> Synthetic Nanomaterials

Risk Assessment and Risk Management
Basic report for the Swiss Action Plan

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>Short Summary

Nanotechnology, based on “small-scale science” is considered to be a key form of technology with a considerable economic potential. It deals with structures that are typically between 1 and 100 nm in size (1 nm = 10^{-9} m). Since nanomaterials often display other, new properties nanotechnology enables new products and processes to be created. Some important areas of application, which are economically promising for the future include electronics, computer technology, the development of advanced materials and medicine (e.g. carriers for targeted delivery of active substances, and new procedures for diagnosis and therapy, for instance in relation to cancer). The safe, successful use of nanotechnology represents a great opportunity for research and industry in Switzerland.

Nanotechnology is a new, technically complex area. Initial studies in Switzerland show that, in principle, citizens have a positive attitude to this new technology, but that there is a general lack of knowledge about it. Possible risks with consumer products and applications (food, cosmetics, etc.) are an important issue, as is the labelling of such products. It is very important to provide information to the public and to discuss these issues, so that citizens' worries and expectations can be recognised and dealt with as quickly as possible.

With a view to producing the action plan on “Risk Assessment and Risk Management for Synthetic Nanomaterials 2006–2009” the Federal Office for the Environment (FOEN) and the Swiss Federal Office of Public Health (SFOPH) called for the potential risks of synthetic nanoparticles to be studied, assessed, and where necessary for appropriate measures to be proposed. The unintentional release of fine particulate matter (e.g. from road traffic) is not included in the present report. This basic report outlines the current state of our knowledge about the potential risks of synthetic nanoparticles, identifies gaps in our knowledge and topics where there is a need for research to be carried out, and provides the basis for formulating recommendations for action to protect the environment and the health of consumers and employees. The Swiss action plan follows on from the EU action plan of June 2005, but concentrates on the situation in Switzerland.

Little research has been done on the potential risks that nanoparticles present for human health. Various studies have shown that – as a result of their small size – unbound nanoparticles can get into the finest structures of the lungs and from there into the blood. They can then spread around the body through the bloodstream and penetrate other organs. Investigations using cell cultures have shown that certain nanoparticles are easily taken up into cells, where they can have a damaging effect, depending on their chemical composition. It is suspected that they can cause inflammation or even changes in tissue. The behaviour and possible effects of nanoparticles are influenced by the dose received, their elemental composition and size, the form of the particle, the surface function, tendency to aggregate and surface charge. To make predictions on the potential risks of nanoparticles, further intensive research must be carried out, and

types, quantities and exposure values e.g. in the work place have to be understood. There is still a lack of uniform test methods and the basic scientific knowledge to carry out a comprehensive characterisation of nanomaterials.

Little research has been done on the inputs of synthetic nanoparticles into the environment or on their translocation and transformation in ecosystems. We lack data on possible sources and quantities of input, or studies on their environmental behaviour and possible bioaccumulation. Processes whereby persistent nanoparticles could accumulate in organisms and in ecosystems are of particular interest. The way in which synthetic nanoparticles spread in water, soil and the air, and their interactions with organisms have hardly been studied so far.

According to our current knowledge, exposure to synthetic nanoparticles in the workplace occurs mainly through processes, which use unbound nanoparticles as raw materials or which produce them as by-products. The recognised principles to reduce exposure at the workplace also apply to synthetic nanoparticles: new materials with unknown properties are to be handled as potentially dangerous. First, organisational protection measures must be taken, accompanied by technical protection measures and the substitution of powdery preparations. However, there is still great uncertainty about the efficiency of technical protection systems and personal protection equipment, especially for nanoparticles with a low agglomeration tendency. The specific physical and chemical properties of synthetic nanoparticles may also present unexpected physico-chemical safety risks such as the danger of fires and of explosions, or of unexpected catalytic activity.

In Switzerland, at the level of laws, there are the basic legislative prerequisites to regulate synthetic nanoparticles, but it will be necessary to adapt ordinances, norms and guidelines. For instance, instead of using threshold values for mass, new parameters such as surface area / volume will have to be considered.

Overall it can be seen that there is not yet sufficient basic information of a scientific or methodological nature for a conclusive risk assessment of nanoparticles to be carried out, and for them to be regulated. It is essential to have estimates of risk based on physico-chemical, toxicological and exposure data (risk framework) in order to set priorities for research on risk and for regulation, and if necessary to introduce measures to reduce risk.

> Extended Summary

Initial position and motivation

Nanotechnology has very promising possibilities and is regarded as a key technology for the 21st century. It is a horizontal or enabling form of technology, which will penetrate all industrial sectors in the medium term. New materials for surface coatings, computers, textiles, cosmetics, packaging and medicines are just a few examples of product groups that can be improved in terms of their functions and quality by nanotechnology. For Switzerland as a site for research and economic activities, nanotechnology offers an enormous potential for innovation and development. On the other hand, nanotechnology also has an enormous potential to improve the environment, through "green chemicals" and the sustainable use of resources.

New technologies are accompanied by new risks. In view of the great importance of nanotechnology for the economy, research and society, and of the expected widespread use of nanomaterials, any possible risks have to be studied by comprehensive, proactive risk estimation and assessment. Based on that, measures can be taken to protect people and the environment, and there can be well-informed discussions within society.

Synthetic nanoparticles are important components of nanotechnology, which are produced industrially and used in products or processes because of their particular properties. Despite the rapid development of nanotechnology, very little is yet known about the exposure of humans and the environment to synthetic nanoparticles or the potential risk. However, from various areas of research, such as occupational medicine, epidemiology and the science of aerosols there are indications that ultrafine particles (unintentionally released particles < 100 nm) can have negative effects on health. Undoubtedly, the toxicological findings on ultrafine particles only cover a small part of the effects that we have to expect from the chemical diversity of synthetic nanoparticles. Synthetic nanomaterials are not dealt with especially in the present legislation on chemicals. However, to ensure safety for companies and authorities, the applicability of the legislative framework has to be checked for nanomaterials. Early estimation and assessment of risks and checking on the "nanosuitability" of the legislative framework are thus crucial factors for safe, sustainable, successful use of nanotechnology.

In spring 2006, the Federal Office for the Environment (FOEN) and the Swiss Federal Office of Public Health (SFOPH) started a project to develop a "Risk Assessment and Risk Management for Synthetic Nanomaterials 2006–2009" action plan. In the context of the action plan, the principals for the assessment of the need for action are to be worked out in collaboration with a professional committee of experts, and concrete measures proposed. Unintentionally produced fine particles (e.g. those produced by road traffic) are not included in this report. The report was produced by a consortium of experts and it is the basis for the action plan. The plan should show what measures can enable synthetic nanomaterials to be dealt with safely. The basic report contains an

overview of current research work, dialogue platforms and regulatory approaches in Switzerland and other countries. Topics dealt with are the human toxicity and ecotoxicity of nanomaterials, occupational safety and occupational health, regulation and standardisation, the assessment of the consequences of technology and communication. Based on the information in this basic report, gaps in research and needs for research should be identified and recommendations should be worked out as a basis for the action plan and implementation plan.

Nanotechnology is an area that is developing rapidly. It is concerned with structures that are typically between 1 and 100 nm (1 nm = 10^{-9} m) in size. Nanotechnological applications and products make use of characteristic effects, which occur in the transition area between the atomic and the mesoscopic scale. This means that nanoscale materials can have different physico-chemical properties than microscale or macroscale materials. These new or altered properties can be used in a targeted way and open new possibilities in practice. The number of products and applications using nanomaterials is rapidly increasing.

Whereas the enormous innovation potential of nanotechnology was previously to the fore, in recent years, the possible risks of nanomaterials for health and the environment have increasingly been pointed out. The focus is particularly on applications and products using synthetic nanoparticles. Synthetic nanoparticles are produced for a specific purpose and have a defined chemical composition and size distribution. They are already in use in various products and applications. The nanoparticles used are in a more or less strongly bound form depending on the purpose for which they are to be used and the type of product. An important aspect of the discussion of the risk with synthetic nanoparticles centres on products and applications using unbound nanoparticles, where the release of synthetic nanoparticles is to be expected.

In principle, there are possibilities for improving most applications and products by the use of nanomaterials or nanoparticles. Some important areas of application are electronics and composite materials that are reinforced by deposited nanoparticles, and cosmetics, medicines and body-care products where nanoscale capsules improve the transport of the active ingredient. Another broad area of application is surface treatments e.g. products to clean or to seal textiles, wood and metal. In particular in the areas of body-care, medicines, cosmetics and textiles direct contact occurs with the nanoparticles or they may even be taken up. For body-care products and medicines, there is likely to be at least indirect input of particles into the environment via wastewater. Considering the basically uncertain risk situation, such applications close to the body have to be considered as potentially likely to lead to conflict.

The state of our knowledge about the risks of nanoparticles

Little data is available on the toxicology, release, environmental behaviour and safety of nanoparticles. Although a few studies have been carried out, not all of their results are meaningful, since many of these investigations were carried out using very high concentrations of particles, and with samples or reference materials that had not been accurately characterised.

In the literature it is often stressed that results for one nanoparticle cannot be generalised to other materials. This is mainly because the factors for classification have not yet been defined in a uniform way. Standardised tests for individual groups of nanoparticles and the use of recommended references would enable comparisons to be made between the different materials and studies. It is important to understand the physicochemical properties of nanoparticles if we are to avoid false positive and false negative results. These not only cause uncertainty for other researchers and the public, but they are detrimental to the general credibility of this area of research.

Health

For most nanoparticles it is not clear whether and how they are taken up in the body, distributed, metabolised, accumulated and secreted. Kinetic models can help in the estimation of realistic doses of particles in target organs that could be affected. Thus, the question can be resolved of which exposure paths are relevant for various nanoparticles and whether certain target organs can be excluded (for the moment), when setting the first priorities. In addition to particles themselves, their breakdown products also have to be considered.

The lungs are considered to be the most critical organs for taking up nanoparticles. They have an enormous exposed area, and inhaled and deposited nanoparticles can get into the bloodstream through the extremely thin air-blood-tissue barrier. Nanoparticles can penetrate lipid bi-membranes and get into organelles such as mitochondria and nuclei, which can cause oxidative stress or damage to DNA. Many studies with model nanoparticles using animals or cell cultures have shown inflammation reactions.

In addition to the dose and the elemental composition of the nanoparticles, factors such as their surface area, the function of the surface, tendency to aggregate, the form of the particles and their surface charge all play decisive roles in their distribution through the body, and their possible (genetic) toxicity.

In addition to the lungs, the skin provides a potential uptake surface. However, no studies have yet shown whether nanoparticles can get into the bloodstream through intact skin.

It seems that nanoparticles are secreted efficiently through the intestine. For small particles (< 100 nm) increased uptake through the intestinal wall has been observed in rats. Data on translocation between organs are based on different approaches, so they cannot yet be considered to have been confirmed. According to various studies surface-modified nanoparticles crossed the blood to brain barrier. It has not yet been experimentally tested whether the blood to testicle barrier or the placental barrier can also be crossed, but it is suspected that these things are possible, in view of the fact that the particles are in the range of nm.

Environment

At present, only a few studies have been carried out on the ecotoxicity and environmental behaviour of nanoparticles. So far, the effects on aquatic organisms have been examined, but frequently high concentrations of particles that are not environmentally relevant were used, and the test material was not sufficiently characterized.

There are not yet any reliable estimates of possible environmental inputs that could occur during the production, use and disposal of nanoparticles or products containing nanoparticles. In particular there is a lack of suitable methods to measure nanoparticles in the environment. Similarly, scarcely any studies have been carried on by-products and breakdown products of nanomaterials. The basic aspects of the behaviour of micrometre-range particles in the air or in aqueous solutions have been clearly described and they can be understood in terms of quantitative models. As far as possible, nanoparticles should be introduced into these existing models, or appropriate new models should be developed. Normally, nanoparticles in gases can be removed relatively simply by rapid agglomeration to bigger structures by diffusion filtration or depth filtration. In liquids this may be difficult under certain circumstances if there are stabilized dispersions. The effectiveness of breakdown in wastewater treatment works has barely been examined so far. Preliminary investigations show that the present treatment process may not be sufficient, but the literature is not all in agreement. So far, there are hardly any data about bioaccumulation and the possibility of the accumulation of nanoparticles in the food-chain. However, investigations show that nanoparticles can be taken up by organisms in the environment. We have to consider on one hand the storage of lipophilic nanoparticles in fatty tissues, and the resultant concentration in the food-chain, and on the other hand the accumulation of persistent nanoparticles in ecosystems and organisms if there are no pathways for their breakdown or excretion.

Dangers through physico-chemical properties

The specific physical and chemical properties that nanoparticles have compared with larger particles can present unexpected safety risks. The most important physico-chemical dangers are the risks of fire or explosion and of unexpectedly increased catalytic activity. So far, these dangers have been classified as relatively low for many synthetic nanoparticles, as nanoparticles are produced in relatively small quantities. However, this is likely to change rapidly in the future.

In clouds of dust, the size of the particles and the related specific surface area are critical for the explosion characteristics. Basically, the smaller the particles are, the greater the risk of a dust explosion will be. However, the physico-chemical properties of many particles are still only partly understood, so it is difficult to estimate these risks.

Occupational safety and health

At the workplace, according to our present knowledge, exposure to nanoparticles occurs primarily through handling nanoparticles that were produced for a specific purpose, and through working practices that generate nanoparticles as by-products. Although there is not yet an overview of the types, quantities, or forms of application of nanoparticles, as by-products they are considered to be the most widespread source of exposure in the workplace.

There have not yet been any epidemiological studies on the health risks of modern synthetic nanoparticles. Concentrations at the workplace have barely been estimated so far, and it is not clear whether the current models for local and temporal concentration profiles apply in the case of new nanoparticles. At present apart from a convention between a few European institutes of occupational safety there are no international standards on methods for measuring nanoparticles and for estimating exposure to them.

ISO has created a committee on nanotechnology[4], in order to produce norms based on scientific knowledge in the areas of health, safety and the environment. Until norms in this area become available, exchanges of experience between measuring engineers and scientists will be particularly important.

The known strategies to reduce exposure in the workplace also apply to dealing with nanoparticles. Appropriate protection measures are evaluated and defined by specialists in occupational health and safety as part of an assessment of risks throughout the company. The principle applies that new substances with unknown properties should be treated as potentially dangerous. Organisational protection measures should primarily be taken, supported by technical protection measures and the substitution of preparations that form powders.

Personal protection equipment can occasionally supplement these measures, but it should not replace them. Current recommendations are firmly based on analogy with handling larger particles. But it is still highly uncertainty how efficient technical protection systems and personal protection equipment can be, especially for new nanoparticles with a very low tendency to agglomerate.

Therefore, there is still a lack of the scientific and methodological basis to carry out a conclusive risk assessment of nanoparticles. Several large-scale programmes are running or being planned in Switzerland and at the international level. These will deal with different aspects of risk research on nanoparticles. In this context, it is important to have a coordinated, strategic approach to deal with the most important issues.

Regulation and standardisation

Basically it can be considered that in Switzerland, at the level of laws, the prerequisites are in place to regulate nanoparticles. It will be necessary to adapt at the level of ordinances, and in the area of norms and guidelines.

The Swiss regulations employ various tools such as authorisation, self-supervision, positive and negative lists, the obligation to provide information and limits for emissions. The approval of nanomaterials in the area of drugs is well regulated, since for any new approval, extensive safety investigations must be carried out on animals and on human beings, during which the kinetics also have to be shown. However, for other areas the question basically arises of whether the framework is adequate for a procedure of self-supervision to ensure a level of protection of humans and of the environment comparable with that obtainable through an authorisation procedure. In certain areas, lists of prohibitions or restrictions on use provide the possibility of banning certain dangerous nanoparticles.

The supply of safety information (safety data sheets) to companies by manufactures and to consumers (declaration of nanoparticles) provides the basis for safe handling and correct disposal of nanoparticles. In addition, declarations of nanoparticles on products can enable consumers to decide whether to buy and use them.

[4] ISO Technical Committee (TC) 229 «Nanotechnologies».

Synthetic nanoparticles used in biocides, pesticides, drugs, etc. are subject to the appropriate legislative regulations. However, in certain areas of regulation there are no specific requirements for particles. There are therefore considerable legislative uncertainties, which can lead to possible risks for health and for the environment not being recognised, and the risks could be minimised by the application of suitable measures. On the other hand this legislative uncertainty can itself have a negative effect on innovation, since businesses are hardly interested in investing in the development of nanotechnologies or products containing nanoparticles, as long as it cannot be foreseen what legislative requirements have to be met, and what restrictions might be imposed on the manufacturer.

At the international level it is worth mentioning above all the EU action plan and the activities of the OECD, the EMEA (European Agency for the Evaluation of Medicinal Products) and the FDA (Food and Drug Administration), which are important for Switzerland. At the national level intensive discussions are being carried out – in particular in the USA and in England – about the validity and applicability of legislative regulations. The regulations must be able to give clear definitions allowing nanomaterials to be registered and classified as "new" or "existing" substances. At the same time the area of validity of the legislative bases must be checked for new possible protection areas involving nanomaterials. The regulations must contain clear threshold values with exemptions and give tolerable pollution levels. As an example, new parameters such as surface / volume ratios must be considered instead of data on mass and threshold values. In view of the very low amounts of nanoparticles produced and their special properties, it seems that having a quantity exclusion criterion (e.g. < 1 tonne per year per manufacturer) would not make sense.

A monitoring system or early warning system should also be developed to further develop and adapt the existing regulations. This could also include the obligation to notify new information on the risks presented by nanoparticles.

Several institutions are active in the area of standardisation, at the international and national levels. At the European and international levels CEN / ISO and the OECD are the organisations in charge, and they have working groups in the area of standardising nanotechnology. The defined objectives are mainly concerned with terminology and nomenclature, metrology, methodology, and the specification of reference materials in the area of health, the environment and safety.

Assessment of the consequences of technology and communication

Nanotechnology will most probably realise its potential and achieve a high level of acceptance if possible effects on health, the environment and society are anticipated as early as possible. This information can also protect society and the economy from making wrong investments and the consequent costs. Technology assessment should help to minimise possible risks during the earliest possible phases of technology development.

The main objective of technology assessment (TA) is to supply decision-makers in business and political circles with a solid basis concerning relevant technical areas.

New controversial technologies are studied as broadly and independently as possible, regarding their societal, ecological, health, economic, legal, social and ethical effects. The parliament and the Federal Council have put the centre for technology assessment (TA-SWISS) in charge of examining the opportunities and risks of new technologies. TA-SWISS fulfils this mandate by carrying out expert studies and through participative procedures (with the population).

There are TA projects on nanotechnologies, which are currently running or have been finished, within Europe and in English-speaking countries. To develop the Swiss action plan, it will be most important to consider the results of the publifocus on "nanotechnologies and their importance for health and the environment" (TA-SWISS) and the results of the consumer conference in Germany (BfR, UfU IÖW). The objective of the TA-SWISS publifocus project, which finished in 2006, was to obtain participants' initial opinions of the conditions for acceptance of nanotechnologies, their wishes, misgivings and open questions. One has to show how the use of nanomaterials and the possible social and economic effects of these new technologies are perceived by so-called laypersons who have been informed about the topic.

The publifocus discussions have shown that only a few people take a deep critical look at nanotechnologies, and that the general level of knowledge is rather low. Therefore, it is necessary to provide further information and to have a debate. However, the participants who received the "Nano! Nanu?" information brochure supplied by TA-SWISS asked a number of tricky questions. It can be seen that at present there are no firm positions on nanotechnologies. The misgivings are mainly in the areas of food, where there is a demand for the requirement to declare or for regulations. The biggest opportunities are considered to be in medicine and for the environment.

General information for and discussion with the public are very important. Dialogue between and with stakeholders, and the inclusion of those members of the public who have an interest must be included as part of technology development. Communication between experts and the public is often emphasised. The involvement of citizens can be through well-know participation methods such as consensus conferences and focus groups, which must deal in a qualitative way with the questions, fears and hopes of citizens.

Fairs open to the public, such as NanoPubli also create great interest and they offer researchers, industry and the authorities the opportunity to exchange information and to talk to citizens. As regards dialogue and participation, in each case it is important to distinguish whether it is a matter of advertising (achieving acceptance), providing balanced information, dialogue or concrete participation. Different methods have to be chosen depending on the level, and the basic rules of participation have to be applied carefully.

The authorities in Switzerland have been involved in discussing the risks in nanotechnology since spring 2005. In addition to the webpages of the Federal Office for the Environment and of the Swiss Federal Office of Public Health, the authorities have taken over the patronage of the annual "NanoRegulation" conference, which takes place in

parallel with NanoPubli in St. Gallen and goes into depth about the regulation of nanotechnology.

In connection with communication on the risks of technology it is important to realise that the debate about opportunities and risks mostly takes place at isolated levels, or about individual topics (scientific, psychological or social sciences) and that this prevents consideration of the risks in an integrated way. Modern means of communication mainly favour one-sided information for users, instead of mutual two-way communication. The establishment of an interdisciplinary communication platform covering the various levels would solve many of these problems.

Assessment of the dangers and risks presented by nanomaterials

Overall it emerges that there is not yet a sufficient scientific and methodological basis for a conclusive risk assessment and regulation of synthetic nanoparticles. In order to set priorities for research on risk and for regulation, and if necessary to introduce risk reduction measures, it is necessary to have estimates of risk based on physico-chemical properties, on toxicological data and on data related to exposure (risk framework). Thus the restricted capacities in risk research can be classified as well as possible, and regulations can be discussed in relation to the relevant categories of particles.

Basically the question arises of whether the assessment approach used for conventional chemicals can also be applied to nanoparticles. For the assessment of danger, the toxicological and ecotoxicological properties are tested, as are the breakdown and the potential to accumulate. Finally, chemicals are classified based on an appropriate set of criteria. All approaches are to a certain extent based on analogy with non-nanomaterials and on toxicological and ecological criteria, which would have to be imposed as minimum requirements for all particles. Based on the lack of basic data and of test standards, such approaches can hardly be used in a meaningful way. In addition, it first has to be shown what differentiation criteria are meaningful and relevant for nanoparticles.

In parallel with that, future projects are being discussed and set up, so that new methods can be developed to test nanomaterials for usability and as far as possible to standardise them.

Recommendations for action

This basic report is the starting point for formulating recommendations for action. In the recommendations for action the areas mentioned in this report should be taken into account though concrete proposals for projects, participation and regulation. In this process, through several steps of work and consultation with the project team, the accompanying group and the pool of experts, 26 recommendations for action should be developed on the following topics: the promotion of research, standardisation, voluntary measures taken by trade and industry, the establishment of legislation, communication and technology assessment. In all this, the various points of view have to come across.