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# SweNanoSafe

Swedish National Platform for Nanosafety

# Functional and Safe Nanomaterials – Collaboration between Academia and Industry

## A report from SweNanoSafe's workshop, 19th September 2019, Lund, Sweden

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## Preface

On 19th September 2019, SweNanoSafe (the Swedish National Platform for Nanosafety) gathered thirty-five participants at Ideon in Lund for a workshop on functional and safe nanomaterials within the area of nanosafety. The presentations and discussions focused on research needs and implementation of research results for regulation, development and safe use of nanomaterials.

The event brought together participants from different stakeholder groups, mainly from academia but also from authorities and industry, thereby providing opportunities for networking and further cooperation among stakeholders. Participants represented primarily Swedish universities, research institutes and industry, as well as one participant from a Dutch research institute and two participants from a Danish university.

On behalf of SweNanoSafe, we express our gratitude to all participants for their valuable contribution to the discussions and results of the workshop.

*Bengt Fadeel, Chair SweNanoSafe Expert Panel, the Expert Panel and Rune Karlsson, Coordinator SweNanoSafe*

SweNanoSafe

National Platform for Nanosafety

Institute of Environmental Medicine, Karolinska Institutet

Address:

Box 210, SE-171 77 Stockholm

Karolinska Institutet

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# Content

# About SweNanoSafe

SweNanoSafe, the Swedish National Platform for Nanosafety, has a mandate from the Swedish Government to promote safe handling of nanomaterials. The platform was originally established in 2016 at Swetox, a former academic research centre. Since 1st January 2019, the platform is hosted by the Institute of Environmental Medicine (IMM) at Karolinska Institutet (KI).

The platform aims to promote the safe handling by, among other things, creating new forms of collaboration between those working with nanosafety. The platform therefore brings together a variety of representatives from academia, authorities, business and organizations. The actors include those who explore and regulate the safety of nanomaterials and those who, in their role within a company or organization, need to know about the safety of the materials and how they should be handled.

The platform is managed by a Steering Committee with members from KI/IMM and the Swedish Chemicals Agency (KemI). The platform also has an Expert Panel comprising of members with specialised expertise in various disciplines related to nanosafety, a Research Network, a Cooperation Council with members from the authorities, businesses, academia and organisations) and a website for information, communication and collaboration (www.swenanosafe.se). In the letter of appropriation issued by the Swedish Ministry of the Environment to KemI (Government decision 21 December 2018), Karolinska Institutet was awarded funds to ”further develop a platform for safe handling of nanomaterials that may help achieve the environmental quality objective for a non-toxic environment and to protect human health.” This assignment involves communicating and disseminating knowledge about the risks involved with nanomaterials to academia, the authorities, businesses and organisations, and to identify any obstacles to safe handling.

# Overview

The main aim of the workshop was to encourage the collaboration between academia and industry, with a focus on how to increase mutual understanding so that research results to a larger degree can be applied by industry, but also to help academic researchers better understand the industry's needs.

Topics/themes for the workshop were:

- collaboration between researchers and industry, including how to make more value out of research,
- early integration of safety aspects in the innovation process (i.e. safe-by-design).

Professor Bengt Fadeel, Karolinska Institutet and chair of the SweNanoSafe Expert Panel, opened the workshop by welcoming everyone and presenting the background, aims and activities of SweNanoSafe. The expert panel has established a network for Swedish nanosafety researchers which was inaugurated at the workshop on Nanosafety Research and Education, 13th June 2018. The network was created on the initiative of SweNanoSafe to support interdisciplinary collaboration, to highlight and to increase the visibility of nanosafety research in Sweden, to identify research needs and priorities for future research, to provide quality-approved information for all stakeholders and act as a pool of national experts for international bodies such as the OECD. SweNanoSafe is

continuously collecting information to identify existing hindrances and suggesting mitigation proposals that can be handled by the Ministry of the Environment and other actors. Bengt Fadeel concluded the introduction by speaking about the aim of the workshop to improve our understanding of each other's needs, towards the goal of developing useful and safe nanomaterials.

Group discussions took place in the morning as well as in the afternoon, using two questions in each session to encourage discussion. The workshop participants were divided into five smaller groups. Concluding discussions were conducted in plenum.

## Background to innovation and safety

Nanosafety means the safe use and handling of manufactured nanomaterials. Safety applies to both human health and the external environment and may affect various stages of a nanomaterial's life cycle such as synthesis, development, production, use and waste management.

At present, innovations are being developed up to the late stages of close to market introduction, before regulatory risk assessors can state the need to manage potential risks for both people and the environment. An innovation may therefore be deadlocked if it becomes clear that regulatory requirements or guidance documents do not fully cover the innovative aspects, leading to uncertainty about how to manage their potential risks. The market introduction can thus be delayed or at worst stopped.

Starting from lessons learned from recent safety assessments of nanomaterials, several approaches could be recommended for different stakeholders (innovators, scientific experts, risk assessors, and regulators), through the different innovation stages to improve safe innovation of nanomaterials and nanomaterials-based products. It has been suggested that a safe and time-efficient innovation process is only possible under the conditions of clear and timely communication between innovators, scientists, risk assessors and regulators (Park et al., 2017). Already at the earliest innovation stage, all involved stakeholders should be made aware of potential risks. It should be specified how potential specific nanosafety issues can be addressed, by what stakeholder and at what stage of the innovation process. Systematic collection of information on hazard, exposure, risks and the effectiveness of risk management measures throughout the innovation chain/life cycle, can guide the process of suitable safe by design options.

## Presentations

The invited speakers covered different aspects of nanosafety that require consideration during the different stages of the innovation process:

1) Risk governance in the nanotechnology area needs to be developed, according to the introduction presentation.
2) Example from a specific nanomaterial, graphene on how to take the material from idea to market and safety issues along the value chain.
3) Safe development and application of nanomaterials and the need of a national road map for nanotechnology that includes safety.

4) An example from the pharmaceutical sector concerning bringing a safe health product to the market through safe by design and pharmaceutical test methods.

5) The final speaker communicated experiences from nanosafety activities at NanoLund.

## Nanotechnology Risk Governance

The first key-note speaker of the day was Monique Groenewold, coordinator of the Risks of Nanotechnology Knowledge and Information Centre (KIR-nano) at National Institute for Public Health and the Environment, the Netherlands (RIVM) since it's foundation 2008, with a speech titled *Nanotechnology Risk Governance*. Monique Groenewold is also the coordinator of the EU project Gov4Nano.

KIR-nano is aimed at using the full potential of nanotechnology and at the same time considering the risks, and research needed to determine human and environmental effects. The centre functions as a bridge between insights gained from scientific research and ongoing developments in legislation and societal issues. Based on monitoring of different areas of knowledge and research, KIR-nano translates the results obtained into policy advice and practice.

For example, KIR-nano is developing recommendations/guidelines for the government on what is needed to harmonise and implement different EU regulatory frameworks, with perspectives from workers, the environment, consumers and general chemicals regulations. A report is written every month for the Dutch Ministry of Health, Welfare and Sport. The main added value from a policy perspective is updated if the report is to be discussed in parliament.

Here are some key points from the talk of Monique Groenewold:

- Improved test methods to exploit the full potential of nanotechnology and at the same time safeguard human health and the environment, will not solve the problem the alone. There also needs to be improvements in areas such as governance, data quality and data management.
- There are plenty of experimental data but serious doubts about quality and usefulness, such as reproducibility, comparability and relevance. A lot of data is not publicly available due to IPR-issues or logistic limitations.
- A solid foundation for nanosafety policy and regulation of nanomaterials is missing since the right data is not yet collected for regulatory purposes. Important lessons have been learnt from a Dutch public-private partnership innovation program, NanoNextNL with 130 partners, and from the EU-projects NanoReg and ProSafe which resulted in the ProSafe White Paper recommendations (https://www.rivm.nl/en/documenten/prosafe-white-paper-updated-version-20170922).
- Improved quality of data requires implementation of additional validated test methods. Sets of experiments should be generated that collects correct data for regulatory purpose. The data should be stored so it could be accessed by all researchers according to FAIR (Findable, Accessible, Interoperable, and Reusable). All projects funded by governments should commit to standards of data collection.

- Harmonized occupational exposure limits should be implemented to protect workers.
- Innovation in risk assessment needs to be developed. To limit the amount of testing as basis for risk assessment, the information gathering process must be efficient. Collecting data from laboratory experiments for risk assessment is costly. New effective test methods are needed, in vitro and in silico, less animal testing, more high-through-put screening.
- Risk assessment strategies could be applied to predict for other closely related substances. Enough information to assess the safety for human health and the environment should be available for each nanomaterial. Grouping and read-across approaches can be utilised to meet these goals. These methods should pave the way for better use of available information on nanomaterials and should be flexible enough allowing for future adaptations to scientific developments.
- Future-proof approaches for risk assessment requires bridging the gaps in collaboration between science, regulation, policy and innovation. Dedicated "regulatory oriented" research is still essential. One of the objectives of Gov4Nano is to develop a Nano Risk Governance Council with early involvement of national, European and international stakeholders.
- A working definition of safe by design was suggested: Reducing potential health and environmental risks and uncertainties of innovative materials, products and processes by addressing safety aspects at an early phase of the innovation process. Technology and innovation are advancing at a dynamic speed and in numbers and it follows that uncertain risks are a growing concern. Lessons from NanoNextNL are very positive, that is integrating risk assessment and technology analyses from the beginning, such as including safe by design in research plans, business plans and innovation models.

## Moving graphene from the lab to the market

Helena Theander, project manager at Chalmers Industriteknik (CIT), held the second talk of the day: *Moving graphene from the lab to the market*. She is also the coordinator of SIO (Strategic Innovation Programme) Grafen that CIT is hosting. SIO Grafen is one of 17 strategic innovation programs in Sweden. CIT has also responsibility for the innovation WP of the EU Graphene Flagship.

CIT is building ecosystems for transfer of university-based research and knowledge into real world commercial applications. The vision is that Sweden should be among the world's top ten countries in deploying graphene to ensure industrial leadership. There are already several Swedish companies that has commercialised graphene.

Hera are some highlights from the innovation program:

- In the first five years of SIO Grafen, 89 innovation projects were started, 130 organisations participated of which 53 were SME: s. CIT works in all steps of the value chains, especially in collaboration. All actors are new and all need to learn the new markets and the regulation. The ecosystems, i.e. the network of organizations that drives the creation and delivery of products and services, include electronics, coatings, energy and composites.

- A lack of graphene production standards has led to many cases of poor-quality products from suppliers. This can impede the use in applications that fundamentally depend on the use of high-quality graphene (< 10 layers). CIT therefore offers characterisation cheques to validate graphene quality.
- Challenges include to get MSDS (Material Safety Data Sheet) that you can trust and to register in Reach (Registration, evaluation, authorisation and restriction of chemicals), i.e. answers about physical-chemical properties and toxicity since no standardised characterisation methods are available.

## Nanotechnology and safety

The second key-note speaker at the workshop Åsalie Hartmanis, CEO at SwedNanoTech, Sweden's first umbrella organization for Swedish nanotechnology players, gave a presentation on *Nanotechnology and safety*.

SwedNanoTech (SNT) engages Swedish nanotechnology actors to jointly shape the landscape of Swedish nanotechnology. The purpose is to influence, create meeting places and to build bridges between academia, industry, business and the public. SNT has organized several conferences and workshops, written an agenda for Swedish nanotechnology in a sustainable society, and published opinion articles. The organisation has about 80 members of which 50 are companies.

SwedNanoTech has been member of several reference groups for the government, for example one that led to the creation of SweNanoSafe, another one to the establishment of the research programme Mistra Environmental Nanosafety. Furthermore, SNT is involved in research projects, in OECD work, standardisation (Standards Nanotechnology, cases graphene and nanocellulose) and dialogue with authorities, for example Swedish Environmental Protection Agency and Swedish Chemicals Agency. One of the concluded research projects has led to the risk assessment tool LICARA nanoSCAN.

Åsalie Hartmanis rhetorically asked if nanosafety is an issue in industry? Occupational safety and health are regulated by law as well as environmental concerns. Since 2018, nanomaterials that are added to chemical products must be reported to the Products Register and there are information requirements on nanomaterials in Reach from 1 January 2020. There are concerns of exposure in the working environment, but no actions have been taken from the Work Environmental Authority. Yet this has not stopped SNT from taking part in a pre-study with IKEM (Innovations- och kemiindustrierna) and Prevent, aiming at useful guidance documents and checklists for field work (working environment). Since safety concerns are considered well-regulated by industry, nanosafety is not really considered a big topic. Therefore, companies do not ask questions daily about safety, they assume it is taken care of by legislation. There is also a time constrain, especially for SME: s that are busy just to stay alive, so safety issues cannot really be prioritized. Small companies need the regulation, but work with regulatory compliance is an additional burden, and needs to be done in a smart and effective way. However, industry has an interest to do it right and understand that safe products and processes are essential for their long-term success.

In the new world of the sharing economy services are developed based on big data, i.e. data sets that are too large or complex to be dealt with by traditional data-processing. Small companies need to survive and grow, and many are dependent on data sharing. There needs to be an effective

process for this since data-driven innovation is a key driver for growth and jobs. One example for sharing instruments and solutions is an online tool that connects European pilot production facilities with industry.

Åsalie pointed out that going from idea to product in the innovation chain is a complex process and not a straight line. It is important to work together and respect each other's competencies.

Most countries have a national plan for sustainable and safe innovation. It is easier to know how to go forward if you have a roadmap, a core strategy to coordinate and align activities of different stakeholders and in different sectors. A national plan can also provide a legal and political framework for action.

## Safety testing of SN123D

The fourth speaker, Oskar Axelsson, is the CEO and VP at Spago Nanomedical, and held a talk titled *Safety testing of SN123D, a tumor selective contrast agent*. Oskar has more than 25 years of experience from pharmaceutical as well as contrast agent research. Spago Nano-medical focuses on the development of novel nanomedical tumor selective products for cancer diagnostics and therapy. The company applies risk-based project management to create a safe product through safe by design and pharmaceutical test methods.

In his presentation, Oscar Axelsson described the process for creating a tumor selective contrast agent for Magnetic Resonance Imaging (MRI) and at the same time an inherently safe product. In the drug design phase, the company had several meetings with the Swedish Medical Products Agency (LMV). The agency provided a lot of advice but will never tell you if your suggestions are good enough to comply with the documentation required.

The contrast agent (SN123D) is based on the active ingredient manganese (II) (an element approved for use in humans) and is designed to have a residence time of about two hours in the body. The contrast agent diameter (5.5 nm) is slightly smaller than albumin, the body's most abundant protein. SN123D consists of a polymer that binds manganese (II), a polymeric network of organosilicon monomers and a Polyethylene glycol (PEG) coating to make it reasonably inert.

The whole life cycle of SN123D was also considered during the development. For example, there are some weak spots in the chemical structure so that the contrast agent easily dissolves to harmless compounds in the environment.

The liver presents one of the biggest problems for using nanoparticles clinically. The sequestration of nanoparticles by the liver may preventing them from targeting extrahepatic (outside the liver) diseased tissue. If nanoparticles accumulate in the liver they will stay in the liver and excessive exposure may cause liver necrosis, if small enough they are broken down as is the case for SN123D. In the first stage SN123D will fall apart into monomers, followed by oxidation leading to phosphates, silicates, etc. then these breakdown products are excreted naturally.

Spago Nanomedical has formally opened the first clinical trial. The primary objective is to document safety, but another important purpose is to investigate SN132D´s MRI-enhancing effects when used clinically in patients with solid tumors.

## Nanosafety at NanoLund

The final presentation was held by Christina Isaxon, coordinator of nanosafety at NanoLund, Lund University on the topic *Nanosafety at NanoLund*. Christina Isaxon is an associate senior lecturer, for example she was responsible for the Nanosafety PhD course in the spring of 2019, while also conducting research.

Nanosafety is one of four (4) focus areas at NanoLund, supporting all nano related activities/research within the university from a safety perspective. In the area of nanosafety, NanoLund is:

- Conducting and disseminating internationally leading research to understand the fundamental connections between particle properties and (eco)toxicology.
- Generating new and transfer existing knowledge on safe handling of nanomaterials throughout the life cycle, to the industrial network.
- A proactive part in the societal debate regarding safe production, use, and disposal of new nanomaterials.
- Supporting all nano related activities/research within Lund University from a safety perspective.

# Group discussions

## Session 1 – Functional and safe nanomaterials

Despite significant investments in research and development, there are still roadblocks preventing the implementation of commercially valuable innovations in a safe and responsible manner. The uncertainty surrounding the potential risks of nanomaterials but also the lack of regulatory clarity influences the development, uptake and exploitation of nanomaterials. This has been identified as a barrier to nanotechnology innovations. So-called *safe by design* may provide a way forward but how to implement this approach remains to be understood.

The morning group discussion on functional and safe nanomaterials was chaired by Åsalie Hartmanis, SwedNanoTech. She introduced the session and led the overall discussion after the conclusion of the group discussions. The participants were divided into five parallel groups. To initiate and stimulate the discussion, two questions were provided for the first session ahead of the workshop:

**Q1: What are the hindrances of any kind in bringing safe nanomaterials or their applications to the market?**

**Q2: What are the hindrances of any kind in bringing about safe-by-design in innovation (note: define safe by design)?**

Below is a summary of hindrances and measures for implementation of safe applications and processes involving nanomaterials that were suggested in the morning group discussion session.

**Hindrances:**

*Results and data*

- Most databases with scientific literature and high-profile journals, such as ACS Nano which are seen as very prestigious, are closed and very expensive to access.
- It takes a long time for nano safety projects to publish useful results.
- It is not obvious that companies will publish since there is a clear incentive to keep the results of their research secret or to patent them in order to transform them into commercially useful products or services.
- Companies publish patents and describe their products very narrowly only revealing what they must, but there is no risk assessment and only advantages are revealed.

*Materials science*

- Generally, there is a lack of support for researchers such as from regulators, in research and technological development.

*Regulation*

- Many companies don't know the regulations and so it is hard to know how to bring products to market.
- At least SMEs are perhaps hindered by Reach etc. since it is difficult for them to understand how to interpret all the regulation.

*Test methods*

- There is a lack of robust validated and/or standardized test methods.

*Exposure*

- Unknown exposure of many nanomaterials in work environments due to the lack of reliable monitoring methods.

*Marketing*

- Many companies no longer want to advertise that their product contains nano materials. There is a risk due to possible toxicity and leakage. A food company for example, must be able to say for sure that its products are safe. The nanomaterials are there for a purpose and all products have a set of unique challenges such as possible specific toxicity.

*Safe by design*

- Many companies don't have the knowledge and resources to implement safe by design.

*Funding*

- The innovation system does not have enough funding.

**Measures:**

*Results and data*

- Create a new database specifically targeting innovators as a complement to current databases.
- Encourage researchers to publish in the open literature and put pressure on publishers to publish in open access.

*Regulation*

- Collaboration is needed between the academy, industry and regulators throughout the innovation chain and thereby building trust is needed, creating so called "trusted environments".
- Regulators ought to reach out to other stakeholders and collaborate according to ethical rules.
- Regulators need to make clear what kind of research they need: challenges, questions, what is missing and getting it matched.
- Regulators are receptive to new test methods, the door is open to regulators right now, using experiences and useful wording from the pharmaceutical sector.
- Therefore, industry should propose regulation based on their own standards and convince the regulators that these are important.

*Pharmaceutical industry (regulation)*

- Acquire information from the approval process in the pharmaceutical industry since this experience could be applied to other sectors.
- Learn from critical experience, such as assessing how chemical structure impact hazard.
- Pharmaceutical regulation is complex but conceptually easy, with approval from the Swedish Medical Products Agency (LMV). It is more complicated to regulate what goes into a medical product. Lessons could also be learnt from agencies regulating Biocidal Products.
- You should not be afraid to ask and get support as soon as you can shape your project. LMV will not tell you if it is good enough, but you get a sense if you are on the right track and indirectly support with suggesting even a better testing program.
- The agency is usually very helpful concerning design of clinical studies and helping in the general drug or medical device development process.

*Life Cycle Analysis*

- There is a need to look at the wider perspective, all phases in the life cycle should be considered from cradle-to-grave. The concept of circular economy aimed at eliminating waste and the continual use of resources, should be considered.
- Acknowledge UN: s 17 sustainability goals, such as toxic free environment for which persistency and degradability of chemicals play a big role.
- Persistent chemicals (such as some nanomaterials) in the environment are of special concern.

*What is "safety"?*

- Consider what is meant by the notion of "safety" regarding nanomaterials from the perspective of human health, the environment and socio-economic aspects (ELSI – ethical, legal and social issues).
- The concept "safety" should be agreed upon on all levels and by all stakeholders. It should be put in the perspective of regulation and adjusted to for example Reach.

*Safe by design*

- You should know what characteristics make a nanomaterial safe or not safe. There are many uncertainties, so more knowledge and data are needed.
- Broader definitions and nomenclature around the safe by design concept and agreed considerations of safety aspects in the design process are needed.
- New nanomaterials should have built-in weaknesses, so they degrade in reasonable time both in the human body and in the environment. In practice however, this is quite difficult to achieve.
- Develop a safe by design tool that can be used to predict hazard from nanomaterial physiochemical structure.
- Resources are needed to develop the safe-by-design concept for nanomaterials but will eventually add to the profitability. If you show that you have applied safe by design when you develop your product, it can give an economical and market niche advantage.
- Establish a position as "safe by design engineer" in companies to promote manufacturing of safer nanomaterials.

*Balancing of safety and economics*

- Find new tools to balance safety and economic benefits, i.e. improved cost-benefit and risk-benefit analyses without jeopardizing basic safety concepts.
- Use examples from biomedical development. Product developer must be responsible for the risks and must follow the steps of the process meticulously because if risks are found in the later innovation stages it will be expensive.

*Risk research*

- Apply target-driven research/research for specific purposes.
- Animal models should be replaced (3R).
- Generate mechanistic information on toxic effects.
- Understand key hazards and risk factors.
- As a start, apply the AOP (Adverse outcome pathway): Reactive oxidative stress.

*Testing and assessment methods*

- Apply pragmatic/alternative approaches.
- Better specific testing methods needed through applied research.

- Academic researchers can contribute to developing standardized test methods.
- Need to have a facility with test methods that industry can use.
- Need for new techniques to measure realistic exposure in work environments. Develop target driven exposure scenarios.
- Validated methods for material characterization and toxicity testing were requested. Implement proper characterization as a prerequisite for in vitro, in vivo testing.
- Assess toxicity based on structure and apply methods for read across and grouping. It was agreed that it is hard to group nanomaterials, therefore an innovative approach is needed.
- Compare with the EU project Gracious that deals with structure-based assessment.

*Public information*

- Even though companies are fulfilling regulations by supplying information to authorities, it would also be of interest to supply information to the public.
- What incentives would there be of interest for industry to supply extra information so consumers can make better judgments and stimulate information sharing that is not about regulation?

*Funding*

- The innovation system needs more funding.

## Session 2 – Collaboration academia and industry

Companies with high ambitions in the area of human and environmental safety would benefit from nanosafety knowledge and contacts with academia and authorities. Using such knowledge already in the early phases of nanomaterial research and development, would save investments in both money and time as materials with safety issues could be identified early and more well-informed decisions on choices of (safer) alternative materials and better ways forward could be taken. There is, however, a disconnect between basic academic research and research that satisfies the needs of industry as well as regulators and it is important to identify hindrances between the various stakeholders.

In the afternoon, there was also two predefined inspirational questions as a start for discussions in five parallel groups:

**Q1: What kind of collaborations would enhance competitiveness and innovation of safe nanomaterials and nanotechnologies?**

**Q2: What are the hindrances of any kind that prevent collaboration between academy and industry?**

Ian Cotgreave at RISE, with experience from risk assessment in the pharmaceutical sector introduced the afternoon discussion session. This industry has extensive experience to build in safety already from the start and now the chemicals industry can learn from its experience. Since

2013, the cosmetic industry cannot use animal testing and have created programs for directed research and coaxed research on how to meet regulators goals with non-animal testing methods. There are funding available for safety research, for example from the EU Commission, in areas such as supporting read across i.e. comparison to closely related (existing) nanomaterials and ab initio (from the beginning) research on very original nanomaterials.

Stakeholders need to learn to work together, academic research, industry, and regulators doing compliance work. Ian asked, how do we get these relations to work, what hinders and what supports collaboration? Sometimes the regulators don't understand the research data that comes out, so they need to learn continuously from the academia and industry.

The academy produces facts and data, mainly through basic research. Most of the applied research is carried out at research institutes and industry. Academia also educates engineers for industry. The industry needs research findings from the academy to produce their goods and services.

Below is a summary of hindrances and measures for collaboration academy – industry but also with other stakeholders, as a result of the group discussions:

**Hindrances:**

- Finding key contacts with the right competence may be an issue for small companies.
- Collaborators may be found through the literature, but many journals are closed and very expensive to access for companies.
- Some participants were not sure how to go about sharing laboratory equipment and finding qualified laboratory assistants. It was considered challenging to set up equipment sharing agreements.
- If companies and academia do collaborate, it may be difficult to find a way to compensate academic researchers since they cannot make a profit.
- Many times, academic researchers must focus on producing scientific papers: "publish or die". Even if they have an interest in collaboration with industry, there is often no time or overhead to cover costs.
- Academic researchers should be carrying out independent "pure" research. If they collaborate with industry on "applied" research, they may be having conflict of interests.
- Companies are protective of their intellectual property (IP rights and patents).
- Lack of knowledge for establishing confidentiality agreements between academy and industry.
- Imbalances in collaboration between stakeholders (academy, industry, regulators).

**Measures:**

- Engage missing stakeholders in the innovation chain for safe products, in general that is, regulators and sensible investors (funders).
- Collaborators from the academy can be found through the scientific literature.
- Publications shouldn't be the only way to disseminate knowledge that indirectly may lead to collaboration.
- If companies and possible other stakeholders talk and are planning collaboration, they need to make sure that all involved gain through win-win situations.
- Develop relations between academic research, industry and regulators and build trust, resulting in creation of innovation spin-offs, for example.
- This should lead to formation of a platform/network for continuous dialogue and information sharing (a trusted environment).
- It was suggested that there should be an administrative "facilitator" for coordination of collaboration between academia and industry.
- Communication channels should be established between academia and industry, industry and regulators, respectively.
- Interaction between stakeholders needs concrete cases to collaborate on, and thereby developing relationships.
- Create a culture of acceptance of failures and an approach to learn from these (fast learning).
- Personal meetings at conferences are good for networking and information sharing and may lead to collaboration.
- Industry should operate based on a moral code and the dialogue between academy and industry should include societal challenges.
- Collaborations could also be carried out around sharing of instruments.
- One way to find key contacts and instruments, go to the research network at SweNanoSafe, https://swenanosafe.se/vad-vi-gor/forskarnatverket/
- Another contact point is EC4SafeNano, a program and platform under construction at the EU-level. To share what you can provide, please contact Ian Cotgreave (ian.cotgreave@ri.se).

# Discussion

Main discussion points were:

- The need of open data and key contacts for innovators.
- Improved risk assessment process based on understanding of key hazards and risk factors and better test methods.
- Learning from the pharmaceutical sector to create safe nanomaterials and their products

- Streamline the innovation process by efficient collaboration between scientific experts, including risk assessors (academia), innovators (industry) and regulators.
- Increased funding for the innovation system of safe products, but also for development, validation/standardization of safety test methods.
- Meaning of "safe" nanomaterials and definition of "safe by design".
- More clear and effective governance, including regulation, promoting safer and faster innovations.

***Data and key contacts***

One of the measures proposed during the discussions was to create an open data base dedicated to innovators that can be utilized throughout the innovation chain. Many companies are dependent on shared data and access to key contacts with right competence. Participants pointed out the general need of open data and open literature.

A core strategy in the European Commission is to improve knowledge circulation and thus innovation, illustrated by the general principle for open access to scientific publications in Horizon 2020 and the pilot for research data. An example is the eNanoMapper database for nanomaterial safety information with flexible data storage, open source components and web services. All new EU projects are dedicated to producing open research data. One of the projects, NanoInformaTIX, is developing a sustainable informatics tool for the risk assessment of nanomaterials, based on the significant amounts of data on properties generated over the last decades, as well as new data coming from research.

***Risk governance***

Nanotechnology risk governance was a key topic at the workshop. Governance describes the ways in which the research, development, application and use of a technology is developed, steered and controlled. Regulation and risk management measures are in general based foremost on an independent and complete scientific risk assessment. Too much time can be spent waiting for the conclusion of risk assessment procedures instead of implementing measures to prevent or reduce possible risks. The Risk Governance Framework developed by the International Risk Governance Council (IRGC), provides an approach for nanomaterial risk analysis (IRGC, 2007). This framework is considered particularly relevant for nanotechnology due to the uncertainties surrounding the potential health and environmental effects of nanotechnology, and hence the need to involve a wide range of stakeholders when making decisions regarding nanotechnology's use and implementation (Grobe, 2012).

***Risk assessment***

Risk assessment of nanomaterials is based on procedures originally conceived for conventional chemicals. The basic components of risk assessment are hazard and exposure assessments, dose-response estimation, risk characterisation and accounting for the uncertainty in the overall

assessment. Each of these steps presents challenges for nanomaterials.

An intelligent and reliable risk assessment strategy needs to be further developed, that includes adaptation of test methods and models adjusted to nanomaterials, such as the OECD testing programme. The risk assessment strategy, methods and models need to be robust enough to be acceptable at different stages of the developmental process up to the stage of regulatory risk assessment.

### *Hazard*

A preliminary hazard assessment could be carried out based on available general knowledge of nanomaterials. The hazard identification is often based on inherent physical and chemical properties, which differ for nanomaterials compared to conventional chemicals. An indication of the hazard can be obtained by collecting information on a limited number of physicochemical properties of the intended nanomaterial product such as size, shape and surface chemistry. Establishing concentration–response relationships for nanomaterials is more challenging than conventional chemicals because particle-specific processes such as agglomeration and sedimentation often will cause exposure concentrations to fluctuate during incubation. To advance more specific knowledge on nanomaterials, research agendas could focus on systemically investigating the relation between physicochemical properties and hazard.

### *Exposure through the value chain and life cycle*

A concern that was expressed is that often exposure in the work environment is unknown since enough sensitive measurement methods are lacking. To address exposure to humans in general, but also to the environment, exposure along the value chain or life cycle of the material or product, should be anticipated timely. The exposure assessment is also challenged by particle-specific processes such as homo- and hetero-agglomeration, dissolution and reactivity.

In the early stages of development, innovators should describe their production processes, as well the materials involved in enough detail to enable identification of potential sources of exposure to nanomaterials, associated impurities and release of other substances during the production process. Standardisation of the production process facilitates a reliable assessment of sources of exposure to nanomaterials and enables the identification of any exposure reduction measures that may be needed.

### *Regulation and innovation*

A subject of discussion was the request for a clear and effective regulation that would result in a faster and safer innovation process. The workshop suggested that industry should propose regulation based on their own standards, such as test methods, as reasonable basis for regulation. It would be advantageous for industry to use experiences and wording from the pharmaceutical sector. On the other hand, regulators need to make clear what kind of research/data/information they need to establish effective regulation. Therefore, enough communication and sharing of information should take place between regulators and innovators thereby building trust and

collaboration, creating a so called "trusted environment". To avoid a delay in the innovation process, it is important that guidelines and associated test methods are in place.

It has been recommended that regulators (i.e., regulatory risk assessors) already in the early stage of the innovation process, should evaluate whether the regulatory risk assessment process is adequate to deal with the intended nanomaterial-based products (Park et al., 2017). If the regulators assess that they do not have enough information, they should specify what type of information is needed to exert a meaningful risk assessment. To facilitate this, scientific experts need to reflect on what specific type of information should be provided, which may be based on innovators' information on their intended products available. In the final premarket stage, innovators should be able to demonstrate to regulators that their product is compliant with regulatory acceptable guidelines.

Regulatory compliance is critical, but cannot yet be incorporated, as a nanomaterial risk assessment framework has yet to be developed and adopted by legislators (Nørgaard Sørensen et al., 2019).

***Safe by design***

The participants agreed that there are still many uncertainties around the meaning of safe by design. More resources are needed to develop the concept, for example by companies and will eventually lead to long term increased revenues. It includes improved cost-benefit analyses without jeopardizing basic safety concepts. Technological alternatives, while maintaining their intended functionality, include modification of the nanomaterial physico-chemical properties to reduce hazard or the release of nanomaterials from a nanomaterial product. Another option is to induce nanomaterials' accelerated alteration/degradation in relevant biological and/or environmental media in order to decrease their persistence, bioaccumulation and toxicity (Costa, 2014).

# Conclusions

Many of the (group)discussions focussed on the need for collaboration between the stakeholders. If innovators, scientists and regulators equally take the necessary actions, this should lead to a more efficient innovation process and increase the chances of success in yielding safe applications of nanomaterials.

The workshop realised the need for a study that would contribute to our understanding on what is supporting and hindering the current interaction between key Swedish stakeholders in the various phases of nanomaterial development, within the responsible research and innovation (RRI) process.

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# Annex 1. Agenda

## 2nd Annual Research Network Workshop: Functional and Safe Nanomaterials – Collaboration between Academia and Industry

### ORGANIZED BY THE NATIONAL NANOSAFETY PLATFORM, SWENANOSAFE

Date: 19 September 2019
Location: Ideon Konferens, Scheelevägen 17, Lund
Meeting room: Knut Wicksell
Time: 10.00 – 16.00
Participants: academic and industry researchers, funding agencies, and governmental authorities
Conference moderator: Lennart Gisselsson, Lund University (LU)

Agenda:

09.30 *Registration*

10.00 *Welcome and introduction* – Bengt Fadeel, SweNanoSafe Expert Panel and KI

10.15 *Keynote Lecture:* Nanotechnology risk governance – Monique Groenewold, RIVM

11.00 Moving graphene from the lab to the market – Helena Theander, Chalmers Industriteknik

11.15 *Group discussions:* Functional and safe nanomaterials [chair: Åsalie Hartmanis, SwedNanoTech]

12.30 *Lunch*

13.30 *Keynote Lecture:* Nanotechnology and safety – Åsalie Hartmanis, SwedNanoTech

14.00 Safety testing of SN123D, a tumor selective contrast agent – Oskar Axelsson, Spago Nanomedical

14.25 *Group discussions:* Collaboration academia and industry [chair: Ian Cotgreave, RISE]

15.40 Nanosafety at NanoLund – Christina Isaxson, LU

15.50 *Closing remarks* – Bengt Fadeel, Chair, SweNanoSafe Expert Panel and KI

16.00 The workshop ends

# Annex 2. List of participants

| Name | E-mail | Organisation |
|---|---|---|
| Zareen Abbas | zareen.abbas@gu.se | Gothenburg University |
| Anna-Karin Alm | anna-karin.alm@ftf.lth.se | Lund University |
| Ann-Charlotte Almstrand | ann-charlotte.almstrand@amm.gu.se | Sahlgrenska U. Hospital |
| Sverker Alänge | sverker.alange@gmail.com | IMIT |
| Rickard Arvidsson | rickard.arvidsson@chalmers.se | Chalmers |
| Oskar Axelsson | oskar.axelsson@spagonanomedical.se | Spago Nanomedical |
| Maria Bille Nielssen | mbille@gmail.com | DTU Environment |
| Tommy Cedervall | tommy.cedervall@biochemistry.lu.se | Lunds University |
| Lauge Clausen | lpwc@env.dtu.dk | DTU Environment |
| Ian Cotgreave | ian.cotgreave@ri.se | RISE |
| Bengt Fadeel | bengt.fadeel@ki.se | Karolinska Institutet |
| Natalia Ferraz | natalia.ferraz@angstrom.uu.se | Uppsala University |
| Julian Gallego | julian.gallego@marine.gu.se | Gothenburg University |
| Lennart Gisselsson | lennart.gisselsson@fsi.lu.se | Lund University |
| Monique Groenewold | monique.groenewold@rivm.nl | RIVM |
| Åsalie Hartmanis | asalie.hartmanis@swednanotech.com | SwedNanoTech |
| Maria Hedmer | maria.hedmer@med.lu.se | Lund University |
| Lena Hellmér | lena.hellmer@kemi.se | Swedish Chemicals Agency |
| Christina Isaxon | christina.isaxon@design.lth.se | Lund University |
| Albin Jakobsson | Albin.jakobsson@cellevate.com | Cellevate AB |
| Rune Karlsson | rune.karlsson@swenanosafe.se | SweNanoSafe |
| Krzysztof Krawczyk | kk@lumito.se | Lumito AB |
| Monica Kåredal | monica.karedal@med.lu.se | Lund University |
| Per-Olof Larsson | per-olof.larsson@hoganas.com | Höganäs AB |
| Eiwe Ljungblom | eiwe@projekttillvaxt.se | TestBed Nano |
| Martin Lundqvist | Martin.Lundqvist@biochemistry.lu.se | Lund University |
| Alexander Lyubartsev | alexander.lyubartsev@mmk.su.se | Stockholm University |
| Gregory Moore | gregory.moore@kemi.se | Swedish Chemicals Agency |
| Björn Persson | bjorn.persson@biochemistry.lu.se | Lund University |
| Jenny Rissler | jenny.rissler@ri.se | RISE & Lund University |
| Sari Scheinberg | sari@actionresearch.se | Action Research Center |
| Sten Sturefelt | sten.sturefelt.ss@hitachi-hightech.com | Hitachi High-Tech. Europe |
| Nicholas Surber | surber@chalmers.se | Chalmers |
| Helena Theander | helena.theander@chalmersindustriteknik.se | Chalmers Industriteknik |
| Lubica Wessman | lubica.wessman@tetrapak.com | Tetra Pak |