Figure 7), which shows some differences in responses for SbD in consumer use and end of life/environmental release.

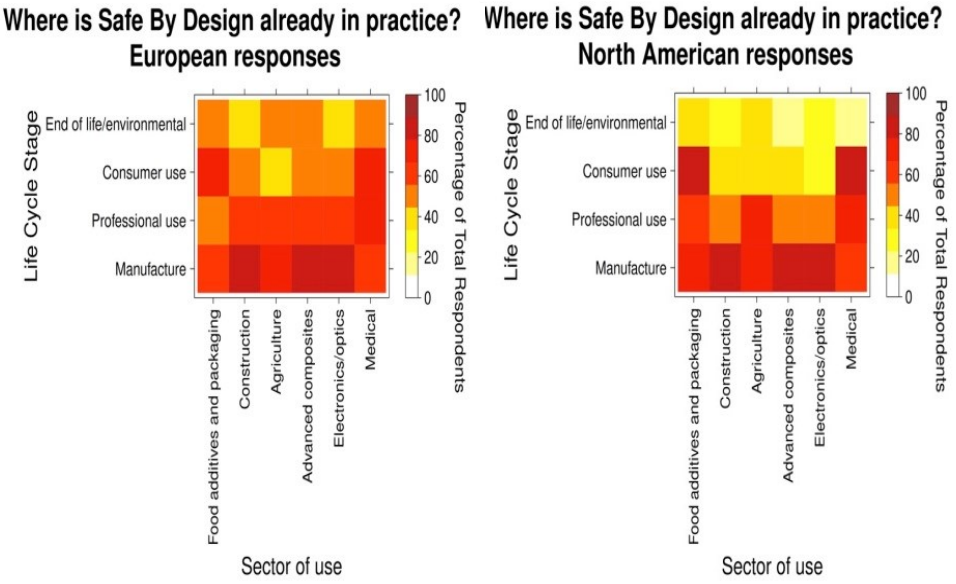


Figure 7 Divided Responses for European and North America for 'Where is Safe by Design already in practice?'

2.3.3.6 First Delphi results: What would facilitate Safe by Design use?

Again using heat maps showing the percent of total experts who checked a box in the grid question shown in Figure 8 it is possible to differentiate response to inform further Delphi forum discussions. When asked about what would facilitate SbD use, participants identified that more research and standards/best practice would be beneficial (Figure 9).

3) What kinds of actions would be most effective to improve our ability to adopt more widespread Safe by Design practices for uses of MNMs?

Sector of use	Leave it alone - it is already here	Standards/best practice	More research	New regulations/laws	Other
Food additives and packaging	☐	☐	☐	☐	☐
Construction	☐	☐	☐	☐	☐
Agriculture	☐	☐	☐	☐	☐
Advanced composites	☐	☐	☐	☐	☐
Electronics/optics	☐	☐	☐	☐	☐
Medical	☐	☐	☐	☐	☐

Figure 8 Question from first round Delphi on what would improve SbD use

The result that almost no one says “SbD is already here” is interesting in light of the heat maps above where it was highlighted that participants thought that SbD is in practice in all areas which may indicate that although it is practice, it’s not done well.

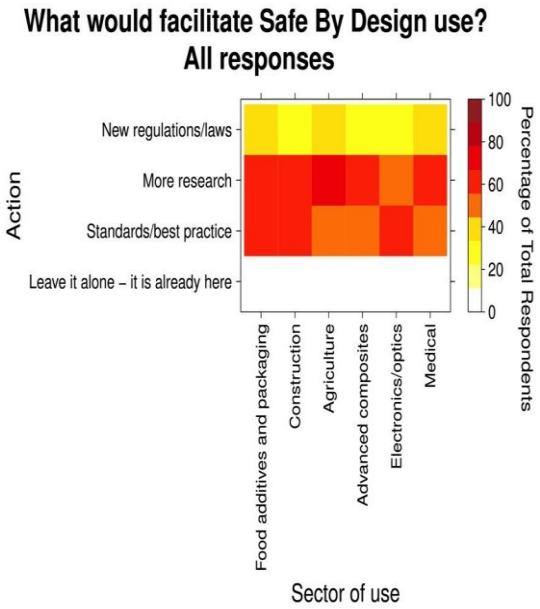


Figure 9 Heat Map of All Responses for 'What would facilitate Safe by Design use?

Figure 10 suggests that there is a broad general agreement between European and North American participants on the question what would facilitate Safe by Design use.

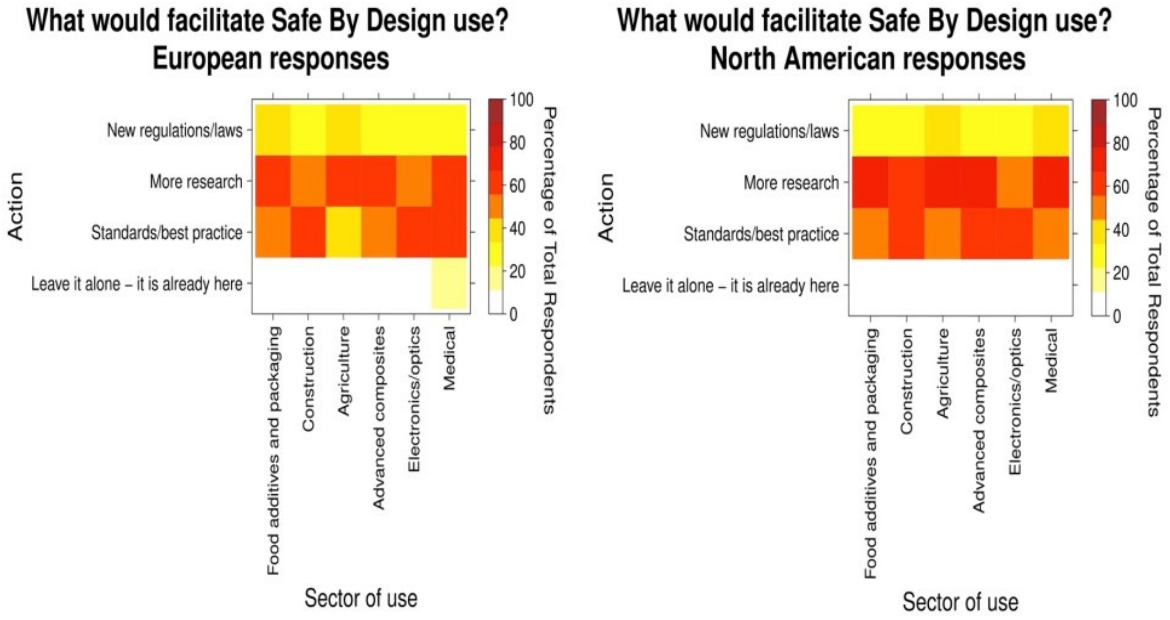


Figure 10 Divided Responses for European and North America for 'What would facilitate Safe by Design use?'

However, researchers identified a need for more research to facilitate SbD use, whereas safety experts identify a need for standard practice (Figure 11). Although perhaps not a surprising result, it did provide a reminder that motivations for responses differed between groups and should be taken into account for developing foresight. For example, foresight regarding the adequacy of methods in use today to support decisions may be better informed by experts making decisions than by the experts developing new cutting edge methods. Experts making decisions may see the uncertainties of the state of the art methods as being manageable (and are looking more to having standard methods in the next few years so that data can be widely comparable). Researchers may see opportunities for great improvements in methods and be looking to a longer time window for the application of the improved methods to new MNM types or decision needs. Therefore, both groups may be right, for different time horizons. These kinds of differences in context between expert groups will probably also affect responses to the kinds of methods that are needed and responses to specific rankings of methods later in the forum. Further exploration of these differences in

selected discussions among specific groups of experts may be beneficial (such as is happening in the ProSafe Task Force in Work Package 5).

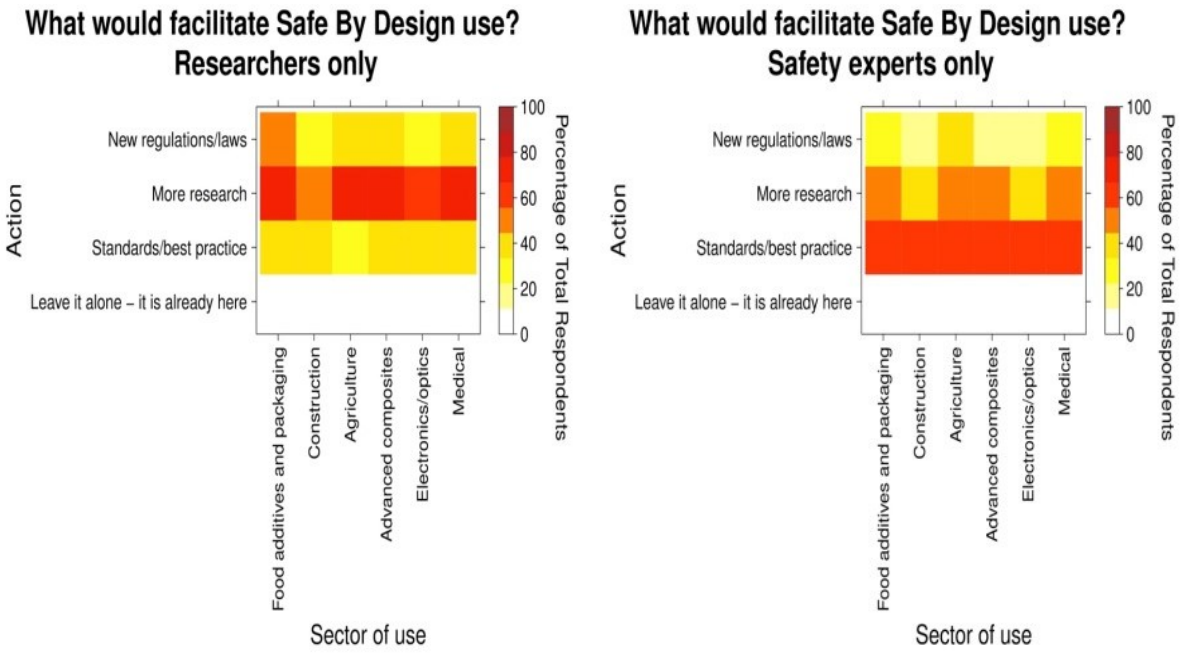


Figure 11 Divided Responses for Researchers and Safety Experts for 'What would facilitate Safe by Design use?'

2.3.3.7 First Delphi results: Where are the biggest gaps in methods to support risk management?

The following two figures present results for four of the six MNMs on the checkbox question that asked "Where are the biggest gaps in methods to support risk management".[2] Figure 12 shows that many participants identified exposure characterization and standard methods as areas with the biggest gaps in methods to support risk management.

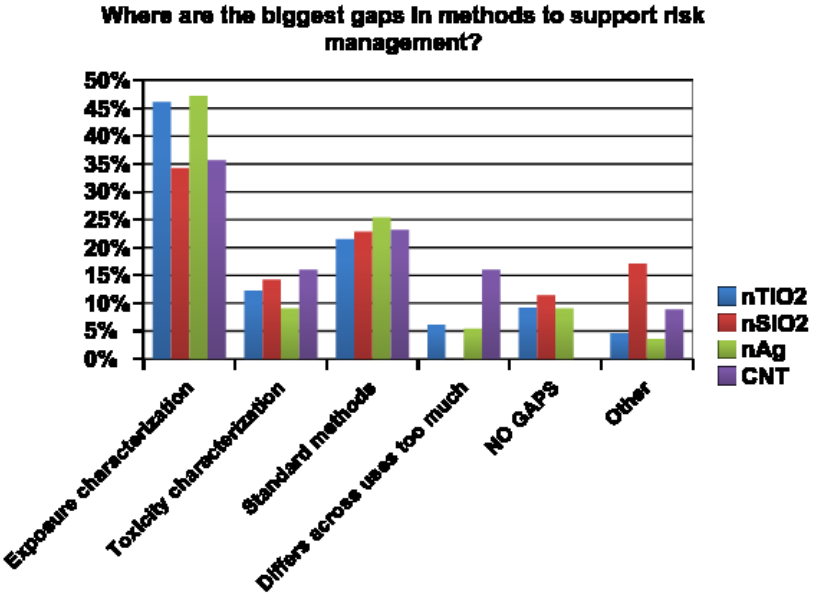


Figure 12 Where are the biggest gaps in methods to support risk management?

[2] Results are not provided for Barium Sulphate and Cerium Oxide as there were too few expert participants for these (<20 and <30 respectively).

2.3.3.8 First Delphi results: When will methods be adequate to support risk management?

Figure 14 analyses responses to questions in each separate MNM set that asked a forced choice of when participants believed adequate methods would be available to support risk management (example from MWCNT shown in Figure 13).

12) WHEN do you believe EXPOSURE ASSESSMENT METHODS for CARBON NANOTUBES will be adequate to make decisions on risk management?

Life cycle stage	Already here	In less than 5 years	In 5 to 10 years	> 10 years
Manufacture	○	○	○	○
Professional use	○	○	○	○
Consumer use	○	○	○	○
End of life/environmental	○	○	○	○

13) WHEN do you believe TOXICITY ASSESSMENT METHODS for CARBON NANOTUBES will be adequate to make decisions on risk management?

- ○ Already here
- ○ In less than 5 years
- ○ In 5 to 10 years
- ○ > 10 years

Figure 13 Screenshot of Round 1 forced choice responses

Using a ratio of those saying more than 5 years to those saying less than 5 we can see that experts are tending to say that we have methods for supporting risk management in professional, manufacture and toxicity methods, but consumer and environmental are further away from being adequate. For MWCNT most experts put methods for exposure at the End of life/Environmental as more than 10 years off. Interestingly, most experts had methods for toxicity assessment as "already here" for all MNMs.

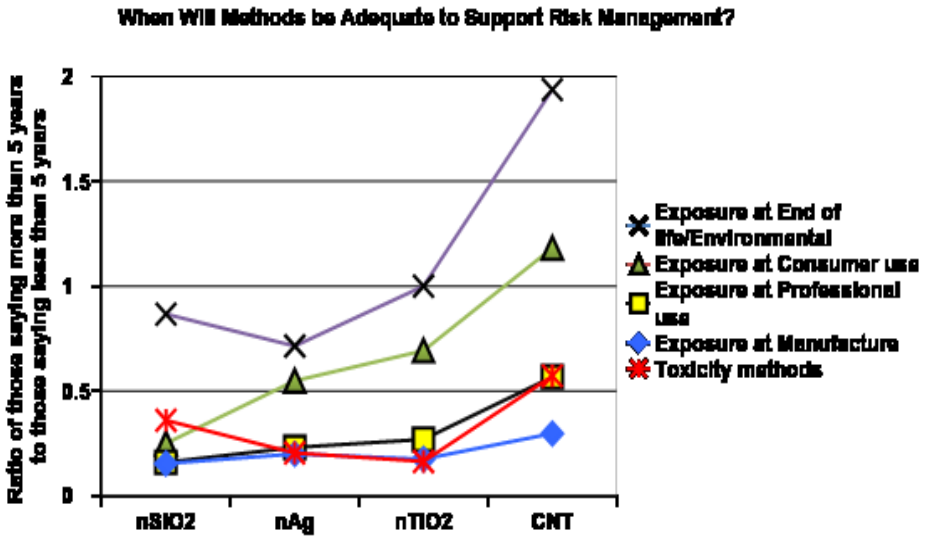


Figure 14 When will methods be adequate to support risk management?

2.3.4 *Step 3: Expert Review Panels Convened at the Society for Risk Analysis*

The workshop component of WP2 (milestone 2) took place as two expert panel review events at the Society for Risk Analysis (SRA) Annual Meeting in Arlington, Virginia, US, from 6th to 10th December 2015. These two events included firstly a roundtable and secondly a meeting of the SRA Risk Governance New Initiative convened by ProSafe and the SRA Emerging Nanoscale Materials Specialty Group, both of these sessions are described below.

2.3.4.1 Risk Governance New Initiative (RGNI) Meeting

A meeting to review the first round of the Delphi forum was sponsored by Horizon 2020 Prosafe project and jointly organised by Prosafe and the Society for Risk Analysis Emerging Nanoscale Materials Specialty Group (ENMSG) and advertised to other SRA specialty groups (Foundational Issues, Decision Analysis, Exposure Analysis) and took place from 7:30–8:30 AM, Tuesday 8th December 2015.

Objectives

The overall topic of the meeting was 'risk governance'. The objectives included raising awareness of the Delphi Forum and initiating discussion through initial graphics from the results. There was overlap in the participation of this panel with the Roundtable and audience following, and so this session provided an opportunity for more detailed preparatory discussions in a smaller panel setting.

Attendees

During the specialty section meeting there were 9 attendees:

- Christian Beaudrie (Compass Resource Management Ltd, Canada)
- Richard Canady (Institute of Occupational Medicine UK and NeutralScience L3C USA)
- Tom van Teunenbroek (Ministry of Infrastructure and the Environment, Netherlands)
- Danail Hristozov (University Ca' Foscari of Venice, Italy)
- Jo Anne Shatkin (Vireo Advisors, USA)
- Igor Linkov (US Army Engineer Research and Development Center, USA)
- Nicolas Geitner (Duke University, USA)
- Jeremy Gernand (The Pennsylvania State University, USA)
- Alice Davis (Institute of Occupational Medicine, UK)

Presentations

The meeting involved presentation slides presented by Richard Canady on the Delphi forum including graphics from the interim first round results; these were accompanied by discussions among attendees. A ProSafe Delphi forum flyer was also provided to attendees (Appendix 4).

2.3.4.2 Risk Governance New Initiative (RGNI) Meeting - Discussion

The focus of the discussion was on the content of the first round of the Delphi and how we could build upon the results from this in the development and implementation of the second round. The main points from the discussions have been extracted and are highlighted below:

- In the Delphi when we state 'biologically relevant', what do we mean? Having definitions in the second round could be useful to have opinion from different areas;
- In the results of the first round it highlights that those that work in research think more research is needed, surely this is a biased result, as researchers are bound to say we need more research?
- Instead of 'we don't know as much' and there being a gap, is it that more is invested in some areas and not others, for example in toxicity rather than exposure characterisation?
- How could more on sociology be incorporated into the Delphi forum?
- In relation to end of life, should there be an environmental and occupational divide? Perhaps in the second round of the Delphi forum consider separating these out, as not all end of life is environmental.
- In the Delphi forum do we mean release or exposure? If there isn't release, then there isn't exposure, how does this relate to SbD design, bound forms and designed release?
- Out of the six MNMs in the first Delphi round, only carbon nanotubes are a recently developed commercial nanomaterial, the others have been commercially available since the previous century.

However for carbon nanotubes the risk of exposure is almost zero. Should we consider other MNMs?

- For the second round more work is needed on the outcomes and standardising of the questions.

2.3.4.3 Roundtable

An expert review panel was convened to gain independent opinion from leading experts including a review of the implementation and interim results. This review panel was delivered through the Roundtable session at the SRA annual meeting and included open discussion among the audience following expert review statements. This session was jointly organised by the Society for Risk Analysis NanoSafety Cluster (SRANSC) Roundtable interest group and the Horizon 2020 ProSafe project. The session took place from 10:30 – Noon, Tuesday 8th December 2015 at the SRA Annual Meeting.

Objectives

The overall topic of the Roundtable was 'risk governance for innovation in nanomaterial uses'. The objectives of the session were:

- How can the first Delphi round be improved in informing foresight for nanomaterial risk governance?
- What insight into risk governance for innovation in nanomaterial uses can be gained so far from the first Delphi round?
- What forms or applications of risk governance methods appear best suited for innovation in emerging technology such as uses of nanomaterials?

Preparation

The panel was made up of 3 members at a senior policy level for risk management in emerging technology. Their role was to provide an independent review of the horizon scan, risk assessment needs, first Delphi round, and Core Group review of the Delphi rounds through the completion of 5 or 6 specific questions in a workshop and breakout group format. Those that agreed to participate on the panel were:

- Tina Bahadori, PhD: National Program Leader, Chemical Safety for Sustainability, U.S. Environmental Protection Agency
- Tom van Teunenbroek, PhD: Program Leader, NanoReg, ProSafe, Ministry of Infrastructure and the Environment, The Netherlands
- Treye Thomas, PhD: Leader Chemical Hazards Program, U.S. Consumer Product Safety Commission's Office and co-chair of the US White House National Science and Technology Council working group on Nanotechnology Environmental Health Implications.

To prepare for the Roundtable a briefing document was circulated before the event which included a description and graphics the first (incomplete) results of Delphi web forum Round 1 (Appendix 5). In addition the panel members were invited to participate in and review Round 1 and were provided a full printout of the responses that had been received as of December 1, 2015. Based on this information, the Roundtable members were asked to address the following charge questions in their opening comments and in discussion during the panel:

- How can the Delphi poll be improved in informing foresight for nanomaterial risk governance?
- What insight into risk governance for innovation in nanomaterial uses can be gained so far from the poll?
- What forms or applications of risk governance methods appear best suited for innovation in emerging technology such as uses of nanomaterials?

Roundtable participants

During the Roundtable there were approximately 24 expert participants from the Society for Risk Analysis (not including the 3 panel members and 4 presenters).

Roundtable presentations

The session began with the following presentations:

- Igor Linkov, PhD, US Army Corps of Engineers, and Danail Hristozov, PhD, University Ca' Foscari of Venice, Italy
    - Introduction to Society for Risk Analysis NanoSafety Cluster
- Ben Trump, PhD candidate, University of Michigan School of Public Health

- Manufactured Nanomaterials Risk Governance: A Review of Method Groups

- Richard Canady, PhD, Institute of Occupational Medicine of Edinburgh Scotland, and NeutralScience L3C
  - ProSafe Foresight, is risk management on pace with innovation? Delphi exercise and white paper (Appendix 6)

In addition to the presentation by Richard Canady on the ProSafe Delphi method and the results to date, there was also a supplementary double sided flyer for attendees providing information on participation and interim results (Appendix 4).

2.3.4.4 Roundtable - Discussion

The main opinions and discussion points of the expert discussants and attendees are presented below around the four main themes of:

I. What is currently known?

II. The future.

III. End users.

IV. Delphi Forum content.

What is currently known?

A challenge discussed in the Roundtable session was that although there is a high volume of data and information available, there are questions around how robust the data are and what we can, and have learnt from it. Parsing through the information for particular materials, uses, and exposure scenarios is a major challenge. Developing uniform or useful policy for risk governance and SbD across uses and materials in the face of this is an even greater challenge.

The future

When considering the future it was highlighted that to progress further with the data and information available we need to consider 'good data' versus 'bad data'. Within this discussion the point was made that there needs to be consideration of how the distinctions between good and bad data for a particular decision need can be identified. In some cases a minimal amount of data can suffice, and in others the current data may be misleading. A further issue is how data quality should be considered overall. As part of this it was highlighted that the validity of the methods (with respect to particular decision needs) that were used to collect this data in previous work, as well as considering its use in future work needs to be considered.

Specific considerations for future research that were discussed at the Roundtable session included:

- Importance of a strategy, including what we need to know and what tools are needed for risk based approaches;
- How a regulatory framework can be incorporated;
- Taking approaches based on exposure pathways rather than purely hazard driven. Exposure pathway based approaches are currently being discussed but not being developed;
- Specific techniques might be needed for specific materials;
- If we want to regulate based on "nanospecific" properties, we need to regulate on functionality, knowing the chemical is not enough;
- Distinctions and connections need to be made between data on pristine nanomaterials versus matrix bound nanomaterials, and the impact that matrix interactions can have.

Within the discussions, it was highlighted that, in addition to SbD for MNM uses going forward, there is also a need for further consideration of consequence based risk governance for MNM that are already in consumer products.

However, the assumption of the experts was that there are lots of MNMs currently being developed and so to prevent it being too late for risk management in the future it was proposed that it might be useful to consider the application of simulation data. Related to this there was also the suggestion that we need to try characterize and estimate what is released from MNM uses in products being considered for development. Through these estimates we can evaluate relative risk of product development alternatives. The assumption was that if we find there is no release for the particular materials and release conditions along the life cycle, then there is no exposure or health risk.

End users

When considering end users, the Roundtable discussion focused on a need to consider MNMs in products used by end users including children's products, for example nanoscale silver particles used in baby bottles. As part of this, it was identified there is a real need for risk communication on exposure including dermal and ingestion. Also, as well as end users there needs to be consideration for not only primary exposure but also later in life cycle exposure, such as in waste water.

Delphi Forum content

Throughout the Roundtable there were various suggestions and questions on the Delphi Forum, these are presented below:

- Are people answering the Delphi on the basis of methods that are available or are the responses more about the data that are available? In other words, the appropriate instrument/methods may be available for many decisions; however, the questions focus on methods to support risk management. Therefore, analysis of responses in the forum may need to consider that some responses are motivated by a lack of appropriate data (and frustration that the right questions were not asked).
- US versus EU comparisons are useful, but there also needs to be consideration of the MNM manufacturing work in Asia and the potential for unrecognized risk of MNMs in production and supply chains;
- It could be useful to separate out "end of life" and "environment" in exploring the life cycle evaluation issues because responses based on these issues may be a mixture of concepts of "recycling facility worker risk", "exposure pathways to human populations through environmental pathways" or "environmental release and exposure to ecological systems" by different participants;
- The forum should consider definitions for some questions (e.g., by defining environmental and biologically relevant) and whether to provide them in the forum. As it was highlighted that this could help to understand the context in which people are responding and highlight convergence/divergence. On the other hand it was discussed that providing definitions may act as a priming mechanism that may bias or inhibit responses.
- The point was raised that emerging technology might be considered as a more generic risk governance issue within the forum, for example children's products and emerging technology, e.g. 3D printing, wearable technology.
- The first round results identified a need for more research by those that work in research as a general stakeholder group. In fact, research includes several subgroups (academic, industry, government) with differing interests, which could be investigated and differentiated further in forum questions and analysis.

2.3.4.5 Outcomes of the Roundtable and Risk Governance New Initiative meeting

Through completing both the Roundtable and Risk Governance New Initiative meetings we identified some suggested actions for consideration in the development and implementation of the second round of the Delphi forum, including:

- Clarify if participants should be completing the questions on the basis of methods that are available or data that are available, or both;
- Include Asia (as well as EU versus US comparisons) in future analyses;
- Consider separating out end of life and environment;
- Consider the use of definitions;
- Consider including other areas (not Nano specific) in the next round, e.g. emerging technology;
- In Round 1 it identified more research is needed, follow up on this finding;
- Clarify what we mean by 'biologically relevant';
- Consider how we could incorporate sociology;
- Clarify the context of the Delphi in the second round, assumed to be professional;
- Clarify where relevant if we mean release or exposure;
- Standardise the questions more than in the first round;
- Further work on the outcomes and what is meant.

2.3.5 *Step 4: Core Group-Advised Development of Round 2 of the Delphi Web Forum*

2.3.5.1 Purpose

A second round of the Delphi forum using the SciPinion web interface was used to continue discussion among the nanotechnology community of the state and pace of risk management within the field and its applications.

Building on the Round 1 Delphi web forum results and analysis and the SRA Expert Panel reviews, the aim of Round 2 was to clarify input received. Round 2 was also intended to feed into the overall ProSafe White Paper that will serve as a tool for risk managers considering priorities for research and regulatory policy and methods development.

2.3.5.2 Design of the second Delphi round

As with the first round of the Delphi web forum, the questions for Round 2 were developed through interaction and collaboration between the project team and Core Group including web conferencing (February 2016, June 2016, and September 2016) and document revisions. Following the development stage the questions were tested using a small group of invited experts in the SciPinion platform for content and functionality.

Questions were also drawn from information needs identified by ProSafe Deliverable 2.2 “Report on Forward thinking and scanning trends and developments.” The Deliverable 2.2 report identified a broad range of instrumentation and methods in use and in development for assessing MNMs in consideration of SbD decisions. However, report authors found it difficult to identify a logical basis for prioritizing the development of particular methods or types of instrumentation. Therefore, Round 2 questions were developed with the review of the Core Group that sought rankings of method types in successive levels of detail. The questions were similar in nature to questions developed for other projects (e.g., the SUN project survey in 2015); however, the level of detail was kept low so that the question set was not so long that it would reduce expert participation.

There were competing issues in development of Round 2 of the forum that required some tough decisions about content and length. The first issue was that excellent comments, criticisms, and guidance were received. The second dominant issue was the belief of the project team that the complexity of Round 1 caused a low participation rate (just over 100 participants in over 2500 invitations and multiple methods for reaching out to recruit participants). There was clearly more information received in the review of the first round than could be incorporated in a second round. Therefore, the burden of interpreting the feedback as part of the form overall fell on the project team.

Given the belief that a recruitment constraint of brevity was needed; the project team chose a subset of simplified concepts taken from the input received. This selection was made in consultation with the Core Group and ProSafe partners. Based on this input it was agreed that Round 2 of the Delphi web forum would seek to clarify the following:

- “Safe by Design” responses for food and medical uses,
- The general response that we need work on exposure methods more than we do on toxicology methods,
- The general response that methods exist to support risk management for occupational exposures,
- The general response that we need to focus research and policy on consumer and environmental exposures.

To achieve clarification on these points it was agreed that the questions should be provocative and ask about why these opinions are held. Also in response to suggestions made in the Roundtable and RGNI meetings, it was decided to include the following definition of SbD in this second round on the introduction page:

*“The concept of **"Safe(ty) by design"** used in the poll refers to a movement that encourages product designers to "design out" health and safety risks during development.”*[3]

Following the definition and introductory text, the second round forum was made up of the following three sections:

1) Information about yourself

[3] https://en.wikipedia.org/wiki/Safety_by_design

This section asked participants about themselves, collecting information on region, sector of work and experience.

2) Clarification of responses in the first round

This section largely asked about whether the participants agreed or disagreed with the Round 1 results, using the scale; agree, agree but needs attention, disagree, no opinion.

3) More detail about methods needs

This section was developed in response to information needs identified in ProSafe D2.2 and asked about methods needs, collecting data by asking participants to rank (1 = most urgent to 7 = least important, or not needed) nanomaterial measurement systems, measurement types and sectors of use.

The structure and number of questions in each of these sections are presented in Table 4 and the full question set is available in Appendix 7.

Table 4 Round 2 Question Structure

Section	Number of Questions
Information about yourself	3
Clarification of responses in the first round	5
More detail about methods needs	5

2.3.6 *Step 5: Delphi forum Round 2*

2.3.6.1 Recruitment

The second round of the Delphi web forum was launched on the 17th June 2016, through invitation to the same expert list of over 2500 experts as were contacted in the first round. This initial contact was followed up by a reminder email in the final week and again on the final day for completion (Friday 8th July, 2016). Due to limited responses from the US, the end date was extended to the 15th July to allow for further direct contact to be made with this group. In total, 240 responses to the second Delphi round were recorded.

Similar to the first round, an incentive offered to participants was to be able to see specific analyses of responses after they had finished entering their data, and to comment on the results and discussion through the debate and comment functions in SciPinion.

2.3.6.2 Content of questions

The data in Round 2 were collected by the following stakeholder information:

- Region
- Employment sector
- Years of experience in the field of nanotechnology

2.3.6.3 Format of the interaction

Using SciPinion in a similar way to the first round there was an introductory page as shown in Figure 15.

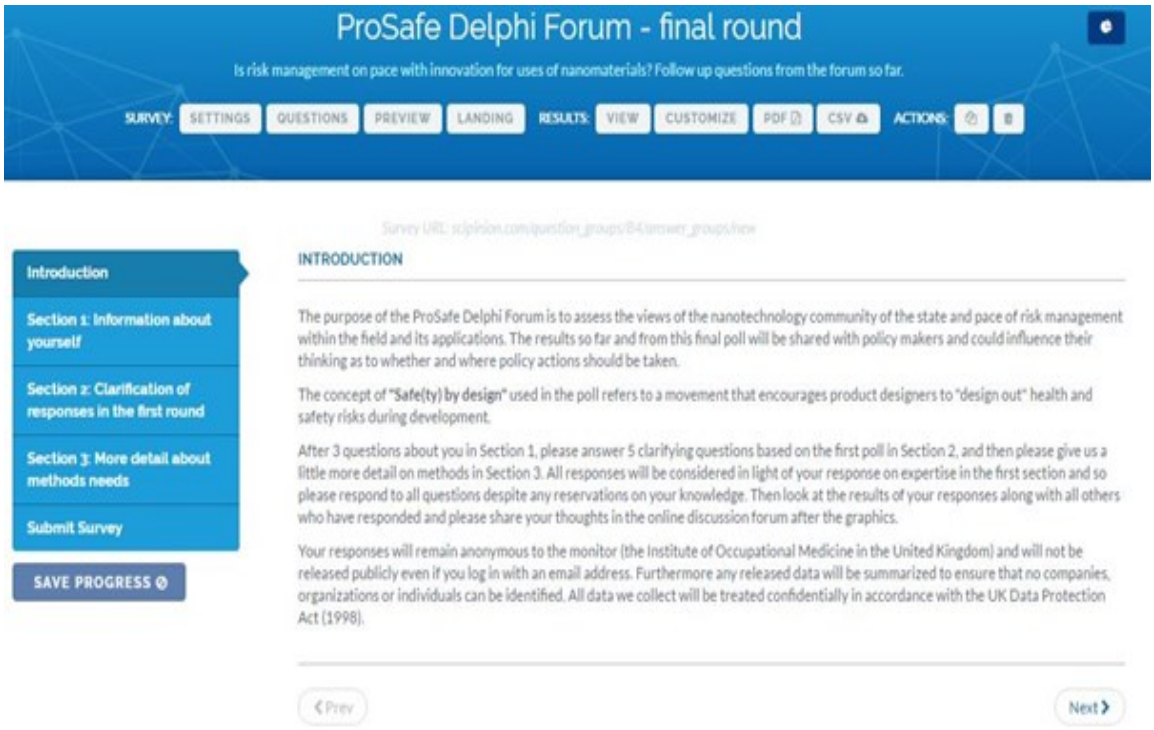


Figure 15 Screenshot of Round 2 Introduction Page

As with the first round, the question response formats included lists, tables of tick boxes, radio button and options for free text. In addition, this second round also made use of a new function in SciPinion where a graphic could be inserted alongside a question. This function allowed us to provide a graphic of the results from the first round and ask whether participants agreed or disagreed, as shown in Figure 16.

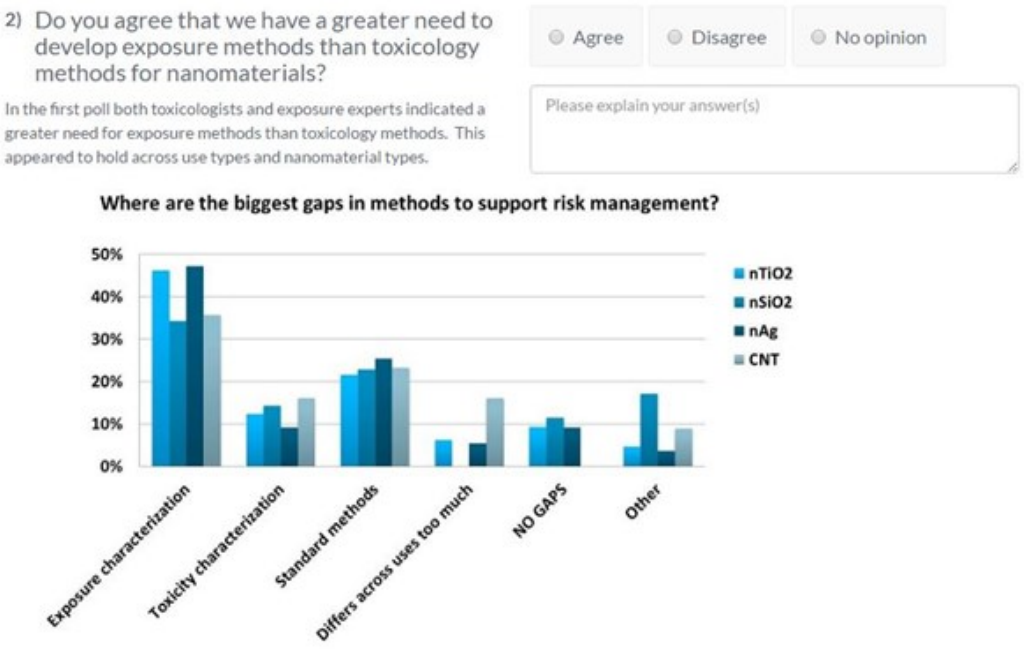


Figure 16 Screenshot of Round 2 Question Structure

Another additional feature that was utilised for the second round was the ability for participants to respond to specific graphics in the results section as shown in Figure 17. This was in addition to the feature to comment on the results as a whole using the debate function used in the first round (Figure 4).

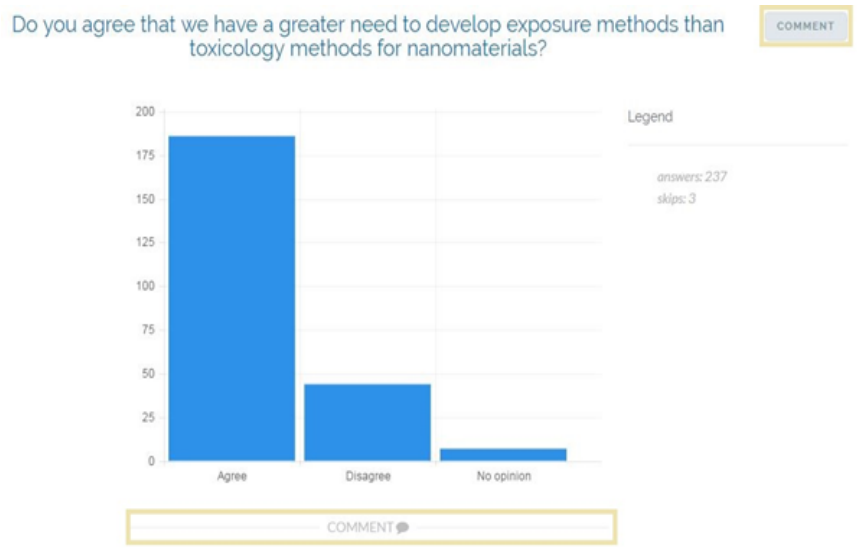


Figure 17 Screenshot of SciPinion Comment Function

2.3.6.4 Second Delphi results: information on participants

Of the 240 expert participants to the second Delphi round the majority were from Europe and worked in 'Research: Academic' (Figure 18), with the majority of the participants having 5 or more years' experience working in the field of nanotechnology (Figure 19).

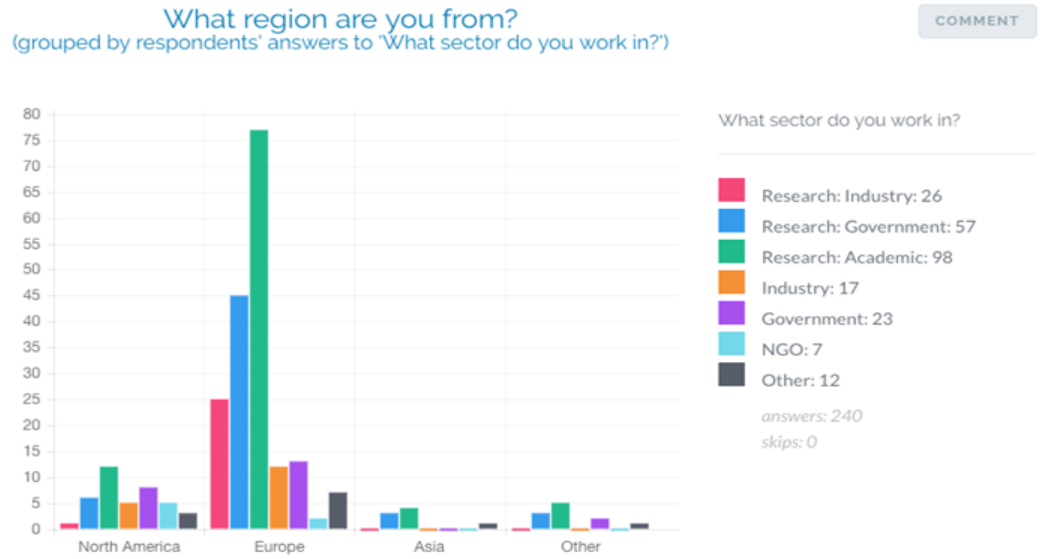


Figure 18 Round 2 Region and Sector results

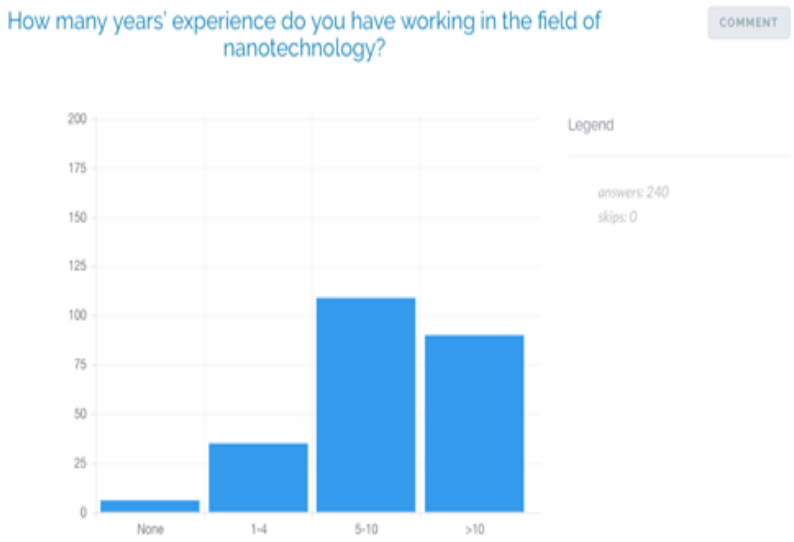


Figure 19 Round 2 Experience in Nanotechnology results

2.3.6.5 Second Delphi results: clarification of SbD, exposure and toxicology

In this section the graphics and selected analyses of the data and comments for each of the questions are presented. Similar to the first round, the full printout of SciPinion graphics for the responses are provided in Appendix 8.

In the second round of the Delphi web forum participants made use of the open text fields following the questions to provide detail on their response choices. As a result of this there were over 40 comments provided for each question, with some questions having up to 80 comments. These comments were collated to allow for a qualitative analysis to identify the main opinions and perceptions of participants. A summary of this narrative has been inserted following each of the graphics below.

Do you agree that safe by design practices are already in place for medical, food additive, or food packaging uses of nanomaterials?

As can be seen in Figure 20 the majority of participants have identified that for food packaging and medical applications SbD is in place, but requires more attention. The response for food additives was somewhat more of a split between those indicating that SbD is in place and not in place.

ID #2127

Do you agree that Safe By Design practices are already in place for medical, food additive, or food packaging uses of nanomaterials?

COMMENT

Is Safe by Design in place for consumer use of nanomaterials in:	Agree it is in place	Agree but needs more attention	Disagree - it is not in place	No opinion	Total
Food additives	7.98% 19	39.50% 94	39.92% 95	12.61% 30	238
Food packaging	11.86% 28	40.68% 96	31.78% 75	15.68% 37	236
Medical applications	28.81% 68	41.53% 98	16.95% 40	12.71% 30	236

Figure 20 Do you agree that safe by design practices are already in place for medical, food additive, or food packaging uses of nanomaterials?

The comments provided in the free text field alongside this question support this view, as it was clear there is uncertainty about the extent to which SbD is in place for medical, food additive and food packaging. One of

the main reasons reported for this uncertainty was the lack of standardisation of the methods and practices. This lack of availability of standardised methods was reported as a contributing factor for the implementation of practices not being thorough enough when being applied. Participants suggested that this will result in inconsistencies. These inconsistencies were identified as occurring along the life cycle in how and what practices are applied, but also inconsistencies in how these are applied within and between countries.

Participants suggested that there is a need for more knowledge in order to increase certainty and consistency in SbD practices. Along with this knowledge, it was identified that there is a need for a system or environment in which this knowledge can be shared and discussed by different stakeholders.

Knowledge gaps in relation to food packaging were a specific concern identified by participants. The knowledge gaps identified by participants focussed around release, leaching of materials from packaging and also uptake by the body. To respond to these it was identified that there is a need for further testing and validation of these tests. Whereas for the use of SbD practices in medicine, participants identified that the practices are more stringent and tightly controlled, therefore bringing more certainty in this area.

Main points:

- Perceptions from those that agree:
    - Practices in medical are more stringent and tightly controlled
- Perceptions from those that disagree:
    - Insufficient standardisation of methods and practices currently in place
    - Inconsistent application of practices
    - Need more knowledge and increased sharing of knowledge

Do you agree that we have a greater need to develop exposure methods than toxicology methods for nanomaterials?

In Figure 21 the results in relation to a greater need to develop exposure methods than toxicology methods have been presented by sector of work. As can be seen the majority of participants agree that exposure method needs are greater.

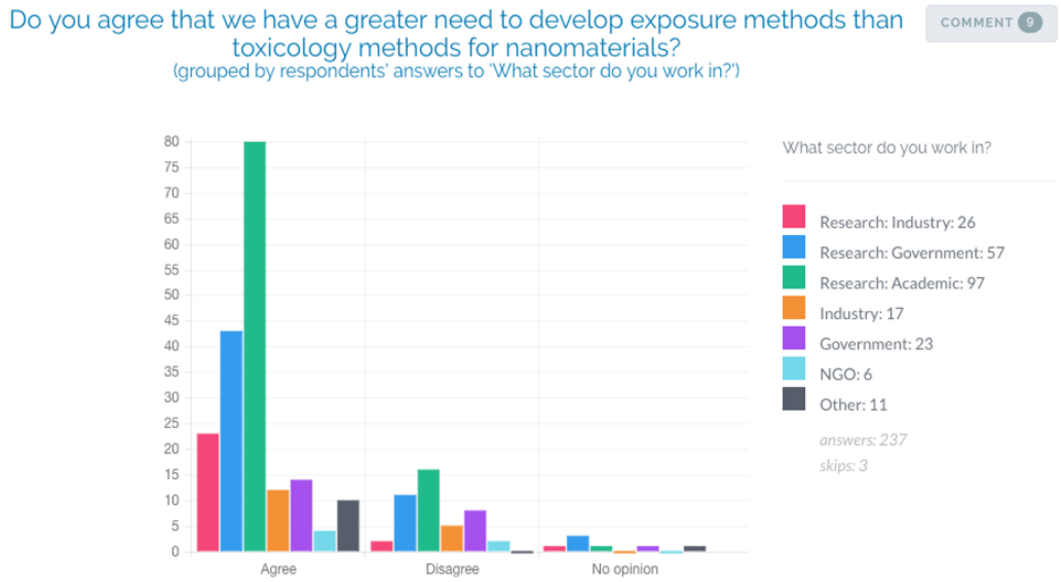


Figure 21 Do you agree that we have a greater need to develop exposure methods than toxicology methods for nanomaterials?

The comments provided in the free text field support the above results. Exposure methods were considered by the participants to be less well developed compared to toxicological methods. More specifically, participant's opinions were that there is a need to develop the knowledge and tools surrounding exposure assessment within the risk assessment process. As part of this the participants also identified that more needs to be done to develop the metrics and methods for measuring exposure. Related to measuring

exposure, it was identified that there is a specific need to understand when exposure gets to a point of being excessive. In other words, the simple knowledge of an exposure may not be sufficient to support SbD development processes. Clearly, an absence of exposure means an absence of risk; however, there are also likely to be exposure levels for which risk is well below levels that would require changing the development characteristics for a product. Therefore, knowing both a relative exposure to compare between development choices and absolute exposure levels in relationship to possible potencies for adverse health effects would be necessary to support SbD. It was also suggested quite simply that the level of understanding of exposure is quite poor and that until we can better measure exposure, it will be difficult to assess risk.

Participants who disagreed with the statement of a greater need to develop exposure methods than toxicology methods for MNMs argued mainly that both are equally important or that it depends on the application. In addition, it was identified that both exposure methods and toxicology methods require further research. This further research was identified as important as there is a need for both methods to be relevant and reliable.

Main points:

- Perceptions from those that agree:
    - Exposure methods are less developed than toxicity methods
    - Need more knowledge and tools surrounding exposure assessment
    - Need to develop metrics and methods for measuring exposure
- Perceptions from those that disagree:
    - Both exposure and toxicity are equally important
    - The need depends on the application
    - Both exposure and toxicity require further research

Do you agree that occupational exposures to nanomaterials during manufacturing can be controlled with existing risk management methods?

In Figure 22 the results in relation to whether or not participants agree that exposure during manufacturing can be controlled with existing risk management methods have been presented by sector of work. These results show that the majority of participants agree the exposures can be controlled, but only with additional attention.

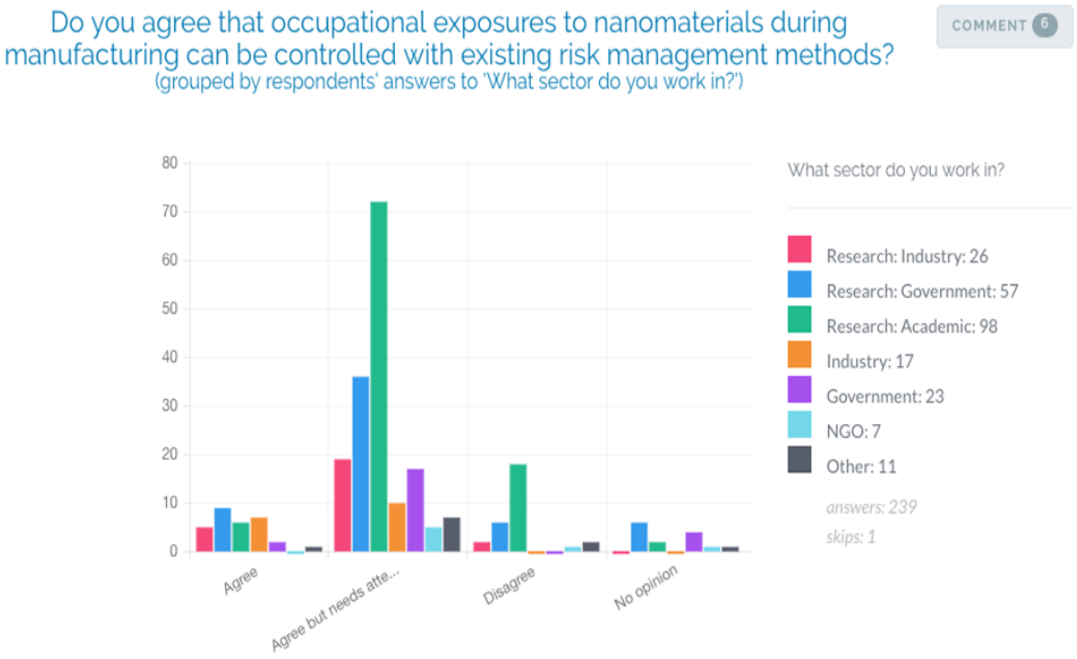


Figure 22 Do you agree that occupational exposures to nanomaterials during manufacturing can be controlled with existing risk management methods?

In support of the overall response “agree but needs attention” the point was made that a company may not be aware of the MNMs they are working with. Therefore, awareness of need to address risk management specific to MNMs is vital. This awareness may be necessary to identify and implement the control measures needed because in many cases the assessment of controls may be dependent on measurement methods specific to the MNM. This awareness and implementation need was noted by participants as being particularly true for SMEs and start-up companies. In addition, it was identified that there is a need for increased support and guidance throughout manufacturing to encourage a culture of knowledge sharing. Sharing of knowledge could then facilitate improved consistency and best practice development in a self-reinforcing cycle, and therefore ultimately employee safety.

Participants who disagreed with the statement that occupational exposures to MNMs can currently be controlled referred to existing knowledge gaps. These opinions focused on the suggestion that not all risks are currently being assessed, as risk management only tells us how we could be safe, rather than how unsafe we are. Another knowledge gap that was identified by the participants concerned the adequacy of exposure controls when materials cannot be fully characterised at different life cycle stages.

Some commenters made the point that current methods are not fully effective or appropriate in controlling exposure in all cases, so a general case is difficult to make. In improving the risk management methods there is a need to focus on and improve measurement sciences. These issues are complex as it can be dependent on the MNM of concern. Other comments questioned the applicability of existing risk assessment frameworks developed for chemical risk management for use with MNMs.

In order to attempt to increase the control of exposure with risk management methods and increase confidence in these, participants suggested that we need more reliable assessment and detection methodologies. It was acknowledged that this is dependent on the MNM.

Responses also highlighted that the best controls in the world may be ineffective unless they are implemented thoroughly and robustly.

Main points:

- Perceptions from those that agree that exposures can be controlled (but identified a need for increased attention):
    - Exposure can be controlled to mitigate risk in most cases
    - While methods exist, they may not be applied consistently across different value chain stages, regions, and company sizes
    - Need to offer guidance and support to facilitate consistency in using the available methods
- Perceptions from those that disagree:
    - Current methods are not fully effective
    - Need to improve measurement, assessment and detection methods

Do you agree that occupational exposures to nanomaterials during professional use can be controlled with existing risk management methods?

As with the question for occupational risk management during manufacturing, the majority of respondents agreed that exposure during professional use can be controlled with exisiting risk management methods, but that this needs additional attention (Figure 23).

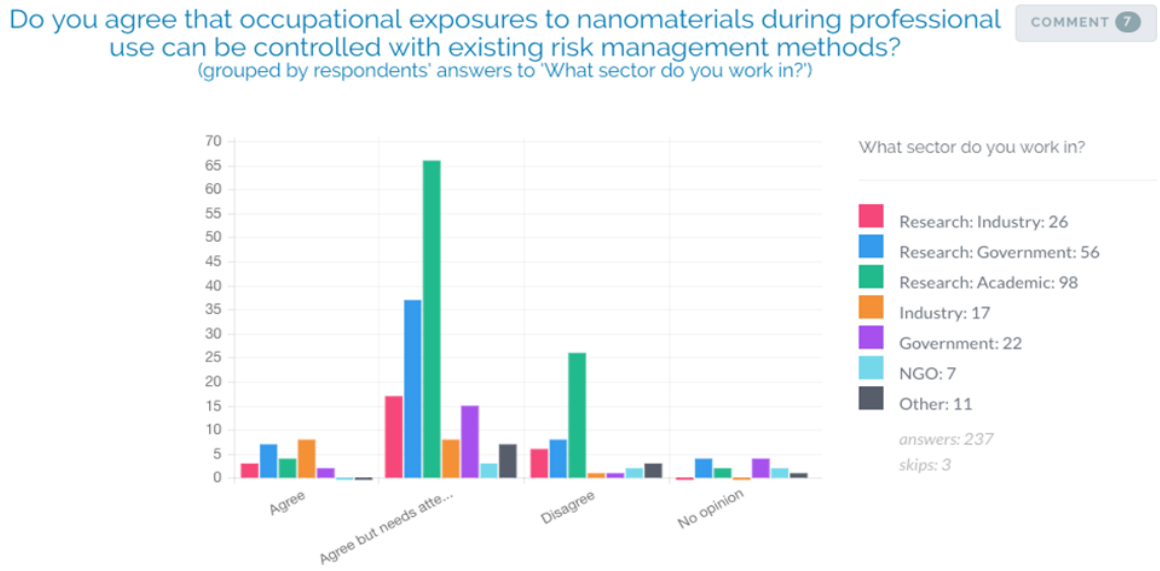


Figure 23 Do you agree that occupational exposures to nanomaterials during professional use can be controlled with existing risk management methods?

In addition to noting that exposure to MNMs in professional use can be controlled, it was also identified that it is more important to develop implementation of these existing risk management methods before investing in new methods.

The majority of the participants were of the opinion that, despite availability of control measures, there is still room for increased control. It was suggested that this could be achieved through further study and validation of risk management methods. In addition, there is a need for authoritative advice (guidance, standards) on effective use of control measures in order to increase consistency in application of control measures. The advice would need to be supplemented with increased education and access to a knowledge base for MNM-specific controls. To correctly and consistently apply this guidance there would need to be a clear link (e.g., through labelling) to the types of MNMs that are being worked with in specific professional use settings.

Participants who disagreed with the statement that occupational exposure to MNMs during professional use can be controlled with existing risk management highlighted issues around the adequacy of methods. Inadequacy was also linked to the specific types of MNM and the definitions that would be applied for the MNM.

Overall it was identified that there is a need for evaluation of current practices of risk management methods in professional use and a greater awareness and knowledge of the variation in application of effective methods for MNM risk management. However, it was also acknowledged that risk management methods only tell us how we could be safe, and not how unsafe we are, or about conclusions on long term exposure.

Main points:

- Perceptions from those that agree that exposures can be controlled (but see need for increased attention):
    - Existing methods are sufficient in all areas
    - Need authoritative guidance on the application of methods
    - Inconsistency in implementation of existing methods
- Perceptions from those that disagree that exposures can be controlled:
    - Need increased control with existing risk management methods
    - Need evaluation of current practices of risk management methods
    - Whether or not it can be controlled depends on the MNM

Do you agree that policies to facilitate safe by design for nanomaterials should now focus more heavily on consumer and environmental exposures?

The majority of participants agreed that policies to facilitate SbD should focus more on consumer and environmental expsoures (Figure 24). One of the main reasons was the assumed complication in characterizing consumer and environmental exposures. In addition, there is concern that more needs to be done in these areas due to the rate at which MNMs are penetrating the market. As a result, there needs to be more policies on SbD and specifically consideration of the pre-market approval requirements. When focusing on consumer and environmental exposures it was suggested that the public should have clearer information on risks and benefits of MNMs being used.

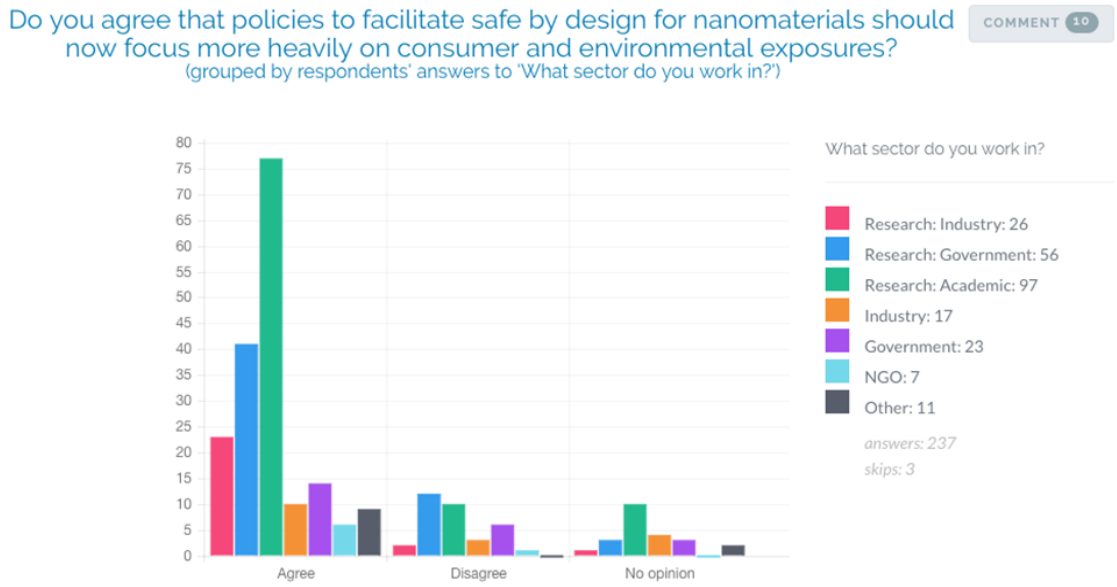


Figure 24 Do you agree that policies to facilitate safe by design for nanomaterials should now focus more heavily on consumer and environmental exposures?

Some participants disagreed with the focus on consumer and environmental exposure as they felt that focus should be in areas where exposure is greatest. To increase clarity regarding where exposure may occur it was suggested to develop an inventory and potential exposure list for the whole life cycle of MNMs. Through this approach it would be possible to evaluate relative need for focus on research methods or redesign for particular products with respect to consumers, workers and environment. Another suggestion was that research on material characteristics should be tailored to meet specific uses of materials and therefore move towards customisation that “builds in” lack of exposure at any potential exposure point.

Comments raised the importance of focusing on the actual exposures that could occur, and stressed that contact with pure or pristine (as manufactured) MNMs may be unlikely through environmental pathways. In relation to environmental exposure, it was noted that there must not be an oversimplification of this as MNMs can undergo important changes and transformation in environmental media. There is a need for careful consideration in the approach to linking health effects in toxicology studies to anticipated exposure pathways and the relative doses expected. The higher exposure potential situations of uncontrolled occupational settings may be more likely to occur with the purer or pristine MNM. Lower levels of exposure through environmental pathways may be more likely to occur to transformed MNM that may not relate to existing toxicology studies. However, in both cases the same MNM additive could be the result of a SbD decision taken in product design. More specifically, it was suggested that SbD policy resources should be directed at products and industries that present the greatest public health threats overall in consideration of actual exposures and forms of exposure.

Overall participant’s comments suggest there shouldn’t be a complete shift in focus, but rather an expansion of attention, including the provision of more research and better defined policy and regulations.

Main points:

- Perceptions from those that agree:
    - Consumer and environmental exposures are more complicated and require more attention
    - More work is needed due to the rate at which MNMs are penetrating the market

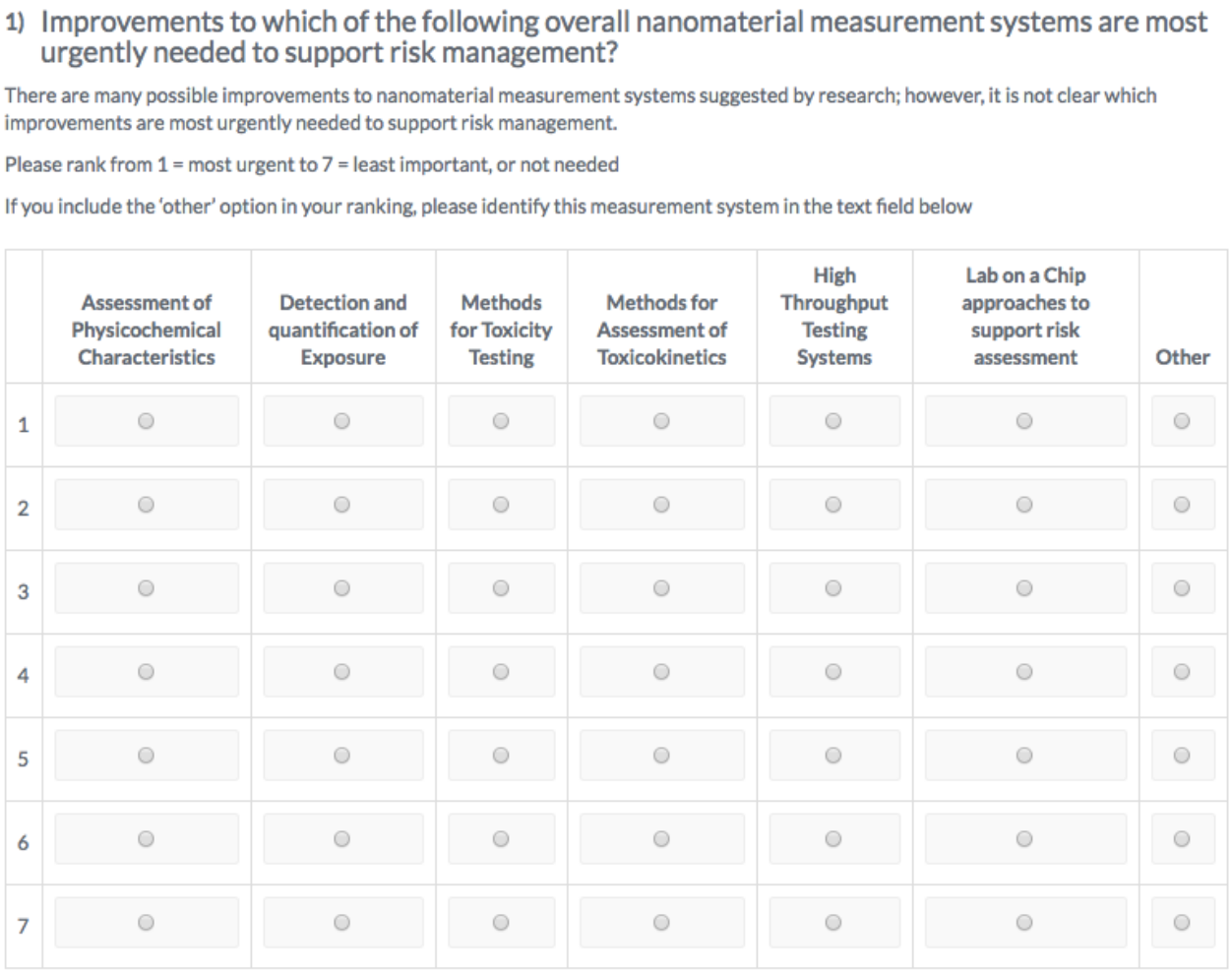
- Perceptions from those that disagree:
    - The focus should be on where exposures are greatest
    - There shouldn't be a complete shift in focus, instead there should be an expansion of attention on the specifics of a use and its life cycle transformations and implications

2.3.6.6 Second Delphi results: SbD methods needs

In this section, the tables of ranking results have been presented for each of the methods needs questions.

Improvements to which of the following overall nanomaterial measurement systems are most urgently needed to support risk management?

A series of rank order questions were posed in Round 2 based on responses regarding specificity of methods in Round 1 and based on feedback from ProSafeTask 2.2 regarding the lack of information useful to prioritize methods development needs. The first of this series is shown in Figure 25. Respondents were asked to select one choice for each column for each rank/row.



1) Improvements to which of the following overall nanomaterial measurement systems are most urgently needed to support risk management?

There are many possible improvements to nanomaterial measurement systems suggested by research; however, it is not clear which improvements are most urgently needed to support risk management.

Please rank from 1 = most urgent to 7 = least important, or not needed

If you include the 'other' option in your ranking, please identify this measurement system in the text field below

	Assessment of Physicochemical Characteristics	Detection and quantification of Exposure	Methods for Toxicity Testing	Methods for Assessment of Toxicokinetics	High Throughput Testing Systems	Lab on a Chip approaches to support risk assessment	Other
1							
2							
3							
4							
5							
6							
7							

Figure 25 Screenshot of Round 2 rank order question

In Figure 26 each row shows the percent distribution of responses for that rank to the question asking about which improvements to MNM measurement systems are most urgently needed to support risk management.

ID #2036

Improvements to which of the following overall nanomaterial measurement systems are most urgently needed to support risk management?

COMMENT 14

	Assessment of Physicochemical Characteristics	Detection and quantification of Exposure	Methods for Toxicity Testing	Methods for Assessment of Toxicokinetics	High Throughput Testing Systems	Lab on a Chip approaches to support risk assessment	Other	Total
1	23.21% 52	48.66% 109	8.48% 19	6.25% 14	5.80% 13	4.02% 9	3.57% 8	224
2	19.64% 44	26.34% 59	19.64% 44	13.84% 31	10.71% 24	7.14% 16	2.68% 6	224
3	16.06% 35	8.72% 19	23.39% 51	23.85% 52	15.14% 33	10.09% 22	2.75% 6	218
4	20.47% 44	4.19% 9	19.53% 42	28.37% 61	16.28% 35	9.77% 21	1.40% 3	215
5	10.29% 21	5.88% 12	15.69% 32	20.10% 41	30.88% 63	15.69% 32	1.47% 3	204
6	8.50% 17	3.50% 7	11.00% 22	8.50% 17	17.50% 35	49.00% 98	2.00% 4	200
7	3.26% 3	7.61% 7	6.52% 6	1.09% 1	8.70% 8	22.83% 21	50.00% 46	92

Figure 26 Improvements to which of the following overall nanomaterial measurement systems are most urgently needed to support risk management?

To visualize the pattern of responses to this question across stakeholder groups, heat maps for the overall response and for selected stakeholder groups are presented in Figure 27 to Figure 32. Note that the rows and columns have been transposed in these figures so that the percent of all participants choosing rank "1" is shown in the first column. In these heat maps green representing the method that was most often selected for a particular rank and red the least.

As can be seen in these heat maps there is a clear pattern for 'detection and quantification of exposure' to rank as either 1 or 2 (75% of respondents overall) and for 'lab on a chip approaches to support risk assessment' to rank as 6 (49% overall). 86% of Government respondents gave detection and quantification of exposure either 1 or 2. It is important to note here, as will be further explored in the discussion section of this report, that these results describe widely held expert opinions; however, the results do not necessarily comprise foresight. The interpretation of these responses should consider both their face value to inform policy decisions about where methods development should go and their importance in shaping risk communication needs if policy decisions are made that go in another direction. Understanding the grain of current opinion will inform likely outcomes of current research and the content of grant proposals in the works. Policy in the face of that opinion may be quite different, depending on the vision of policy makers.

Total responses						
	1	2	3	4	5	6
Assessment of Physicochemical Characteristics	23%	20%	16%	20%	10%	9%
Detection and quantification of Exposure	49%	26%	9%	4%	6%	4%
Methods for Toxicity Testing	8%	20%	23%	20%	16%	11%
Methods for Assessment of Toxicokinetics	6%	14%	24%	28%	20%	9%
High Throughput Testing Systems	6%	11%	15%	16%	31%	18%
Lab on a Chip approaches to support risk assessment	4%	7%	10%	10%	16%	49%

Figure 27 Heat map of total responses to the question "Improvements to which of the following overall nanomaterial measurement systems are most urgently needed to support risk management?"

Non-Research: Industry, Government, NGO, Other						
	1	2	3	4	5	6
Assessment of Physicochemical Characteristics	15%	25%	19%	25%	8%	6%
Detection and quantification of Exposure	53%	24%	8%	2%	6%	4%
Methods for Toxicity Testing	14%	20%	20%	10%	20%	10%
Methods for Assessment of Toxicokinetics	6%	12%	16%	24%	24%	16%
High Throughput Testing Systems	10%	13%	10%	23%	23%	17%
Lab on a Chip approaches to support risk assessment	2%	6%	16%	12%	10%	39%

Figure 28 Heat map of non-research responses to the question "Improvements to which of the following overall nanomaterial measurement systems are most urgently needed to support risk management?"

Research: academic, government, industry						
	1	2	3	4	5	6
Assessment of Physicochemical Characteristics	27%	19%	15%	19%	10%	9%
Detection and quantification of Exposure	48%	27%	9%	5%	5%	3%
Methods for Toxicity Testing	7%	20%	25%	22%	13%	10%
Methods for Assessment of Toxicokinetics	7%	15%	26%	29%	17%	5%
High Throughput Testing Systems	5%	11%	17%	15%	32%	17%
Lab on a Chip approaches to support risk assessment	5%	8%	8%	9%	16%	46%

Figure 29 Heat map of research responses to the question "Improvements to which of the following overall nanomaterial measurement systems are most urgently needed to support risk management?"

Government, Research: Government						
	1	2	3	4	5	6
Assessment of Physicochemical Characteristics	36%	19%	19%	12%	10%	3%
Detection and quantification of Exposure	46%	40%	6%	1%	4%	1%
Methods for Toxicity Testing	6%	18%	21%	32%	14%	8%
Methods for Assessment of Toxicokinetics	7%	15%	27%	23%	22%	5%
High Throughput Testing Systems	6%	4%	17%	20%	30%	19%
Lab on a Chip approaches to support risk assessment	1%	4%	7%	11%	15%	56%

Figure 30 Heat map of government responses to the question "Improvements to which of the following overall nanomaterial measurement systems are most urgently needed to support risk management?"

Research: academic						
	1	2	3	4	5	6
Assessment of Physicochemical Characteristics	24%	15%	12%	22%	13%	12%
Detection and quantification of Exposure	48%	23%	7%	6%	7%	4%
Methods for Toxicity Testing	9%	24%	28%	15%	12%	10%
Methods for Assessment of Toxicokinetics	4%	16%	26%	34%	14%	4%
High Throughput Testing Systems	4%	12%	17%	14%	31%	18%
Lab on a Chip approaches to support risk assessment	5%	11%	10%	7%	14%	41%

Figure 31 Heat map of academic responses to the question "Improvements to which of the following overall nanomaterial measurement systems are most urgently needed to support risk management?"

Industry, Research: Industry						
	1	2	3	4	5	6
Assessment of Physicochemical Characteristics	8%	28%	21%	33%	5%	5%
Detection and quantification of Exposure	54%	14%	19%	5%	3%	5%
Methods for Toxicity Testing	18%	18%	16%	13%	16%	11%
Methods for Assessment of Toxicokinetics	10%	10%	18%	18%	26%	18%
High Throughput Testing Systems	9%	26%	9%	14%	26%	14%
Lab on a Chip approaches to support risk assessment	8%	5%	16%	11%	18%	34%

Figure 32 Heat map of industry responses to the question "Improvements to which of the following overall nanomaterial measurement systems are most urgently needed to support risk management?"

For toxicity and toxicokinetics, which measurement types most urgently need methods development to support risk management for current nanomaterial uses?

As can be seen here the responses are more spread across methods types than for overall measurement systems in the previous question. However, a majority list 'distribution/accumulation' for toxicity and toxicokinetics rank as first with 'absorption' second in the ranking order (Figure 33). This again continues the exposure side of the risk equation, with methods for understanding of modes of toxic action generally ranking lower than understanding entry into the body and distribution to organs.

Comments for these methods ranking questions provide a rich array of information on the kinds of methods that should be stressed in research and policy. Unfortunately, the range and detail of the comments is not easily digested into summary statements. The input does offer a source of insight for those interested in reviewing it when the data set is made public.

ID #2039

For Toxicity and Toxicokinetics, which measurement types most urgently need methods development to support risk management for current nanomaterial uses?

COMMENT 10

	Cytotoxicty	Inflammation	Oxidative stress	Genotoxicity	Absorption	Distribution /accumulation	Other	Total
1	7.69% 16	10.10% 21	9.62% 20	12.98% 27	19.23% 40	37.02% 77	3.37% 7	208
2	8.50% 17	13.50% 27	12.00% 24	12.50% 25	29.50% 59	22.50% 45	1.50% 3	200
3	15.46% 30	17.01% 33	24.23% 47	20.10% 39	10.31% 20	11.86% 23	1.03% 2	194
4	20.83% 40	20.83% 40	16.15% 31	22.40% 43	8.85% 17	9.38% 18	1.56% 3	192
5	15.51% 29	20.32% 38	24.06% 45	13.37% 25	17.11% 32	9.09% 17	0.53% 1	187
6	27.62% 50	14.36% 26	9.39% 17	16.57% 30	16.02% 29	14.92% 27	1.10% 2	181
7	9.38% 6	9.38% 6	6.25% 4	9.38% 6	3.13% 2	4.69% 3	57.81% 37	64

Figure 33 For toxicity and toxicokinetics, which measurement types most urgently need methods development to support risk management for current nanomaterial uses?

For detection and quantification of exposure, which measurement types most urgently need methods development to support risk management for current nanomaterial uses?

For detection and quantification of exposure the results show that 'number size distribution concentration' was most frequently ranked as first and second (Figure 34).

ID#2038

For Detection and Quantification of Exposure, which measurement types most urgently need methods development to support risk management for current nanomaterial uses?

COMMENT 10

	Number Concentration	Number Size Distribution Concentration	Mass Concentration	Surface Area Concentration	Other	Total
1	15.74% 34	40.74% 88	16.20% 35	23.61% 51	3.70% 8	216
2	26.92% 56	29.81% 62	16.83% 35	25.00% 52	1.44% 3	208
3	32.49% 64	18.27% 36	20.81% 41	25.89% 51	2.54% 5	197
4	21.99% 42	9.42% 18	41.88% 80	24.08% 46	2.62% 5	191
5	9.38% 6	7.81% 5	14.06% 9	6.25% 4	62.50% 40	64

Figure 34 For detection and quantification of exposure, which measurement types most urgently need methods development to support risk management for current nanomaterial uses?

For physicochemical characterisation, which measurement types most urgently need methods development to support risk management for current nanomaterial uses?

For physicochemical characterisation the measurement types of 'solubility or dissolution rate' and 'chemical composition (including surface) rank most frequently as first and second (Figure 35).

ID#2037

For Physicochemical Characterization, which measurement types most urgently need methods development to support risk management for current nanomaterial uses?

COMMENT 15

	Particle Size Distribution	Volume Specific Surface Area	Aspect Ratio (shape)	Particle Rigidity	Solubility or Dissolution Rate	Chemical Composition (including surface)	Other	Total
1	23.58% 50	9.91% 21	6.60% 14	1.42% 3	25.94% 55	28.30% 60	4.25% 9	212
2	14.15% 30	13.21% 28	13.21% 28	6.60% 14	28.77% 61	23.11% 49	0.94% 2	212
3	16.91% 35	15.94% 33	16.91% 35	14.98% 31	17.39% 36	14.49% 30	3.38% 7	207
4	12.94% 26	28.36% 57	20.90% 42	17.41% 35	10.95% 22	8.96% 18	0.50% 1	201
5	17.95% 35	18.97% 37	26.15% 51	16.41% 32	11.28% 22	7.69% 15	1.54% 3	195
6	15.14% 28	7.57% 14	12.97% 24	40.54% 75	6.49% 12	15.14% 28	2.16% 4	185
7	6.58% 5	10.53% 8	6.58% 5	14.47% 11	3.95% 3	7.89% 6	50.00% 38	76

Figure 35 For physicochemical characterisation, which measurement types most urgently need methods development to support risk management for current nanomaterial uses?

Please rank the following sectors of use with regard to need for development of High Throughput Test Systems to support risk management decisions

Figure 36 presents the results from the ranking of sectors of use in relation to need for development of High Throughput Test Systems to support risk management decisions and shows that the majority of participants identified that toxicology testing ranks highest in need for development.

ID#2126

Please rank the following sectors of use with regard to need for development of High Throughput Test Systems to support risk management decisions.

COMMENT

	Physicochemical characterisation	Toxicology testing	Ecotoxicology testing	Other	Total
1	36.82% 81	44.55% 98	16.36% 36	2.27% 5	220
2	16.20% 35	36.57% 79	44.91% 97	2.31% 5	216
3	44.66% 92	14.08% 29	37.38% 77	3.88% 8	206
4	11.76% 8	11.76% 8	11.76% 8	64.71% 44	68

Figure 36 Ranking of sectors of use with regard to need for development of High Throughput Test Systems to support risk management decisions

2.4 Evaluation and conclusions

2.4.1 *Discussion*

The general task of the foresight project was to try to identify whether risk management capabilities to support SbD are on pace with the development of nanomaterial uses. The project was successful in developing foresight information on gaps applicable to implementation of SbD approaches for MNM in general, and for methods to assess some specific types of MNM that may be used in the near future. The project also informed areas of strength in methods and policies applied to SbD for products to be developed. However, it is important to put the information in the context of its provenance because the foresight of this report is based on interpretation of freshly gathered opinions of many experts and other interpretations may be possible.

To develop foresight for this report the project team reviewed expert opinion gathered through a Delphi forum administered in 5 steps over the course of 12 months. The Delphi forum was structured to gather expert opinion about the types of methods that will be needed to support SbD, and whether those methods will be available when needed. A Delphi forum was used for this task in part because a review of existing literature on foresight for nanotechnology, and a literature search on forecasts for new methods and technology for nanotechnology risk management (both reported in ProSafe Deliverable 2.2) were unsuccessful in developing the kind of information needed for the foresight task.

This outcome for literature searches is perhaps expected when the foresight involves emerging methods to measure entities that are themselves the result of emerging technology. Foresight for risk management of an emerging technology, like nanotechnology, is a second order problem wherein the first order is to understand the technology applications that are emerging. The second order is then to understand the methods that may need to be developed to measure the possible risks from the uses of those technology applications. There may be a third order as well, which is understanding of what measurement methods are possible, which may in turn involve a need to understand emerging technology (e.g., of image processing, rapid individual particle characterization, functional assays, high throughput data acquisition/analysis). Therefore, it was necessary to develop foresight for the project through a process of guided discussions with the people who are developing the technology applications and with the people who are developing the methods to measure the health risk-related outcomes of the applications.

A further reason for the Delphi approach taken by the project is the complexity of the undertaking of considering such a broad topic of all health risks, of all possible uses of a technology. Nanotechnology is used or is being developed for possible use in a tremendous range of applications. The materials that are considered nanomaterials are also tremendously varied. Furthermore, the conditions of use and of release to exposure pathways can further increase the complexity of measuring the effects of a given use because they can affect the physical and chemical properties of those nanomaterials. Furthermore the methods to measure or assess nanomaterials can vary and the data needed to assess exposures can vary from one nanomaterial type to another. For this reason it was difficult to ask simple questions about “nanomaterial risk management” because the answer given by one expert or in one study could be different from the answer by or in another. The structured conversation of the Delphi approach allowed separation of issues and clarification of context so that, for example, a response about the safety of dendrimer use in cancer therapy was not confused with the safety of carbon nanotube use in construction materials. The detailed conversation also allowed separate consideration of methods needed for risk management support so that

methods needed for decisions about worker safety while using the pure form in a manufacturing facility were not confused with methods needed for containment of potential exposure through possible environmental release at the end of the use of products in which the nanomaterial was used.

2.4.1.1 Caveats for the use of the data

This Delphi forum used in the foresight was intended to provide a structured conversation among experts as a way of elaborating the kinds of opinions and perceptions that experts have for the complex set of issues addressed. However, the data were not collected in a way that provided representative samples. This was just not possible given the breadth of information to cover and the depth of evaluation needed. Therefore, the data cannot be used to say that one particular grouping of characteristics of participants is related to a particular response for all experts with that characteristic. Furthermore, while many of the participants indicated that they had 10 years or more of experience in aspects relevant to the questions; the sampling also does not allow statements about what "all experts" say about any particular issue.

It should also be noted that prevailing expert opinion about any issue in science can of course be wrong, and in the face of transitions in science such opinion has been famously wrong.[4] The emergence of nanotechnology may present the need for such a transition from health risk decision science based largely on chemical risk assessment to one better suited for particle risk assessment. It could be the case that the future of risk management for uses of nanotechnology will actually go in the direction of a few dissenters or visionaries.

Therefore, the value of this foresight report is about the insight gained from expert discussions of what may come and what is needed, not the comparison of bar graphs or t-tests of differences between groups or the number of experts who hold a certain belief. Sometimes the greatest value will be in what is stimulated by the discussion rather than by what the text may seem to prove or disprove. Review of the discussion and prevailing opinions can also offer insight into perceptions and misperceptions among experts, and where further communication may be needed.

It must also be noted that the response rate for some stakeholder groups was very low, and so elaboration of potential differences in opinion based on stakeholder perspective was not as useful as was hoped in the design and implementation of the forum.

Finally, this report is a single narrative evaluation of expert opinions, and thus presents one additional set of opinions through that narrative. Other evaluations of the same set of expert opinions may result in a different narrative and stimulate different insights. It would therefore be useful to continue this forum through alternate evaluations of the expert opinions collected for this project.

2.4.1.2 Summary of major themes of discussion (not conclusions)

Sequencing development of understanding of exposure and toxic effects of exposure.

The Delphi forum explored the relationship between development of exposure methods and development of toxicology methods needed in order to implement Safe by Design. When asked directly whether exposure methods were needed more than toxicology methods, the responses overwhelmingly favoured exposure. However, comments by participants in the second round of the Delphi forum illustrated a finer point about the need to sequence knowledge generation appropriately to support risk characterization as new uses develop rather than preferring exposure methods over toxicology methods development. The potential for risks associated with some properties of the nanomaterials that make it into exposure pathways from new uses may only be discernible when we understand the forms that are actually released, and thereby the properties to which exposure occurs. Therefore, developing toxicology or hazard based decision rules for SbD on current data for MNMs before we understand the actual exposures would be premature. For example, based on the comments, it seems likely that a high percentage of participants would have said "yes" if the Delphi forum had asked a question such as "should we provide an approach to sequence exposure and toxicology methods development so that it addresses the particular decision needs of products that are coming to market".

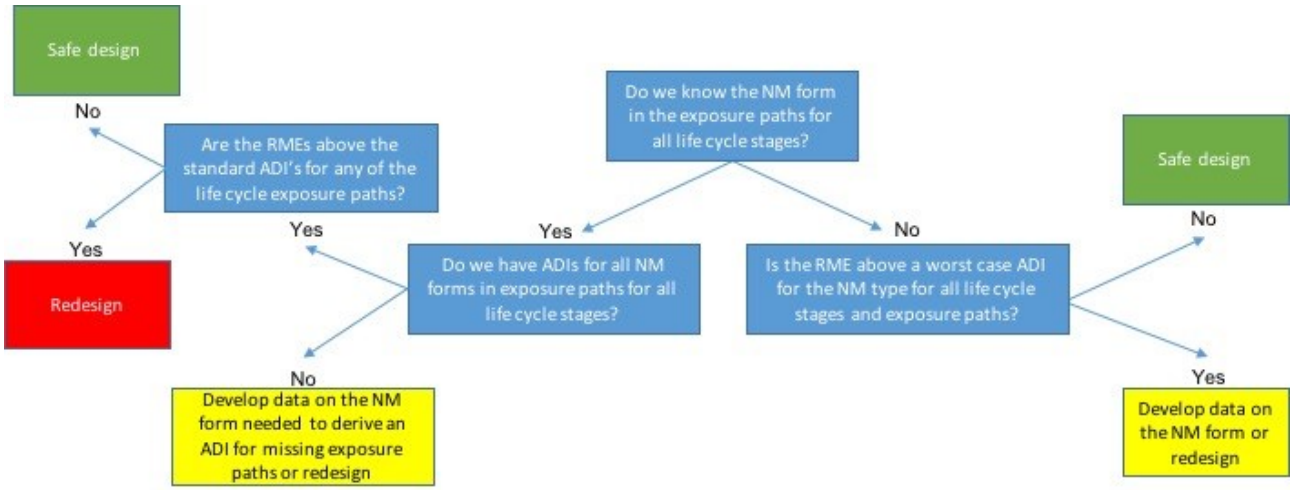
In some ways this line of reasoning is a case by case argument wherein the point is made that research to create a toxicological assay system to be applied uniformly to all nanomaterials will waste resources if it is created before we understand which characteristics will survive to exposure pathways in a particular case. We may need specific sets of methods for different types of uses and types of MNM, and until we have

[4] Kuhn, Thomas S., and David Hawkins. "The structure of scientific revolutions." *American Journal of Physics* 31.7 (1963): 554-555.

Kuhn, Thomas S. *The structure of scientific revolutions*. University of Chicago press, 2012.

studied those use-NM combinations, we will not understand what the sets should be or what the assay system should include. Of course, a case can be made (and was referred to in comments) that there are some emergent, nano-specific properties that should be evaluated for toxicological implications. Tests of toxicology endpoints for these nano-specific properties could be included in the toolboxes or screening that SbD would employ as a way of getting a leg up on the long sequence implied by need to a) develop the use, b) determine the released material, and c) develop methods to test the hazard of the released material.

The sequencing of understanding line of reasoning may also indicate that a tiered or strategic testing approach based on understanding of exposure and toxicity should be used even after the methods are developed that engages exposure characterization first, and then toxicity tests when they are needed. If a developed material gets to a third or fourth tier where the unknowns for risk are still present and the methods are insufficient to address the uncertainties, then methods development is needed. However, if the tiers are developed well, then the risk evaluations for many use types may be sufficiently resolved in earlier and less resource demanding tiers. An example decision approach could be as in Figure 37.



- **ADI** – acceptable daily intake
- **RME** – reasonable maximal exposure
- A **worst case ADI** could be mass-based using an uncertainty factor to account for particle surface area, reactivity and morphology. In contrast, a standard ADI would be developed using measures appropriate for the particle type and exposure medium.
- **Exposure path** – is the combination of 1) a completed exposure pathway from a source to a receptor and 2) a route of entry to the body (dermal, oral, inhalation)

Figure 37 Example Decision Approach

The relative difficulty of assessing the MNM released to environmental matrices vs control of MNM exposure in other settings

The forum asked a number of questions about the readiness of methods to support SbD in ways that differentiated discussion across nanomaterial types, use types, and across points in the life cycle (see for example, Figure 3). The forum was structured this way so that apparent disagreements in the press and in some reviews regarding risk management of nanotechnology uses could be teased apart to true disagreement vs different frames of reference. It seems clear from this structured discussion that indeed there are areas of fairly broad agreement and areas where the apparent differences of opinion are due more to frames of reference than to true differences.

For example, one theme that came across in the responses and comments is that many experts feel that methods are generally not available to adequately assess exposures to MNM that have been released to environmental exposure pathways. For example, through responses to questions and from comments, the ability to find concentrations of MNM at some point after emission from a use was noted as limited. In contrast, there was similar consistency in responses and comments that methods to measure and manage risk at other life cycle points, such as occupational exposures during manufacturing or professional use, are generally better covered. In fact, many experts appear to believe that there may be little to do in methods development for most contexts and decisions for risk management of occupational exposures.

Similarly, another theme that came across was that risk management for some consumer exposures, such as consumer exposures to MNM through medical products or through foods, is supported with existing methods. Therefore, one interpretation of the discussion is that when a statement is made that risk management is not done well for MNMs, or that methods do not exist to support MNM risk management, it is critical to specify the context under which the general statement is made. Similarly, expert opinion that MNM risks are well controlled may be correct but can also be misinterpreted as an over-generalization, if not put into the proper context. The discussions and conclusions about research and policy needs for SbD development of MNM uses will be quite different, depending on these contextual frameworks.

The view that there is variation in future implementation of SbD even where SbD is possible in principle

While the responses and comments indicated a clear perception that SbD is in place in principle to address safe design of consumer use of foods and medical products and safe design that would allow risk management of most occupational exposures, the discussion and responses to questions also pointed out the prevailing opinion that there is a need for attention to consistent implementation of safe design. This opinion was expressed in several discussion themes.

One theme was the variation in regulatory and best practice structures for different sectors of industry and different product types. In this theme some commenters pointed out that support for SbD that works for uses in one development context may not provide the necessary information for other contexts. For example, pre-market requirements for safety data (e.g., for medical products or direct food additives) are viewed as making it more likely that risks will be identified at appropriate times in SBD decision making or in later fabrication steps for materials and consumer products. In contrast, SbD for materials and products where premarket controls are not in place may be viewed as not having the same level of data collection and would rely more on post-market monitoring of effects.

Furthermore, SbD for precursor materials early in value chains, such as pre-pregs[5] for composite materials that are then used by manufacturers for a variety of commercial products falling under different regulatory programs, may not be able to foresee all applications for which the design for safety can be mapped out. In this context of value chain uncertainty, the concept of SbD may be limited in nature so that it only applies to immediate next steps in product fabrication.

Another theme of discussion for variation in implementation was that there is variation in enforcement of best practice or regulation across different settings. One place where variation in enforcement was noted was due to differences in resources available for risk management in small vs large companies. Even if methods to implement SbD are available, it may be the case that smaller enterprises may be unable to implement either through lack of access to information or through lack of capital to invest in expertise or equipment to assess safety at key SbD decision points. This variation would play out in manufacturing as well as in professional use, such as SbD for products or materials used by professionals in construction. Large construction firms would be expected to have industrial hygiene practices and monitoring capabilities, whereas home construction by small local companies or even do it yourself use of the same construction materials would not. These conditions could present a higher uncertainty barrier for SbD decision steps and a longer lead time for product development as it would need to build in time for methods and practices to be extended to a broader and less resource ready market for use of products. Alternatively, SbD decision steps could be used to identify use scenarios (e.g., only by licensed professionals in specified construction applications) that limit risk management uncertainty.

A further theme for variation in implementation stemmed from variation in the availability of standard methods (e.g., characterization, exposure, toxicity) or widely accepted best practice in data development to support nanomaterial risk management. There are many methods available to measure and assess characteristics, and characteristics that were most important to measure to support risk management were discussed both through responses to questions and through comments. The variety of responses in the forum alone may raise an issue of comprehension in the community regarding priority across nanomaterial risk management as a whole. For example, responses to the questions of which methods were most urgently in need of development in the second round of the Delphi forum showed some higher responses; however, nearly all methods had champions and responses. Comments received to the questions about urgency of development of methods also identified methods and evaluation approaches that were not considered in the questions. This variety in response may be expected from a group that includes many researchers; however,

[5] a fibrous material pre-impregnated with a particular synthetic resin, used in making reinforced plastics.

when asked in the context of supporting risk management it may also mean that there is little clarity in how to address risk management through application of specific methods.

The lack of specificity of the questions probably contributed to the lack of clarity in overall response. However, even in the more specific questions of the first round of the Delphi for the 6 individual MNMs, the responses had more variety than might be expected. Further rounds of Delphi with greater specificity may help address this variety. However, the variation in response and methods discussed is also likely to be a factor of the many material, use, media, background exposure levels, transformations, and exposure contexts that may occur for MNMs used in commercial materials.

Development of widely accepted best practice and international standard methods in support for particular SbD decision stages for classes of materials and uses may also address this need for greater clarity and specificity. A need for standard methods was frequently expressed in response to questions and in comments about support for risk management using SbD. More consistent implementation of available methods through development of standard methods would also help ensure that all manufacturers and all professional users would have access to the best understanding of effective controls.

Furthermore, it should be noted that the opinion was also expressed that some manufacturers and some regions were more able to determine and apply the most effective methods than others, because of the lack of standard methods, thus contributing to safety inequity and supply chain inconsistency.

The view that methods for measuring exposure for (some) consumer and environmental scenarios are years behind in development and should be accelerated

The topic of when methods would be available was also explored through several questions and through comments. Themes affecting the timing of methods included the kind of decision being made, the type of MNM, and competing analysis factors that may exist for a given scenario. The timing of availability of requried methods may potentially mean that SbD approaches will need to consider limitation of MNM uses to those that can be contained or identification of control points in MNM emissions management.

With respect to the kind of decision, screening level or “hot spot” decisions were noted in comments as being adequately covered by current methods. In contrast, methods adequate for dose estimation for epidemiologic or distributed source evaluation are lacking and seem difficult to envision with current instrumentation and methods. So, methods may be adequate to identify the local extent of a spill if it is quickly identified in soil whereas identifying MNM contributions to widespread occurrence of a metal oxide in a pigment used in paints may be difficult in years following use.

The effect of type of MNM was exemplified by comparison of the 6 MNMs evaluated in the first Delphi round. As shown in Figure 8, MWCNT evaluation is consistently rated as needing more time for methods development than the metal oxides or silver. Whether this differential across MNM types is accurate or not probably depends on environmental matrix conditions. In fact a number of comments made the point that environmental analyses of MNMs face much more complex analytic challenges than chemicals due to matrix effects. Background particle interference was referred to when attributing source or novelty of the exposure to MNMs vs naturally occurring nanomaterials. Matrix interference of food, soil, dust, sediment was also raised in comments. MNM transformations through the physical and chemical processes of release from matrices, and transformations through interaction in environmental media were also mentioned. The implication of this complexity and longer anticipated lead time for methods development would need to be addressed within product development and may lead to early abandonment of some material choices in a SbD approach.

2.4.2 *Summary and Recommendations*

The primary goal of this report is to inform the ProSafe White Paper. Therefore, each of the recommendations in this section should be taken in light of the intentions of the overall ProSafe project outcomes and how they would feed into development of actions and policies to support implementation of SbD approaches for MNM uses.

2.4.2.1 What do we learn from the Task 2.4 foresight project?

The project used a Delphi forum process to develop and refine our understanding of opinion across hundreds of experts and literally dozens of combinations of MNM types, uses, and life cycle exposure points. This approach provided useful information about prevailing opinions of experts and it provided useful experience on what works to understand such a complex risk management challenge.

2.4.2.2 A broad scope makes it difficult to generate practical/useful foresight

Foresight regarding uses of MNMs for such a broad scope of materials, use types, and value chain positions is difficult to generate. Much of the difficulty lies in the fact that the knowledge of use development exists in

confidential files in competitive business interests. However, some of the difficulty also stems from the multiple possible uses for sometimes unique materials that are value added components of products. In other words, for some MNM uses, a 10% change in commodity may represent a large change in release and exposure potential if that 10% change is applied to a new sector of use with differing life cycle release points. For example, a relatively small total volume shift of a commodity used widely in composite construction materials to a new use as a similar composite in food packaging would not be a large change in annual production of the MNM for composite uses; however, it may potentially be a large increase in that MNM in new exposure pathways. In contrast, for a high value addition to small volumes of other uses (e.g., specialty composites that use a new and specifically formulated high value MNM) the appropriate metric may be the initiation of a use that is unlike any other which would be a 100% increase. Comparing the potential exposure potentials of these examples may show that the "100%" increase is in fact of a much lesser volume and lesser risk than the "10%" increase. This distinction of absolute volume vs novelty was difficult to draw out in broadly stated questions necessary in the Delphi forum.

Discussion among many experts on a broad scope for research about methods tends to result in requests for funding or attention to too many research topics. A broad scope also tends to make it difficult to differentiate between relative need for specific methods choices.

2.4.2.3 There is a trade-off between working with many expert voices and having foresight clarity

Useful foresight seems to be that which pertains to a well-defined topic through narrative and interpretation provided by a few voices. It is important to recognize that a commonly held perception among experts about what will or should happen is informative to foresight generation, but it does not in itself constitute foresight. Furthermore, the nature of the question and response format of the 5 stage Delphi forum used for the complex set of issues covered in this report will have created misperceptions and false conclusions about the meaning of terms used. These communication errors are sometimes difficult to recognize and consider in the analysis of the responses. Therefore, independent analysis of the Delphi forum results by multiple leading experts is likely to provide added value. These multiple perspectives would constitute a continuation of the Delphi forum.

2.4.2.4 About the foresight gained

The complexity of the undertaking and the difficulty in navigating the combinations of physical and analysis factors to be considered was itself a lesson regarding the complexity of making judgements about SbD for nanomaterial uses in general. The expertise disciplines, application areas, and stakeholder perspectives alone were challenging to navigate. Adding a layer of foresight regarding markets and regulatory policies on top of this complexity is a further challenge. Therefore, a lesson learned regarding foresight for SbD application to MNM uses is that general principles applied to all future nanomaterial uses at any particular SbD decision step are probably rare.

Furthermore, general statements about sufficiencies and gaps in methods or management capabilities should be taken as broad advice about avarages with a clear expectation that the exceptions will be many. For example, decisions to shift research funding proportionately to a greater emphasis on exposure through environmental pathways may follow from the expert advice about averages in the current Delphi forum. However, dramatic shifts and categorical exclusion of toxicology research would not be called for from these results.

Approaches to address complexity as new materials and new understanding emerges appears to call for a stepwise decision process, like SbD, where each step considers the context for the use and the implications of alternative material and use choices. Foresight for methods needs to support this would seem to favour understanding of exposure in step with understanding of hazard. The clear implication of many of the responses and comments in the Delphi forum was that support of SbD decision steps for future use developments may face exposure uncertainties that preclude decisions of risk.

2.4.2.5 Regarding potential implications for other ProSafe activities

WP3

The pace and value of data acquisition is clearly affected by the methods and their utility to supporting decisions. Comments made in the Delphi forum regarding the utility of the current data have stated that the data may not be useful because characterization was inadequate or because the wrong forms of MNM were tested. This opinion implies that general understanding to support risk management objectives through SbD decision making may be lacking for some MNM, and perhaps many MNM. Therefore, data acquisition will need to address the utility issues of the current data set while at the same time developing ontologies and data analysis methods that can incorporate the newer and more relevant data sets to the body of useful knowledge.

Task 2.3 attempted to navigate a complex matrix of conditions and materials and in so doing illustrated the complexity of the data structures that may also be needed if they are to be applied across all MNM types and

uses. Given the complexity of forms and exposure contexts for MNM risk management across life cycles and uses, it is likely that some of the new functionality, exposure, and toxicity measurement methods will need to be able to collect and relate data for single uses that cross multiple released MNM forms and environmental transformations leading to different use conditions and exposure contexts. These scales and kinds of data collection and collation approaches speak to a need for “high throughput“ as well as for more complex relational structures than may be used for standard chemical risk management.

International (WP1, 5)

The Deplhi forum included participation by over 250 experts from Europe and North America, including extended discussions of the Core Group (including experts currently in Europe, USA, Canada), ProSafe partners, and through two separate expert meetings at the annual international meeting of the Society for Risk Analysis. Several discussion themes were explored for diffferences between regions, and generally similar patterns of response were seen for some themes. The similarities and differences in perception of methods needs and priorities between North America and Europe should be considered in developing policies that involve international trade.

In particular there was agreement in patterns of responses regarding that:

- Methods were judged as available for supporting risk management for occupational exposures (if implemented consistently and appropriately)
- Methods were judged as lacking to support risk management for end of life/environmental release and
- Methods may not be available for some MNM for greater than 10 years.

Futhermore, no differences in patterns were seen for the specific methods types in Figures 26-31.

Outreach also included multiple stakeholder groups. The response rates for NGO were unfortunately low, however, comparison of industry, government, and academia responses provided similar agreements on these issues.

Differences were also seen between regions. Increases in use for construction and electronics were predicted in Europe but not North America for some MNMs (see Figures 39 and 40 below for example from nano Silicon Dioxide in Delphi Round 1). The low number of respondents may have contributed to this difference; however, it may also be that differences in awareness or differences in regulatory criteria affected the response. In either case, a risk communication need may exist to come to a common level of understanding on products developed for these sectors. It seems likely that the suppliers and markets for these use types would not differ between North America and Europe.

Task force

The ProSafe Task Force was developed and implemented in parallel to the Task 2.4 foresight process. Similar to Task 2.4, the Task Force used a process to elicit detailed responses from experts. The process differed in the focus and complexity of the engagement of the experts. The charge questions, methods reviewed, and MNM focus of the Task Force differed in some specific details. These differences may be informative on their own, and in fact the results are likely to be constructively inter-related as the differing level of integration and wider participation of Task 2.4 is filled in by detailed reports of individual experts of the Task Force. Results from both tasks will be reviewed by ProSafe partners at the same time, and so it is hoped that the findings of one can serve to illuminate or expand on the other. At the time of this drafting, the results of the Task Force were not available. Further evaluation of the Task 2.4 foresight may be added following review of the draft Task Force report.

2.4.3 *Recommendations for further work*

2.4.3.1 Other analyses of the data set

This report evaluated selected responses for selected questions and used the responses and comments to explore selected discussion themes. These selections were made through decisions made by the authors to develop a narrative in support of the needs of the ProSafe White Paper. Specific comparisons among stakeholder groups on these issues were, again selectively, chosen to aid in the narrative description of the discussion themes. Other discussion themes and comparisons of groupings within the responses are possible and should be explored. In particular, the Delphi provided information about stakeholder type, region, expertise, and focus areas for individuals (see Table 2, Table 3, Figure 18 and Figure 19) that may be informative for comparison of responses.

2.4.3.2 Sector/material specific evaluations of future products/uses

The scope for this task was too general to be useful for specific methods or for understanding trends in specific material uses. One commenter made the point that within the classification of SiO_2 there were a wide

range of forms and uses that ranged from property enhancing fillers for polymers to specific catalysts for chemical synthesis. These two categories alone for one MNM may have dramatically different innovation pipelines, measurement requirements, and toxicity profiles. Furthermore, the experts for each use type may be in quite different fields (e.g., coating/pigment development vs chemical engineering) with specific trade associations and regulatory oversight. For these reasons, a similar style discussion forum with a much more focused material forms or use types should be developed for key MNM sectors.

The breadth of the scope of Task 2.3 also made it difficult to differentiate foresight for future uses. Responses for "what are the future uses" of each of the MNM types in the first round of the Delphi forum gave histograms that essentially said all uses may increase and all exposures would increase (Figure 38 and Figure 39).

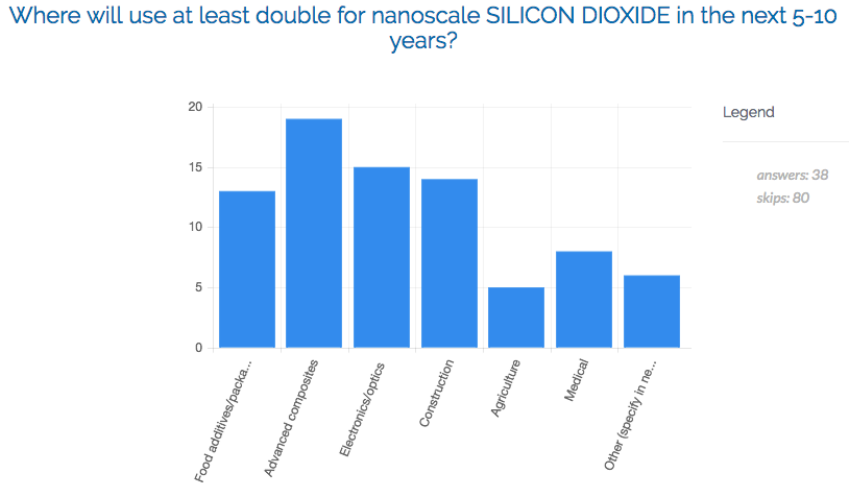


Figure 38 Where will use at least double for nanoscale Silicon Dioxide in the next 5-10 years?

ID#1539

Where will exposure to nanoscale SILICON DIOXIDE change (per individual user or exposed population) in the next 5-10 years?

COMMENT

	Decrease	Same	Increase	Total
Food additives/packaging	5.56% 2	47.22% 17	47.22% 17	36
Advanced composites	0.00% 0	41.18% 14	58.82% 20	34
Electronics/optics	2.78% 1	55.56% 20	41.67% 15	36
Construction	0.00% 0	41.18% 14	58.82% 20	34
Agriculture	2.86% 1	74.29% 26	22.86% 8	35
Medical	2.94% 1	73.53% 25	23.53% 8	34

Figure 39 Where will exposure to nanoscale Silicon Dioxide change in the next 5-10 years?

It may be possible to further differentiate the responses across expertise levels as capture in the Delphi forum to refine the data. As seen in the differentiation of responses in Figure 40, Figure 41 and Figure 42, the responses of differing sectors and regions may be informative with regard to further discussions that are needed. However, the numbers of responses (and the limitations of the questions that were asked) make it difficult to elaborate further. Therefore, further Delphi style discussions are recommended with more specific MNM form focus for these questions as well.

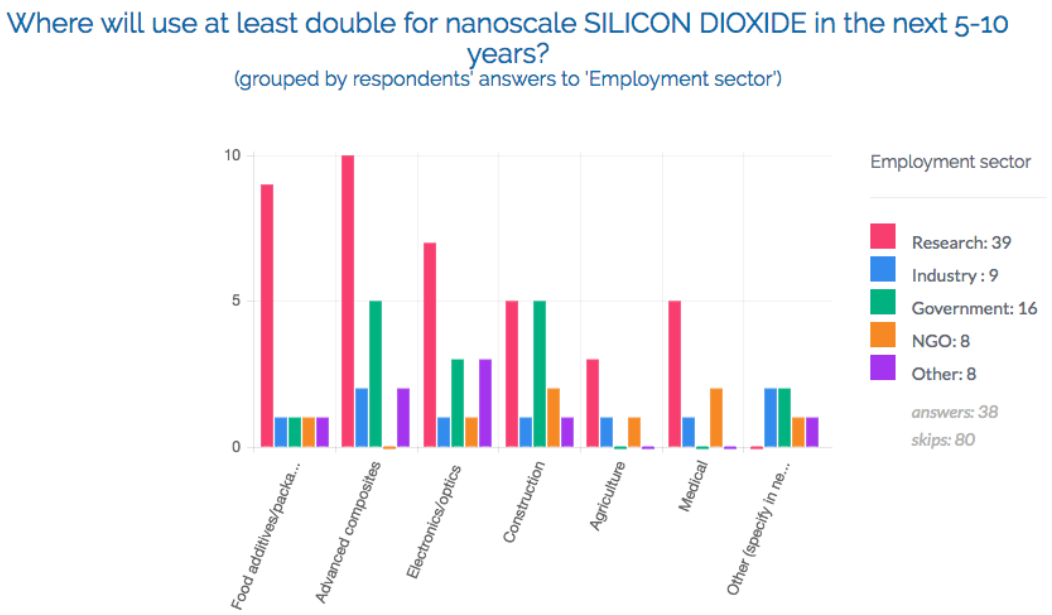


Figure 40 Where will use at least double for nanoscale Silicon Dioxide in the next 5-10 years? (grouped by employment sector)

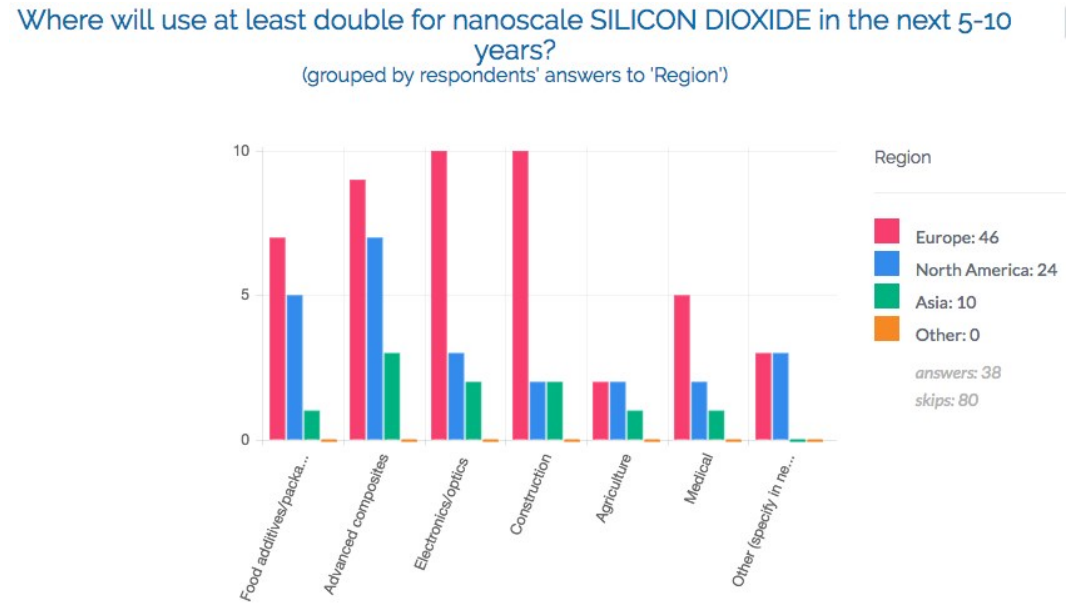


Figure 41 Where will use at least double for nanoscale Silicon Dioxide in the next 5-10 years (grouped by region)

ID#1575 Where is it likely that biologically relevant exposure may occur to nanoscale SILICON DIOXIDE as it was manufactured. COMMENT

Life cycle / Sector of use	Manufacture	Professional use	Consumer use	End of life/environmental	Check all	Not applicable	Total
Food additives/packaging	15.25% 18	6.78% 8	16.95% 20	7.63% 9	3.39% 4	3.39% 4	118
Construction	17.80% 21	15.25% 18	3.39% 4	10.17% 12	2.54% 3	4.24% 5	118
Agriculture	10.17% 12	6.78% 8	3.39% 4	9.32% 11	1.69% 2	10.17% 12	118
Advanced composites	15.25% 18	9.32% 11	1.69% 2	5.93% 7	1.69% 2	2.54% 3	118
Electronics/optics	16.95% 20	5.93% 7	0.00% 0	8.47% 10	1.69% 2	3.39% 4	118
Medical	12.71% 15	8.47% 10	11.02% 13	5.08% 6	1.69% 2	5.93% 7	118

Figure 42 Where is likely that biologically relevant exposure may occur to nanoscale Silicon Dioxide as it was manufactured?

2.4.3.3 Specification of scope through Standards work

As stated multiple times, the complexity (e.g., of the MNM types, uses, regulatory oversight, and disciplines, and stakeholder groups of experts) of the scope for Task 2.3 makes interpretation of results difficult. One of the lessons learned through developing the questions and considering the responses for the task was that the specification of topic is necessary prior to a discussion of foresight and methods needs. For example, a question of methods needs for SbD development of a new use of nanoscale SiO2 will differ by MNM form, life cycle stage, use, and regulatory category. The opinions of stakeholders will also differ. Therefore, framing a question to support policy about specific methods is not possible at some aggregate level of general policy making. For nanomaterials, the level of aggregation may be as simple as a single MNM with multiple uses, or a grouping of MNM types with similar surface characteristics, or a grouping of functionalities. Instead of developing general questions to bridge these differences, it may be necessary to create specifications that can then be used to generate finer grained data about methods needs and markets. The finer grained data can then be aggregated into overall policy needs. Making such specifications is the province of standards development organizations (SDO).

Therefore, in order to be useful to SbD decision making, discussion of foresight may need to be carried out through scope narrowed to a material type or use or life cycle stage and a similarly structured parsing of the other specifications. Such a structured discussion is also needed so that issues of one material, use, or regulatory decision context are not inappropriately taken as relevant to another. This kind of structure through specification could be further formalized in standards processes such as Technical Reports and Standard Methods also developed through standards development organizations. Several groups are attempting to address this kind of specificity in methods development/standardization in regions and internationally. Including an awareness of foresight needs for SbD in the standards process would be a valuable addition to these efforts to facilitate safe innovation.

3 Deviations from the work plan

The scope of the work plan included improving understanding of what MNM uses would be coming to market in the near future and whether analytic methods, existing or in development, would be available in time to support SbD approaches for those new uses. It turned out to be easier to develop information about methods than it was to develop information about new MNM uses. Finding information about uses for MNM is difficult for a number of reasons. In the implementation of the Delphi forum the project was structured to avoid one of them, which was reluctance of innovators to reveal proprietary information. It was hoped that sufficient responses would be received to then allow parsing of information to specific MNMs, uses, and regions. However, the forum was not successful in generating enough responses to provide information about new uses to support any conclusions for foresight. Therefore, the application of the foresight must be considered to be general in nature with respect to the MNM types that will be the most commonly developed in the near future.

4 Performance of the partners

Partners were asked to provide feedback during development of the Delphi forum and to participate in recruitment of participants. In all cases the performance was sufficient, and in some cases the performance was outstanding. For example, several partners participated in the Core Group and provided extensive input to the design of the questions used in the Delphi forum. Other partners provided their contact lists and sent invitation emails out to improve chances of the invitations being read and acted upon. The support provided by the project web page was not as useful or responsive as desired, partly because of choices of web page structure that were difficult to adapt to the this tasks of reporting and outreach for graphics and data structures that the Delphi forum generated.

5 Appendices

Appendix 1 ProSafe Core Group Members

1. Alan Reilly (invited/accepted, did not participate after first 2 calls of the group): Adjunct Professor, Institute of Food and Health, University College Dublin and former CEO of Food Safety Authority of Ireland, Dublin, Ireland.
2. Christian Beaudrie, M.Eng., Ph.D.: Compass Resource Management Ltd., Vancouver, BC, Canada
3. Christian Micheletti, Ph.D.: PROSAFE PARTNER, Senior Researcher, EcamRicert – ECSIN, Rovigo, Italy
4. David Carlander, Ph.D.; PROSAFE PARTNER, Director General, Nanotechnology Industries Association, Brussels, Belgium
5. Hugues Crutzen: PROSAFE PARTNER, European Commission, Joint Research Centre, Directorate F – Consumer Product Safety – Via E. Fermi 2749, Ispra, VA, Italy
6. James Mittra, Ph.D.: Deputy Director of the Innogen Institute, Science, Technology and Innovation Studies (STIS), University of Edinburgh, Scotland
7. Rob Aitken, Ph.D.: CEO, Institute of Occupational Medicine (IOM), Edinburgh, Scotland
8. Shaun Clancy, Ph.D.: Director and Regional Head, Product Regulatory Services, Evonik Corporation, Parsippany, NJ, USA.
9. Steffi Friedrichs, Ph.D.: Director General, Nanotechnology Industries Association, Brussels, Belgium (through 2015) and Policy Analyst, Organization for Economic Co-operation and Development, Paris, France (2016-present)
10. Treye Thomas, Ph.D.: Office of Hazard Identification and Reduction, Consumer Product Safety Commission, Bethesda MD, USA, and Co-chair of the Nanotechnology Environmental Health Implications Working Group of the National Science and Technology Council, Executive Office of the President, Washington DC, USA.

Appendix 2 ProSafe Delphi Round 1 Question set

Appendix 3 ProSafe Delphi Round 1 SciPinion Default Results Graphics

Funded by
The European Union

Appendix 4 ProSafe Delphi Round 1 Flyer

ProSafe

Promoting the Implementation of Safe by Design

Is Risk Management On Pace with Innovation for Nanomaterial Uses?

Join other leading experts in an anonymous online Delphi Forum on what nanomaterials are in commerce and whether they are being managed properly.

The Delphi forum is online **NOW**, take part and gain access to data and analysis in real time!

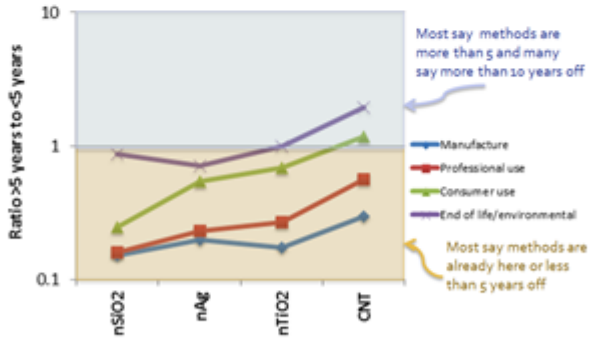
Have **YOUR** opinion added to the results on this flyer and more!

What do we want your opinion on?

- What uses will increase the most for the following nanomaterials; **titanium dioxide, silicon dioxide, cerium oxide, barium sulphate, silver, and carbon nanotubes?**
- What is missing (if anything) in our risk assessment abilities?
- When we will be able to fill in what is missing?

In the graphic below you will find the current results from the Delphi Forum on respondent's opinions on whether exposure methods are here now or are more than 5 years out. Overleaf you will find heat-map comparisons of results on agreement and what facilitation in Safe by Design is needed. Do you agree or disagree with these results, have your opinion heard by joining the discussion; instructions on how to get access to the Delphi Forum are at the bottom of this page.

When Will Exposure Methods be Adequate to to Support Risk Management?



- To join the discussion please follow this link https://scipinion.com/
- In the access code box for "ProSafe Delphi Poll" insert "Prosafe2015"
- Click 'take survey'
- Enter your email address to enter the poll

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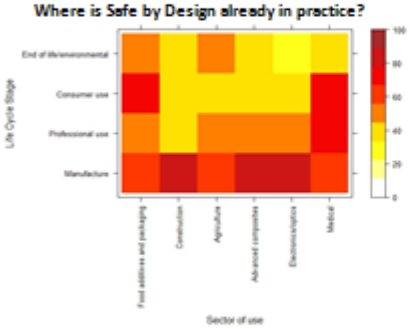
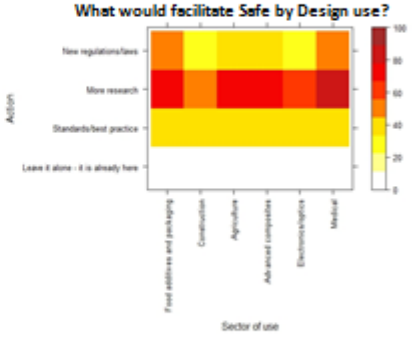
Where do we tend to agree?

Where is Safe by Design already in practice?

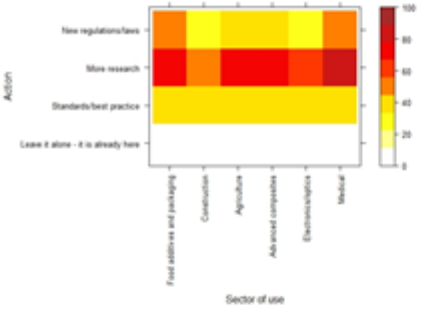


What would facilitate Safe by Design use?

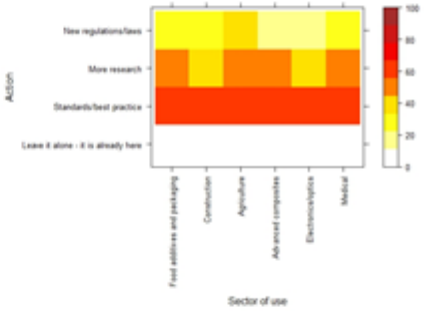


What would facilitate Safe by Design? – Perspectives of stakeholders

From research perspective

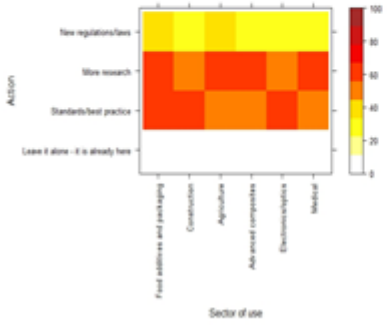


From safety expert perspective

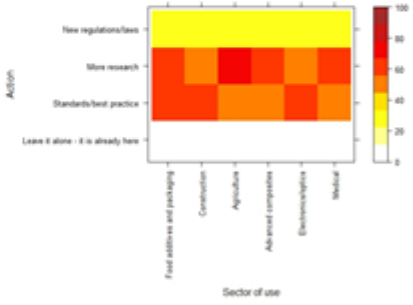


What would facilitate Safe by Design? – Showing areas of agreement

From European perspective



From North American perspective



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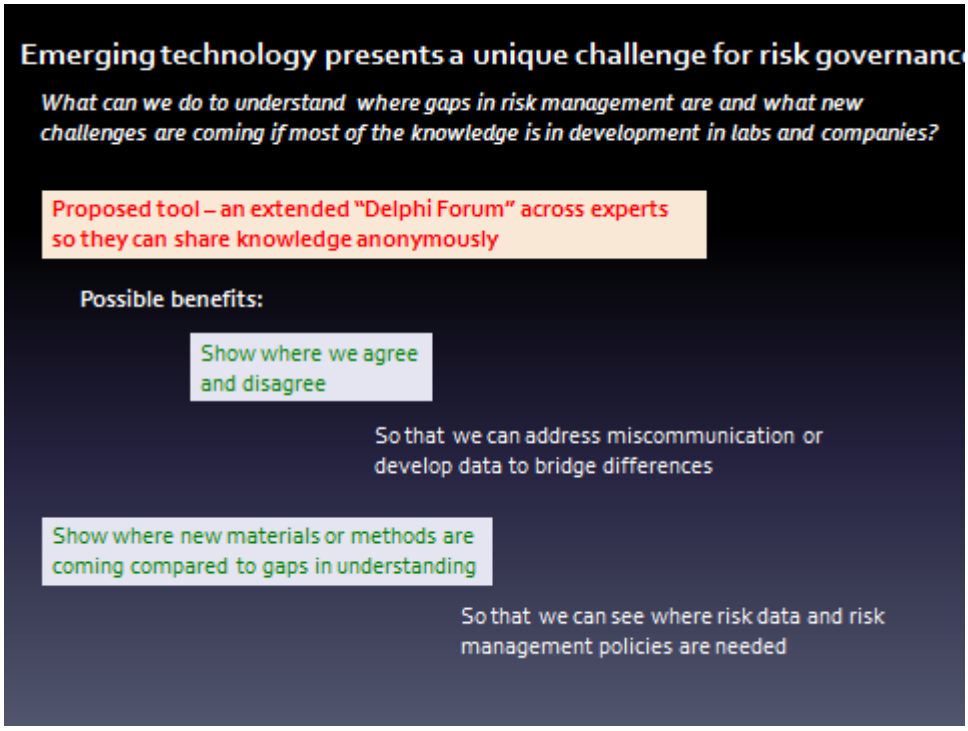

Prosafe Foresight Delphi process

ProSafe

Promoting the Implementation of Safe by Design

A Delphi process is structured communication to clarify consensus or divergence among anonymously participating experts

- *Generally exploring: "is risk assessment/management development on pace with development of MNM uses?"*

Expert invitation list worldwide, with 3 interaction points

1. Poll 1 and discussion forum beginning Oct 2015
2. Expert roundtable 2015 SRA Annual Meeting
   Tuesday December 8, 10:30-Noon
3. Poll 2 (revised based on panel review and discussion forum) March 2016

To participate in the Delphi polls send email to Prosafe.project@iom-world.org

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Topics covered by the 1st Delphi poll

Aiming for just enough specificity to facilitate discussion of RA/RM readiness across nanomaterials and exposure scenarios

Manufactured NanoMaterial types

- ❑ Titanium dioxide
- ❑ Silicon dioxide
- ❑ Cerium oxide
- ❑ Barium Sulphate
- ❑ Silver
- ❑ Carbon nanotubes

Use types

- ❑ Food (additives including from packaging)
- ❑ Construction
- ❑ Agriculture
- ❑ Advanced composites
- ❑ Electronics/optics (including solar)
- ❑ Medical products

Life cycle stages

- ❑ Manufacturing
- ❑ Professional use
- ❑ Consumer use
- ❑ End of life/environmental

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Questions about expertise

4) Level of training and experience in the following areas.

	None	1-4 years	5-10 years	>10 years
Material science/chemistry	○	○	○	○
Toxicology	○			
Exposure science	○			
Risk Assessment	○			
Nanomaterial applications	○			
Product stewardship	○			
Public health	○			
Finance or insurance	○			
Other	○			

1) Region

- ○ Europe
- ○ North America
- ○ Asia

2) Emplo

1) Knowledge of use or risk management for Manufactured Nanomaterials (MNMs) in these material categories.

MNM	None	Working knowledge	Specialist
Titanium dioxide	○	○	○
Silicon dioxide	○	○	○
Cerium oxide	○	○	○
Barium sulphate	○	○	○
Silver	○	○	○
Carbon nanotubes	○	○	○

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Responses sought for all MNM's

Promoting the Implementation of Safe by Design

2) Where is Safe by Design already in practice for new use development for MNMs?

Life Cycle Stage / Sector of Use	Considering manufacturing	Considering professional use	Considering consumer use	Considering end of life / environmental	Check all
Food additives/packaging					
Construction					
Agriculture					
Advanced composites					
Electronics/optics					
Medical					

3) What kinds of actions would be most effective to improve our ability to adopt more widespread Safe by Design practices for uses of MNMs?

Sector of use	Leave it alone - it is already here	Standards/best practice	More research	New regulations/laws	Other
Food additives and packaging					
Construction					
Agriculture					
Advanced composites					
Electronics/optics					
Medical					

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Responses sought for each MNM in turn

Promoting the Implementation of Safe by Design

Titanium Dioxide | Silicon Dioxide | Cerium Oxide | Barium Sulphate | Silver | Carbon Nanotubes

1) For each sector of use, which life cycle stage has the highest exposure potential for manufactured nanoscale TITANIUM DIOXIDE.

Life cycle/ Sector of use	Manufacture	Professional use	Consumer use	End of life / environmental	Not applicable
Food additives/packaging					
Construction					
Agriculture					
Advanced composites					
Electronics / optics					
Medical					

2) Where is it likely that biologically relevant exposure may occur to nanoscale TITANIUM DIOXIDE as it was manufactured.

Life cycle / Sector of use	Manufacture	Professional use	Consumer use	End of life/environmental	Check all	Not applicable
Food additives/packaging						
Construction						
Agriculture						
Advanced composites						
Electronics/optics						
Medical						

3) Check the boxes to indicate where you are confident that risk management for nanoscale TITANIUM DIOXIDE can be supported with current methods.

Life Cycle Stage / Sector of Use	Manufacture	Professional use	Consumer use	End of life / environmental	Check all as confident	Not applicable
Food additives/packaging						
Construction						
Agriculture						
Advanced composites						
Electronics/optics						
Medical						

4) What is the biggest gap in methods to support risk management for nanoscale TITANIUM DIOXIDE?

- Exposure/dose characterization
- Toxicity characterization
- Standard methods
- Differs too much to say
- No gaps
- Other (specify in next question)

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Sorting responses

As responses rise, we can sort across expert views on

- What uses will increase the most for these nanomaterials
- What is missing (if anything) in our risk assessment abilities
- When we will be able to fill in what is missing?

Comparisons of the above and more according to

- Region
- Stakeholder
- Experience level
- Nanomaterial type
- Use category
- Life cycle stage

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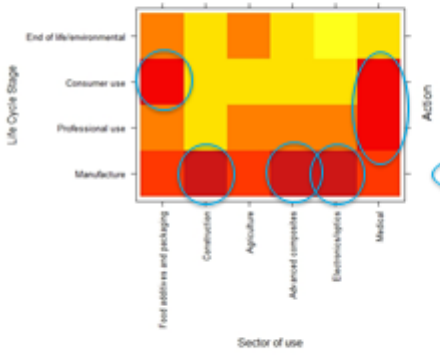
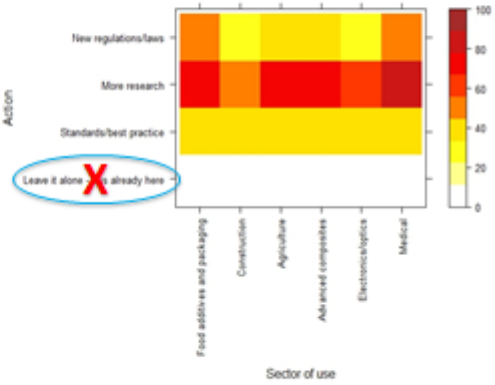
Where do we tend to agree?

Where is Safe by Design already in practice?



What would facilitate Safe by Design use?



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Sorting responses – perspectives of stakeholders

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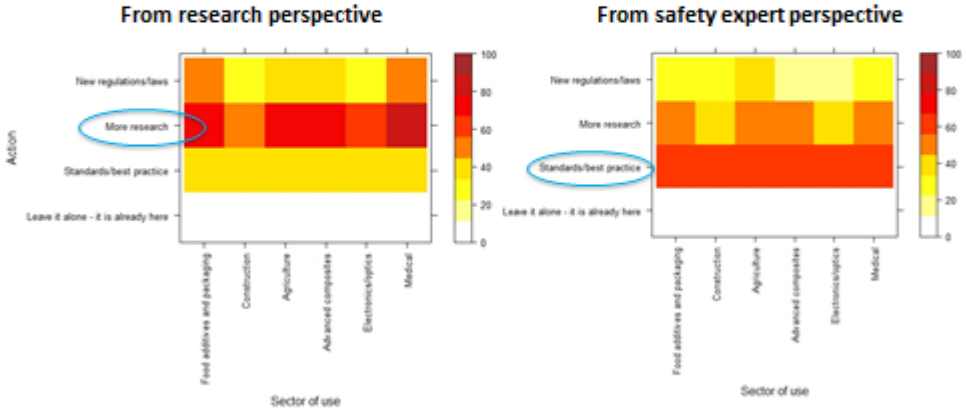
What would facilitate Safe by Design?



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Sorting responses – showing areas of agreement

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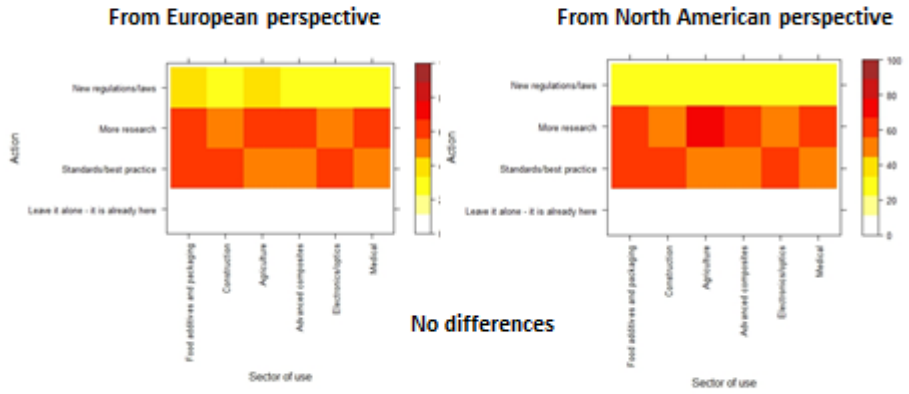
What would facilitate Safe by Design?



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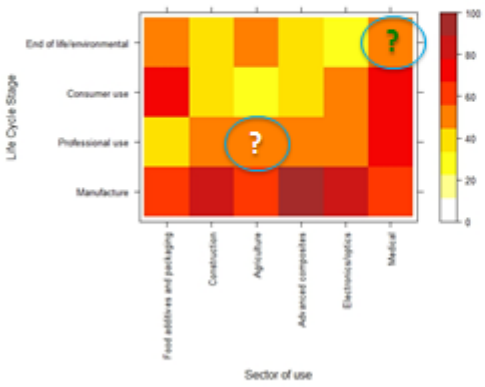
Sorting responses – need followup in next round of the Delphi?

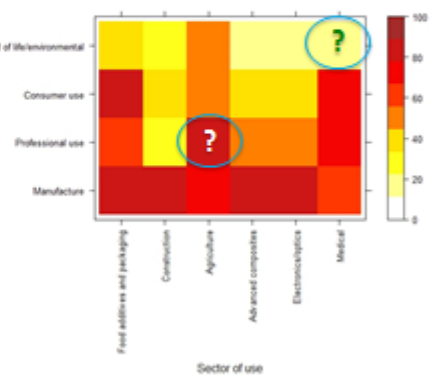
Promoting the Implementation of Safe by Design

Where is Safe by Design already in practice?

From European perspective



From North American perspective



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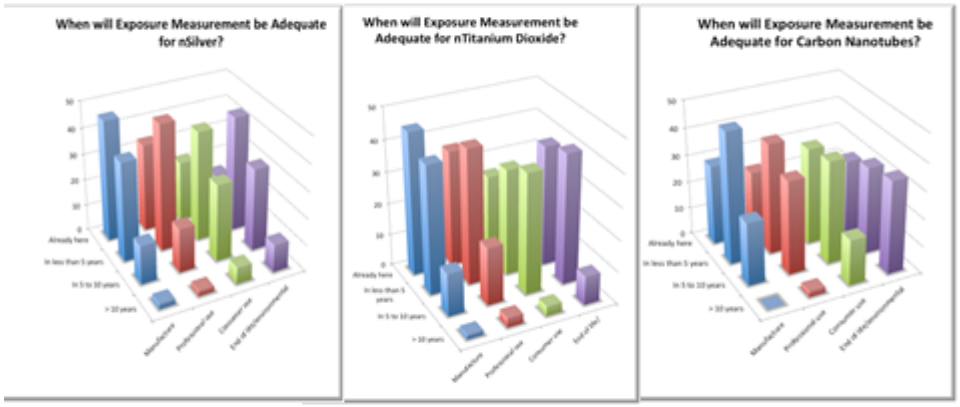
Where are we with methods development across MNMs compared to decision need?

Promoting the Implementation of Safe by Design

Are methods here now or more than 5 years out. Across life cycle stages



Do we need to be emphasizing non-occupational exposure methods development?

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More comparisons in real time on the forum site.

Please join the forum! Stimulate agreement and clarify disagreement.

- www.scipinion.com
- Create a login and join the Prosafe Delphi Poll
- Participant code is **Prosafe2015**

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Thank you

Richard Canady
Martie van Tongeren
Alice Davis
Carla Alexander

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Prosafe Foresight

Is risk management on pace with innovation?

Delphi exercise and white paper

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Emerging technology presents a unique challenge for risk governance

What can we do to understand where gaps in risk management are and what new challenges are coming if most of the knowledge is in development in labs and companies?

Proposed tool – an extended "Delphi Forum" across experts so they can share knowledge anonymously

Possible benefits:

Show where we agree and disagree

So that we can address miscommunication or develop data to bridge differences

Show where new materials or methods are coming compared to gaps in understanding

So that we can see where risk data and risk management policies are needed

Prosafe Foresight Delphi process

A Delphi process is structured communication to clarify consensus or divergence among anonymously participating experts

Expert invitation list worldwide, with 3 interaction points

1. Poll 1 and discussion forum happening now (please join in)
2. Expert roundtable review 2015 SRA Annual Meeting

   Today December 8, 10:30-Noon
3. Poll 2 (revised based on review and discussion forum) March 2016

To participate in the Delphi forum send email to Prosafe.project@iom-world.org

Or go to www.scipinion.com and use the code "Prosafe2015" in the Prosafe Delphi Poll

We need your participation!!

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The forum gathers information on expertise to help sort through areas of agreement and disagreement

4) Level of training and experience in the following areas.

	None	1-4 years	5-10 years	>10 years
Material science/chemistry				
Toxicology				
Exposure science				
Risk Assessment				
Nanomaterial applications				
Product stewardship				
Public health				
Finance or insurance				
Other				

1) Region

- Europe
- North America
- Asia

1) Knowledge of use or risk management for Manufactured Nanomaterials (MNMs) in these material categories.

MNM	None	Working knowledge	Specialist
Titanium dioxide			
Silicon dioxide			
Cerium oxide			
Barium sulphate			
Silver			
Carbon nanotubes			

2) Emplo

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It gathers opinion for each MNM in turn (do as many or few MNM as you want)

Then we can sort responses to see where there is agreement or disagreement

As responses rise, we can sort across expert views on

- What uses will increase the most for these nanomaterials
- What is missing (if anything) in our risk assessment abilities
- When we will be able to fill in what is missing?

Comparisons of the above and more according to

- Region
- Stakeholder
- Experience level
- Nanomaterial type
- Use category
- Life cycle stage

And you can see graphics of the responses online as the forum proceeds.

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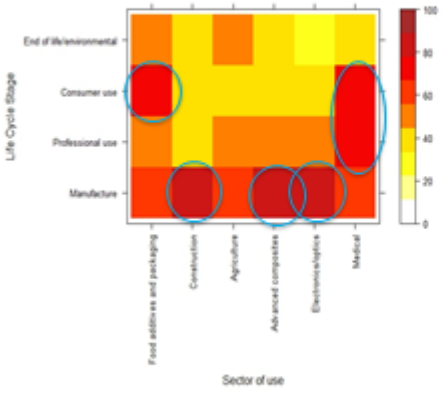
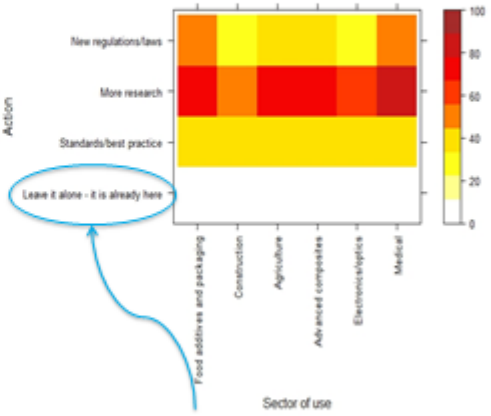
Initial views on the responses: Where do we tend to agree?

Where is Safe by Design already in practice?



If you look across use types and life cycle stages, there are some where most say we are already using "safe by design" practices.

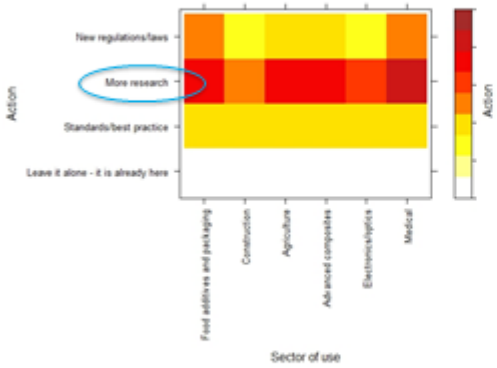
What would facilitate Safe by Design use?



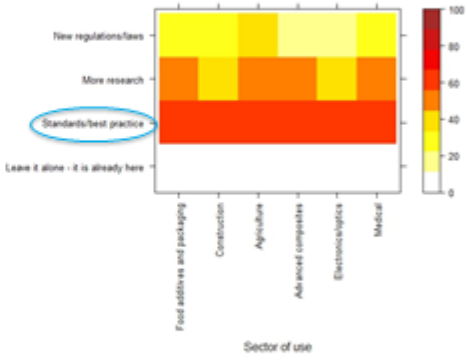
However, if you ask what more needs to be done, almost no one says "its already here" for all life cycle stages.

What action would facilitate Safe by Design?

From research perspective



From safety expert perspective

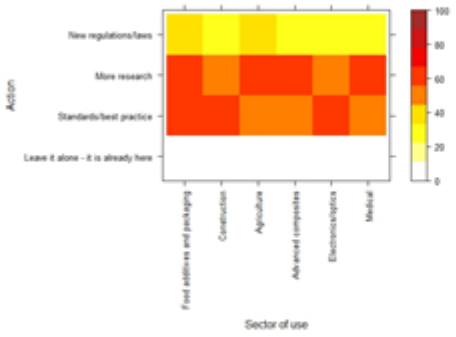


Researchers tend to say we need research to facilitate Safe by Design, and safety experts tend to say we need standard methods.

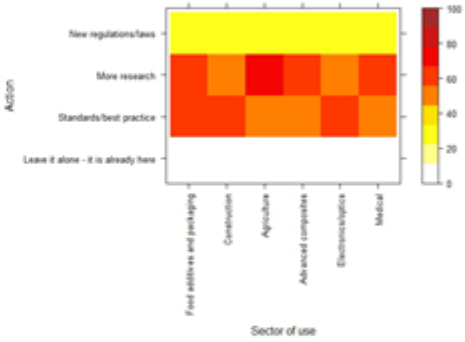
How do we factor these different views into risk governance?

What action would facilitate Safe by Design?

From European perspective



From North American perspective

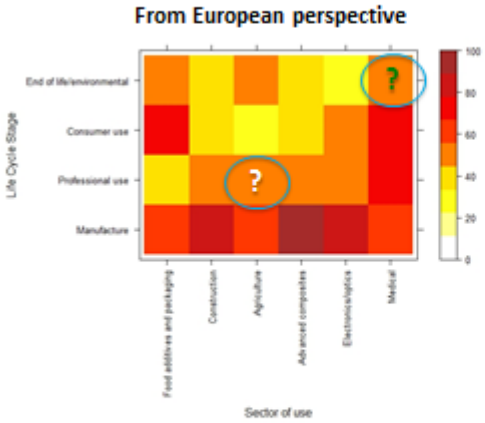


No difference seen acrossthe Atlantic.

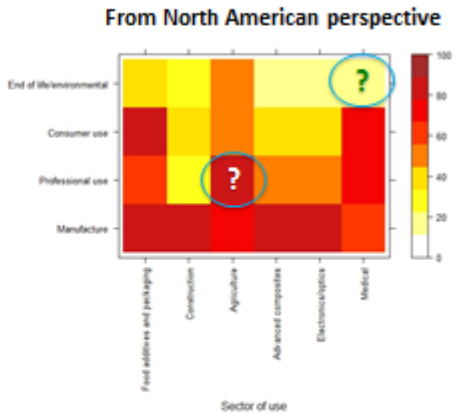
Not enough participation in the forum yet to see if there are differences across other stakeholder perspectives

Where is Safe by Design already in practice?

From European perspective



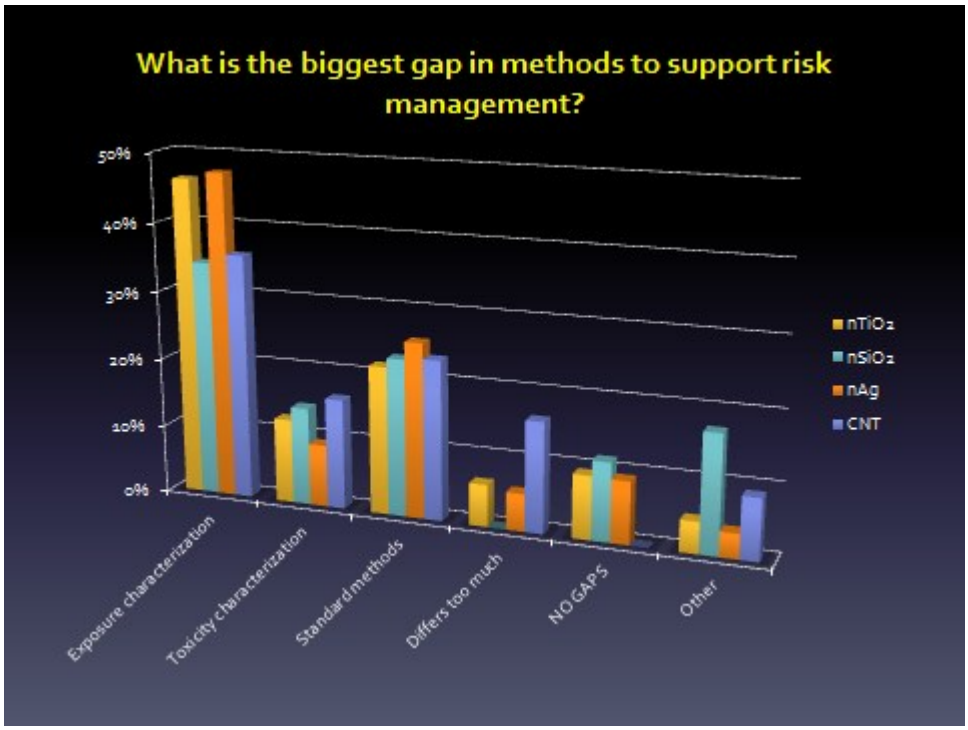
From North American perspective

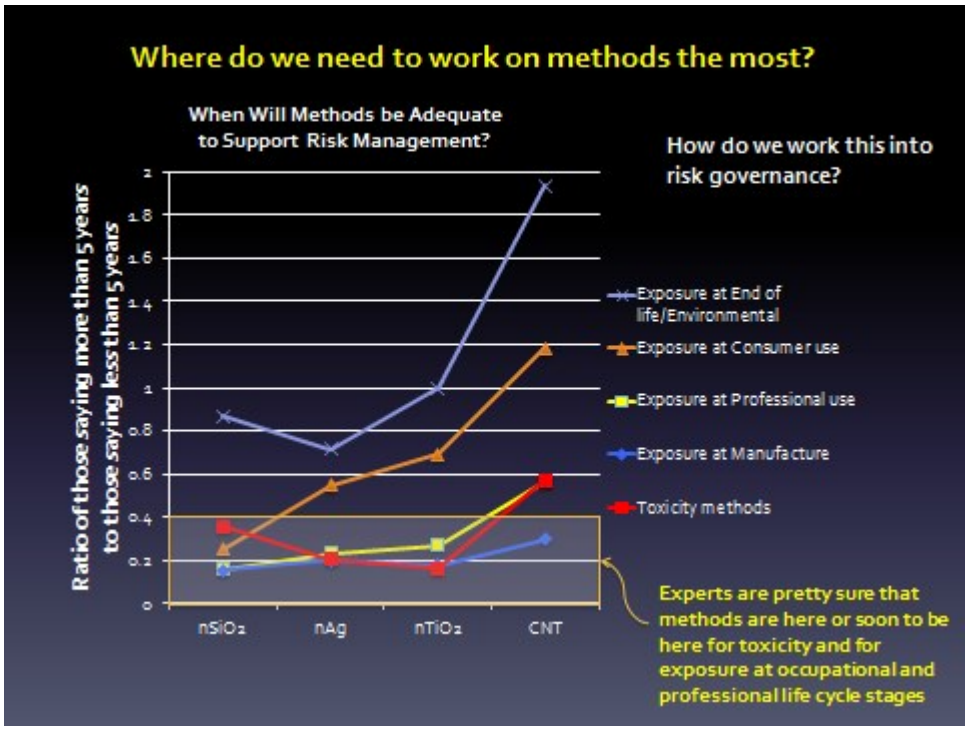


However, there may be differences when you look at specific use types and life cycle stagesfor safe by design implementation.

This needs to be followed up in the next round of the Delphi.

How do we work this into risk governance?

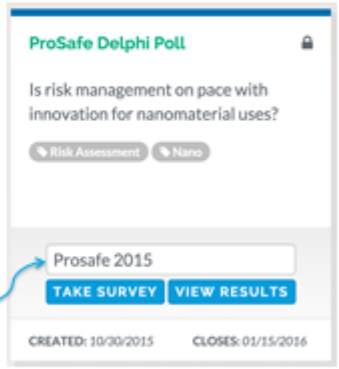

What is the biggest gap in methods to support risk management?
50%
40%
30%
20%
10%
0%
nTiO2
nSiO2
nAg
CNT
Exposure characterization
Toxicity characterization
Standard methods
Differs too much
NO GAPS
Other


Where do we need to work on methods the most?
When Will Methods be Adequate to Support Risk Management?
Ratio of those saying more than 5 years to those saying less than 5 years
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
nSiO2
nAg
nTiO2
CNT
How do we work this into risk governance?
Exposure at End of life/Environmental
Exposure at Consumer use
Exposure at Professional use
Exposure at Manufacture
Toxicity methods
Experts are pretty sure that methods are here or soon to be here for toxicity and for exposure at occupational and professional life cycle stages

More comparisons in real time on the forum site.

Please join the forum! Stimulate agreement and clarify disagreement.

- www.scipinion.com
- Create a login and join the Prosafe Delphi Poll
- Participant code is **Prosafe2015**



Richard Canady, Alice Davis, Martie Van Tongeren, Carla Alexander
Institute of Occupational Medicine, Edinburgh Scotland

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Appendix 7 ProSafe Delphi Round 2 Question set

Appendix 8 ProSafe Delphi Round 2 SciPinion Default Results Graphics