Coordination and Collaboration in European Research towards Healthy and Safe Nanomaterials

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Abstract. Nanotechnology is becoming part of our daily life in a wide range of products such as computers, bicycles, sunscreens or nanomedicines. While these applications already become reality, considerable work awaits scientists, engineers, and policy makers, who want such nanotechnological products to yield a maximum of benefit at a minimum of social, environmental, economic and (occupational) health cost. Considerable efforts for coordination and collaboration in research are needed if one wants to reach these goals in a reasonable time frame and an affordable price tag. This is recognized in Europe by the European Commission which funds not only research projects but also supports the coordination of research efforts. One of these coordination efforts is NanoImpactNet, a researcher-operated network, which started in 2008 promote scientific cross-talk across all disciplines on the health and environmental impact of nanomaterials. Stakeholders contribute to these activities, notably the definition of research and knowledge needs. Initial discussions in this domain focused on finding an agreement on common metrics, and which elements are needed for standardized approaches for hazard and exposure identification. There are many nanomaterial properties that may play a role. Hence, to gain the time needed to study this complex matter full of uncertainties, researchers and stakeholders unanimously called for simple, easy and fast risk assessment tools that can support decision making in this rapidly moving and growing domain. Today, several projects are starting or already running that will develop such assessment tools. At the same time, other projects investigate in depth which factors and material properties can lead to unwanted toxicity or exposure, what mechanisms are involved and how such responses can be predicted and modelled. A vision for the future is that once these factors, properties and mechanisms are understood, they can and will be accounted for in the development of new products and production processes following the idea of “Safety by Design”. The promise of all these efforts is a future with nanomaterials where most of their risks are recognized and addressed before they even reach the market.

1. Introduction: Nanoparticles are reality in today’s industry
Nanomaterials have structures in the nanoscale, i.e. below 100 nm [1]. The physico-chemical properties of such materials often are different from the same, but larger structured materials. Prominent examples are altered interactions with light such as invisibility or photocatalytic effects, different conductivity or increased chemical reactivity due to increased surface and altered material structure and configuration [2].

These changing properties of materials in the nanoscale make them interesting for numerous kinds of applications and products. Research in the field of nanotechnology is developing fast and has
generated already a considerable number of novel manufactured nanomaterials (MNM) and related products, as evidenced by the large number of research publications and patents filed. Industries already started with the manufacturing of products and goods that are based on these nanotechnological accomplishments. For example, a recent representative survey [3] in Switzerland showed that about 0.6% of all companies already handle, use or produce nanoparticles (MNM that are in three dimensions smaller than 100 nm). However, many of these companies still seemed to be in an early phase of production, which is characterized by manual handling steps and heavy reliance on personal protective equipment, as also evidenced in a more detailed, targeted study among the same type of companies [4].

The presence of novel physico-chemical properties makes it plausible that these materials will show interactions with biological systems and behavior in the environment that are different from larger-structured materials composed of the same substances. To what degree this will manifest in real effects is something that needs to be evaluated and that is subject to research programmes worldwide. Such a risk assessment needs information about material characteristics, potential exposures and hazards. This information can then be used to develop strategies for the management and control of the associated risks. Seen the multitude of aspects that need to be studied, it makes sense to address these issues in a multidisciplinary and well coordinated approach. Otherwise, valuable time towards safe nanoproducts would be lost to prevent human and environmental harm and loss of investments by governments, industry and the financial sector.

2. The need for exposure assessment

Information on potential human exposure and liberation into the environment is currently being generated and many aspects need to and will be further studied. To evaluate the human health risks, one needs to know the number of exposed people, the type and quantity of exposure and the associated health effects. For environmental risk assessment the quantities of permanently or accidentally released nanoparticles need to be known.

An ongoing study sponsored by the European Commission’s 7th Framework Programme (NanEx - Development of Exposure Scenarios for Manufactured Nanomaterials, project number 247794) collects and reviews available exposure information, evaluates the applicability of existing models for occupational and consumer exposure assessment and for environmental release from these scenarios, and carries out a small number of specific case illustrations and gap analyses of the available knowledge and data.

The project already identified challenges and roadblocks towards the creation of exposure scenarios. Notably, exposure information available in scientific literature seems insufficient to create specific exposure scenarios, and the currently published literature focuses mostly on small, laboratory scale manufacturing processes, even though the majority of applications are in the use of these materials [3] with only few companies producing relatively large quantities of MNM. The case illustrations of the NanEx study revealed that, if companies have direct access to workplaces and consumer product information, there are relatively few gaps in the data needed to generate exposure scenarios (even though finding a coherent and consistent approach to build them is a challenge even for experts in exposure assessment).

Exposure to nanoparticles is special compared to “normal” chemical exposure in that it cannot be described by one single number such as an airborne concentration. Instead, in addition to the information about the material itself, size distribution, mass and probably also surface area, particle number, morphology and in some cases even more metrics are needed to sufficiently describe the exposure (Figure 1).

This information alone, however, is not sufficiently informative, because the approach how this information was generated also needs to be known. Notably the involved type of activities, the processes, the context, the sampling strategy and probably more information is needed. This is information that can easily be collected during a measurement campaign. However, to compare
exposures and to allow subsequent pooling of data for meta-analyses, common metrics and a standardized approach to describe this secondary information are needed.

### Metrics
- Size distribution
- Mass
- Surface area
- Particle number
- Morphology

(and probably more)

### Approach
- Activities
- Processes
- Context (frequency, duration, room size, ventilation, ...)
- Sampling strategy (background, sampling location, data treatment...)

(and probably more)

**Figure 1.** Key metrics and information about the approach to obtain the data that are needed for a good comparison of exposure data and for pooling data for meta-studies (conclusions of the FP7 NanEx-study).

Reports are expected to be published in 2011 that will provide a detailed description of the findings of the NanEx study, notably the case studies, consumer and occupational exposure scenarios, the inclusion of environmental aspects and the integration and gap analysis.

### 3. Hazards of nanomaterials and what to learn from ambient air pollution
Nanomaterials have new properties, which are expected to result in different biological responses as compared to existing materials with larger structure. However, the basic principles established for particles seem to apply also to particulate nanomaterials whether nanoparticles or larger nanostructured entities (Figure 2). In the most simple case, (nano)materials overload the target organ: even completely inert materials can disturb the function of an organ if there are excessive quantities deposited. This overload effect can also be expected for nanomaterials. Second, particle can be the carrier of toxic substances. This applies again to MNM with the addition that nanoparticles were reported to easily transfer biological barriers implying that they can carry the toxic substances through membranes [5] into cells and, by translocation [6] to other organs even though only very small quantities do translocate. Thus, this opens the way to novel effects in cells or organs.

**Figure 2.** Established paradigms in particle toxicology. The paradigm that particles can produce toxic substances is relatively new. This is a lesson learnt mostly from ambient air pollution research.
The morphology of material can play a critical role in the hazardousness of biopersistent materials, which is well known for asbestos fibres. Initial research suggests that multi-walled carbon nanotubes provoke a similar response as asbestos fibres provided they are sufficiently long [7].

The concept of toxic substances being produced by the particles (as opposed to a mere activation by metabolic processes) comes from epidemiological studies of airborne particulate matter. Ambient air pollution is associated to adverse health effects such as cancer, cardiovascular and pulmonary diseases [8]. The production of Reactive Oxygen Species (ROS) and the generation of oxidative stress is believed to be one of the key mechanisms. Oxidative stress is an imbalance between oxidants and antioxidants. In the presence of particulate matter, the natural antioxidant defenses may be overwhelmed (Halliwell and Gutteridge, 2007). A model [9] to explain how this is possible is shown in Figure 3.

![Figure 3](image.png)

**Figure 3.** Proposed model how particles deposited on the lung surface generate oxidative stress that causes direct damage and initiates an endothelial cell response that is pro-thrombotic, pro-inflammatory and can release substances that can interfere with the cardiac rhythm.

It proposes that oxidative stress can build up quickly in the thin liquid layer of the alveolar region surrounding the deposition site of the particle by the production of ROS on the particle surface but also the adsorption of antioxidants on particles [10]. This is a site with a high oxygen concentration and antioxidants can quickly be overwhelmed. The presence of the ROS leads to epithelial cell damage and to the release of pro-thrombotic and pro-inflammatory mediators from the adjacent endothelial cells [9]. Some of these factors, such as endothelin can also influence the heart rate [11]. This stress also can lead to DNA-damage in the surrounding cells and subsequent DNA-repair [12]. Ambient air pollution particles and also nanoparticles are small and can easily reach all parts of the lungs. Consequently, the above-described cellular responses to oxidative stress can occur over large parts of the surface of the lungs, resulting in a response that is visible and relevant on a systemic level.

In conclusion, the existing paradigms of particle toxicology can be used to explain many of the toxic effects of nanomaterials. However, they may need to be adapted to account for the special characteristics of nanomaterials. It is also unclear what consequences can result from translocation of particles into cells and to novel target organs, to what extent one has to consider morphological effects of nanomaterials on large biological molecules such as DNA and proteins, and what potential interactions can occur with the immunological system. The answer to these questions will most likely require close multidisciplinary collaborations.

### 4. Risk management tools and safety by design

Risk management starts with the assessment of the hazards and the extent of contact to the hazard - the exposure level and frequency and duration of exposure. Once the risk is known, appropriate management and control strategies can be developed. This concept also can be applied to nanomaterials. In an ideal world, the potential risks and strategies to manage them are known already in the early phase of product development, when concepts and product design are developed. In the idea of Safety by design, product and material developers will define the material characteristics and
the design of a product to be inherently safe, or at least they will give priority to approaches that avoid characteristics where health and environmental problems are likely to occur. Figure 4 illustrates the benefits of this concept. In the beginning of the development, the design options are very large and the developers have considerable flexibility in their choice. At the same time, the costs for safety approaches are quite reasonable. However, further down the development and production chain, the costs for correcting an earlier decision towards “unsafe design” increase more and more, which is paralleled by a decrease in design flexibility.

Figure 4. Schematic representation of the value chain including the flexibility of the design to address health and safety concerns and the increase of cost to correct safety approaches down the value chain.

This is a classical problem of step-wise optimization along the value chain, where one step can generate problems for later steps. In theory, an overall system optimization will yield a higher benefit. There are several challenges with this approach, for example that there are different actors in along the value chain with different interests, risks and benefits. The ones carrying the risk might not be the ones having the benefits and finally, monetary benefit maximization might yield different outcomes than health or environmental benefit optimization. There is again nothing special “nano” in this concept per se. The challenge lays in the many knowledge gaps and the multidisciplinarity that is required to correctly design the products to be safe. There is not only uncertainty (and disagreement) about the most relevant characteristics to explain the hazards and exposure potential of nanomaterials; there is also considerable complexity in the system where the links between the elements must be well understood to make clear statements about which parameters a product developer should optimize.

While a refined risk assessment and safe design approach does not yet seem possible, there are already simplified approaches (toolkits) to evaluate and manage the risks at the different levels. The recommended health and safety approach to new, unknown substances is to treat them as if they were very hazardous. These approaches are then refined as novel knowledge is generated about the hazards, exposure potential and appropriate strategies to protect workers, consumers and the environment. This tiered approach is already in use for “normal” chemicals and is also reflected and supported by the REACH-regulation, which requires an extensive dossier for substances exceeding certain production quantities. For nanomaterials, initial tools exist. For example the precautionary matrix [13] allows testing the potential for nano-specific risks. Also, ISO started a working group to develop control banding strategies that are specifically adapted to nanomaterials.

The challenge is now to develop sufficiently accurate toolkits in a situation where the number of applications and the extent of industrial production are rapidly growing, and therefore where the toolkits need to anticipate the next technological development steps. This requires the joint efforts of
researchers, engineers, producers and distributors who must ensure that products are inherently safe, that the potential for acute but also long-term effects is appropriately understood, and that production and use are accompanied by adequate and appropriate good working practices.

5. Coordination and collaboration efforts in Europe

There are clear knowledge-gaps that need to be addressed. They are of multidisciplinary nature and should be addressed on a European and global level. On this background, scientists started to collaborate, first independently, now also with support by the European Commission. One of these efforts is NanoImpactNet, the European Network on the Health and Environmental Impact of Nanomaterials (FP7 project number CSA-CA 218539). The objective of the NanoImpactNet is to create a widely supported scientific basis to ensure the safe and responsible development of engineered nanomaterials and products containing them. This includes a strong two-way communication with the various stakeholder groups, notably policy makers, industry and SMEs, and the public interest groups. This communication provides a way to disseminate scientific information while at the same time obtaining input from these groups about their knowledge needs and questions.

Another special feature is that NanoImpactNet is open for participation to all scientists and stakeholders with an interest in the topic, thereby guaranteeing open and transparent discussions. Funding for NanoImpactNet will be provided until early 2012. Already now, new structures are being built that will allow continue NanoImpactNet.

There is still considerable work to be done on the road towards healthy, safe and environmental nanomaterials. Coordination and collaboration is especially needed for the development of best practice to ensure that studies are comparable in terms of basic parameters such as particle type, cell types, dispersion and characterisation protocols and appropriate testing methodologies. Also, close and continued collaboration and discussions are needed if one wants to draw policy-relevant recommendations from the activities mentioned, especially in terms of the occupational and public health and environmental impact potentially associated with the findings of the studies. The European Commission already funds over 20 projects in this field and encourages the researchers to collaborate through networks such as NanoImpactNet or the NanosafetyCluster [14].

NanoImpactNet was able to bring together the leading European groups in the fields of nanosafety, nanorisk assessment and nanotoxicology. This unique opportunity already allowed to reach consensus on some of the issues [15, and www.nanoimpactnet.eu]. It also allowed giving recommendations to the research agenda and proposing priorities in this arena for the coming years. Finally, the development of standardized guidelines and protocols will ensure that the research performed in the individual groups (whether funded by other EU programs or nationally) is of the highest quality. Overall, the exchange of ideas and information between researchers and stakeholders leads to very constructive discussions and it makes way to the development of strategies that can ensure the safe and responsible development of nanomaterials.

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