Pavel Danihelka - Martie Van Tongeren - Lucie Sikorova - Tana Brzicova *

NANOTECHNOLOGY SAFETY AS A NEW CHALLENGE FOR OCCUPATIONAL HEALTH AND SAFETY

Nanotechnology as a key enabling technology offers great potential for economy and society, but may also bring new threats to workers´ health due to new aspects of hazard, ways of transport, nanoparticles transformation and accumulation. Even if principal paradigms of classical toxicology are probably applicable to nanostructured materials, important gaps still exist. One of the most important topics to be developed is the occupational exposure assessment with special attention paid to the exposure measurement and exposure scenarios building. This article brings insight into the state-of-the-art of the nanotechnology safety and analyses key needs in this new safety domain.

Keywords: *Nanomaterials, nanotechnologies, risk management, occupational health and safety.*

1. Introduction

Nanotechnology is a tremendously developing branch of modern science and technology. Despite the fact that materials, understood today as nanotechnology-related, have been used in certain domains of ceramics, pigments and metallurgy since ancient times, the concept of nanotechnology was introduced in 1959 by Nobel physicist Richard Feynman [1]. The real boom of nanotechnologies started in this millennium, when their importance was recognized by industrial and societal leaders. The development of nanotechnologies in USA was promoted by the vision of US President Bill Clinton, who, on January 21, 2000, delivered a speech at the California Institute of Technology: "Just imagine, materials with 10 times the strength of steel and only a fraction of the weight; shrinking all the information at the Library of Congress into a device the size of a sugar cube; detecting cancerous tumours that are only a few cells in size. Some of our research goals will take 20 or more years to achieve. But that is why there is such a critical role for the Federal Government." In parallel, similar nanotechnology initiatives were launched in EU and Eastern Asia countries. Over the last fifteen years, nanotechnology has evolved from a domain of research and investment into the fully developed industrial branch which is regarded as the Key Enabling Technology (KET) in the EU [2]. Sales forecasts [3] for products incorporating nanotechnology range from $1 trillion to $3 trillion by 2015. As a direct consequence of such a tremendous development, nanomaterials have moved from research laboratories to industry and commercial products. Today, 300 to 400 thousands of workers are involved in the EU nanotechnology production sphere [4] and many times more in processing of materials involving nanostructured objects. Soon, if not already, each and every inhabitant of developed countries will be exposed to some types of synthetically and intentionally produced nanomaterials and it is expectable that the most exposed part of population will be workers in related industrial branches. Besides novel technological properties and functionalities, some nanomaterials exhibit new hazardous properties.

The need for sound safety management of nanotechnologies arises both from health & environmental concerns and weak trust in implemented safety measures, as expressed by the US President's Council of Advisors on Science and Technology [5]: "By creating jobs, stimulating economic growth, and providing solutions to some of the toughest challenges facing humankind, nanotechnology has great potential to change the world for the better. Yet realizing this potential may be thwarted if the safety of new materials and products arising from nanotechnology is not addressed up front. In the absence of sound science on the safe use of nanomaterials and of technologies and products containing them, the chance of unintentionally harming people and the environment increases. At the same time, uncertainty and speculation about potential risks threaten to undermine consumer and business confidence." Practically identical conclusions are presented in EU documents, e.g. in the Second Regulatory

* [1]Pavel Danihelka, [2]Martie Van Tongeren, [3]Lucie Sikorova, [1]Tana Brzicova
[1]Laboratory of Risk Research and Management, Faculty of Safety Engineering, VSB-TU Ostrava, Czech Republic
[2]Institute of Occupational Medicine, Edinburgh, United Kingdom
[3]Department of Occupational and Process Safety, Faculty of Safety Engineering, VSB-TU Ostrava, Czech Republic
E-mail: pavel.danihelka@vsb.cz

Review on Nanomaterials [6] or in the research strategy on nanotechnology safety prepared by the NanoSafety Cluster [7]. "Nanosafety" is today commonly used as an abbreviation for nanotechnology safety. In addition, nanotechnology safety is widely involved in the EUFP7 and Horizon 2020 research programs. Without any doubt, nanotechnology safety is one of the greatest challenges of today science and regulation and among various fields of nanosafety the occupational safety will play the pivotal role.

2. Nanotechnologies and nanomaterials

Nanotechnology is the understanding and control of matter with at least one dimension between approximately 1 and 100 nanometres where unique behaviours enabling novel functionalities and applications emerge. It should be mentioned that the range between 1 and 100 nm, known as the nanoscale, is at least partly arbitrary, based on a symbolic value of planet Earth (and meter dimension derived from it) and decimal numeral system – as there is no step change in behaviour exactly at these material sizes. Moreover some distinguished nanomaterials, such as fullerenes or certain nanofibres, may not fit this size-based definition. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modelling, and manipulating, as well as making use of matter at this dimension scale. Unusual physical, chemical, and biological properties can emerge in materials at the nanoscale, being driven by quantum mechanics, high surface/volume ratio and self-assembling behaviour. These properties may significantly differ from the properties of bulk materials as well as single atoms or molecules.

There are many well-known examples of nanotechnology outputs: Electronics, in which existing semiconductor industry is based on extensive adoption of nanotechnology to date. Current integrated circuits are based on components and structural features in the nanometre range. Modern energy is more and more using nanotechnologies in batteries, solar panels, blades of windmills and other applications. Crucial domain of nanotechnology involves catalysts and catalytic processes that depend on specific nanoscale structures to steer chemical reactions. Nanoparticulate formulations of conventional drugs are being used in medical treatment of various diseases including cancer, as well as in diagnostics. Nanomaterials are to a growing extent employed in environmental engineering and environment protection. Nanoscale structures and nanoparticles are increasingly used as ingredients in cosmetics, particularly in sunscreens, and in food products. It is estimated that there already exist thousands of everyday commercial products that rely on nanoscale materials and processes. During various production processes, nanomaterials are synthetised, stored, transported, handled, transformed, incorporated in various structures and as a consequence, workers are potentially exposed to them. Because of the fact that not only technical properties, but also behaviour in working environment and interactions with biological systems may significantly differ between bulk material and nanomaterial, a need of nano-specific occupational health and safety(OHS) issues has appeared. Its importance is confirmed by many institutions such as the European Commission (EC), Organisation for Economic Co-operation and Development (OECD), International Labour Organization (ILO), National Institute for Occupational Safety and Health (NIOSH) and World Health Organization (WHO). At national level in the Czech Republic, nanotechnology-related occupational health and safety (nano-OHS) has been declared as one of the priorities by the Ministry of Labour and Social Affairs. Despite the huge effort and much progress in the nanosafety, important gaps still exist and the specific "nano-OHS management" is not yet in the state of being fully consolidated. Principal gaps in the OHS management of nanomaterials and challenges arising from this situation are described in the following chapters.

3. Nanomaterial-related OHS management

3.1. General remarks

Nanomaterial-related occupational health and safety management is one of the specific aspects of OHS management and as such it should respect general rules of safety management and OHS principles. It means that rules, described in the OHSAS 18000 or in the ISO 31000 as standards for OHS management and risk management systems, are appropriate guidelines also for nanomaterials. From a general point of view, we can distinguish two different fields of nanomaterial hazard, similarly as for "classical" chemical substances: physical and biological ones.

Physical hazard is related to the large surface area of nanomaterials and high ratio between surface and volume of materials. This is why some authorities accept high specific surface area (namely, a specific surface per unit volume greater than 60 m^2/cm^3) as one of the criterions of nanomaterial definition. This phenomenon increases the reactivity and sorption capacity and may lead to effects such as pyrophoric behaviour, formation of explosive aerosols or self-ignition. Fatal accidents with ultra-fine metallic iron dust have already been reported by the US Chemical Safety Board [8]. The European standards body, CEN (Comité Européan de Normalisation) involved the topics of specific flammability and explosiveness of nanomaterials in the mandate M 461 of CEN/ 352 "Nanotechnologies". Nevertheless, it is not expected that physical hazard of nanomaterials will bring principally new or breaking safety situations. Thus, renewed measurement protocols applied together with already existing rules will be probably sufficient to assure high level of occupational safety.

More complicated situation appears in the domain of biological hazard. Nanomaterials are developed for their new and specific functionalities, however, these novelties may bring new situations in the interactions between nanomaterials and living organisms, as well as new behaviour in the environment, new ways of accumulation, transformation and transport. This is why several nanotechnology risk oriented projects have been launched across the world. As mentioned in the overview done by the European NanoSafety Cluster [9], more than thirty projects focused on nanomaterial safety have been financed within the FP7. The importance of nanosafety research is so high that special type of project was designed. This project with acronym NANoREG (see www.nanoreg.eu) uses bottom-up approach and contrary to the majority of research projects, focused on answering scientific questions posed by researchers, its main goal is to bring scientific answers to questions raised by regulators.

There is a prevailing opinion across the European society, expressed in the official position of the European Commission [6] that despite the specificity of nanomaterials it is not necessary to prepare specific nanomaterial-oriented safety legislation. A more efficient and convenient way is to adapt existing chemical legislation to nanomaterials. The process of adaptation has already started in the EU and specific affix "nano-" can be used for nanomaterials. Till February 2012, seven substance registrations and 18 CLP notifications had selected "nanomaterial" as the form of the substance in voluntary fields [6]. In February 2013, European Chemical Agency (ECHA) released the IUCLID User Manual "Nanomaterials in IUCLID 5" which includes instructions on how registrants can explicitly report when a nanoform of substances are used in (experimental) studies. This will help registrants to prepare or to update registration dossiers for substances that are nanomaterials or include nanoforms. The manual also includes references and links to recently updated guidance for nanomaterials published on the ECHA website and links to recent reports from projects, such as the REACH Implementation Projects on Nanomaterials (RIP-oNs) and the OECD Working Party on Manufactured Nanomaterials (WPMN). Recently, in October 2014, ECHA organized the Topical Scientific Workshop Regulatory Challenges in Risk Assessment of Nanomaterials where OHS concern was one of the key priorities. The workshop participants concluded that despite considerable progress, important gaps still exist in nanosafety knowledge and practice.

3.2. Nanomaterials and OHS management as a multi-stakeholder process

In principle, safety management of nanomaterials is composed of steps analogous to those of the "classical" substances safety management and based on principles generally used in safety management process, as described e.g. in [10]. Even if there is no need to construct principally a new scheme, a lot of research and regulatory work should be done to reach a fully working OHS system for nanomaterials.

The basic scheme of the nanotechnology-related safety management process is presented in Fig. 1.

The specificity of nanosafety is linked to the fact that most steps in the safety management process are still accompanied by high degree of uncertainty, partial or even missing knowledge

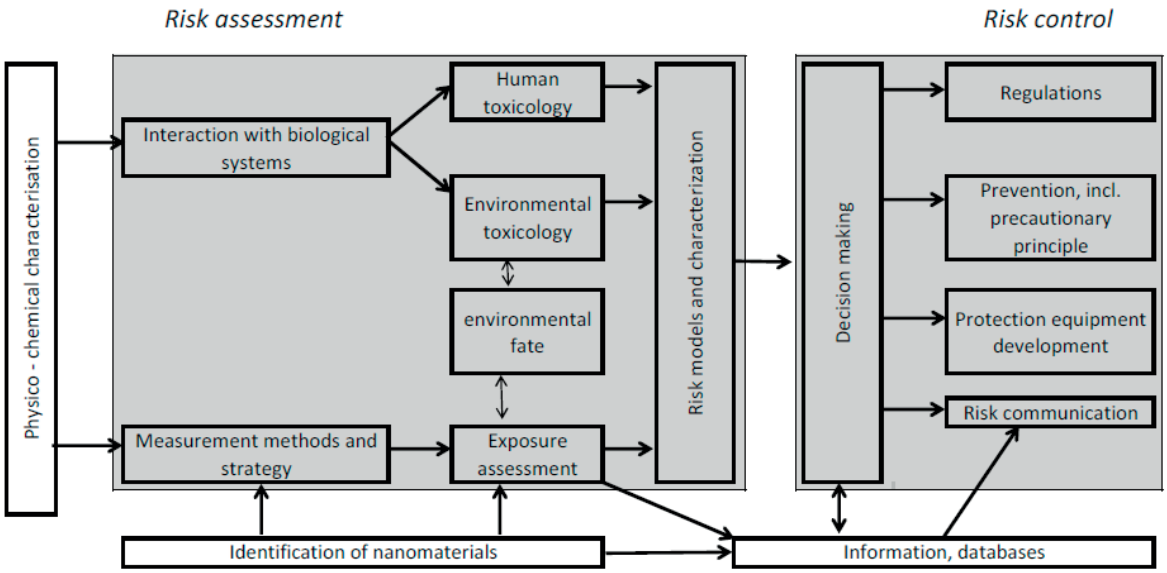

Fig. 1 Process of nanomaterials risk management

and the absence of unambiguous procedures and decision-making tools. Moreover, the safety management process often suffers from limited communication among specialists in individual steps of the management process. Experts tend to concentrate more on the deeper and narrow parts of problems than on the overall process of sound risk management, including searching for general views and cooperation across disciplines. Fortunately, many research projects [9] address this problem and intend to apply holistic approach to nanomaterial safety management. As the most exposed part of population are workers, especially with regard to the newly synthetically produced (so called "engineered") nanomaterials, occupational health and safety should be addressed at first.

Some of gaps related to nano-OHS are, together with the state-of-the-art of the respective discipline, described in following paragraphs.

3.3. Definition of nanomaterials, their identification and characterisation

Occupational health and safety as a subject of regulation is based on a good definition of what has to be monitored, controlled and regulated; then the clear, unambiguous and comprehensible definition of nanomaterial should be agreed upon. The other demand is the possibility to measure all definition parameters by accessible and technically and economically viable methods. The situation is complicated by the fact that at least 8 different institutions (EC, CEN, ISO, SCENIHR - Scientific Committee on Emerging and Newly Identified Health Risks, American Chemistry Council, ICCR - International Cooperation on Cosmetic Regulation, ICCA - International Council of Chemical Associations and German Chemistry Association) and 7 states (Australia, China, France, USA, South Korea, Switzerland and Taiwan) have issued their own definitions of nanomaterial which are rather far from being identical. Moreover, at least four EU regulatory acts use the definition of nanomaterial different from EC recommendation (EU Cosmetic Products Regulation No 1223/2009, Food Information to Consumer Regulation No 1169/2011, Biocides Regulation No 528/2012 and Medical Devices Regulation, last amendment 2007/47/EC). Occupational health and safety regulation does not use specific definition and the EC one, applied by the REACH regulation, has been adopted. Several parameters are used to define nanomaterials and the only one, where consensus was more or less found, is the external size range between 1 and 100 nm. Paradoxically, this range is immediately amended by notice that fullerenes, graphene flakes and single walled carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials as well [11]. The lower size limit of nanoparticles, 1 nm, brings another complication which arises from the fact that most of measuring techniques are not working well with particles below about 5 nm. In scientific literature covering the topic of nanomaterial toxicity, the size of particles over 100 nm is frequently exceeded and SCENIHR recommends in its report [12] to use tiered approach covering the whole nanoscale 1 – 999 nm in three tiers. Moreover, also material which has the surface/volume ratio over 60 m^2/cm^3 is considered as "nano", which corresponds to the hypothetic division of compact mass to cubes smaller than 100 nm.

Generally, only few nanomaterials are homogenous in size (mono-dispersed) and the question arises what portion of material in the size range 1-100 nm makes the mixture to be classified as nanomaterial. Here, the opinions vary in both metric and value. Weight (mass) or number metric is used. When weight metric is applied to describe a size distribution of particles in a material, 10% of nanoparticles is usually the limit but the applicability to the toxicity characterisation is limited. Number based distribution thresholds vary from 0.15% proposed by SCENHIR through 1% (Switzerland) to 50% recommended by the EC. The fact is that if aggregates and agglomerates are included, several materials widely used in traditional industries, e.g. paints, pigments or cements will be classified as nanomaterials.

Other parameters, such as solubility, novel properties, agglomeration and aggregation or the fact, whether the material is produced intentionally or accidentally, serve for identification of nanomaterials. Nevertheless, the approaches are different for different subjects. It is important to point out that nanomaterials *per se* are not new in our world; they occur in nature, in many industrial products not supposed to be nanotechnologies and as by-products of combustion, tarnishing and friction processes. From the OHS point of view, the most interesting are engineered nanomaterials whose production is growing exponentially. As they are new in a working environment and exhibit new functionalities; they may also display new properties in the safety domain.

The variability of nanomaterial definitions, even in valid regulation, brings one important point: the need to be aware of the definition which relates to the situation under study. Moreover, resulting conclusion is that the definition is not clear and stabilized yet.

3.4. Hazard characterisation

Principal OHS-related hazard of nanomaterials is toxicity. Nano-toxicity differs from toxicity of substances present in a solution or in a bulk form by certain aspects:

- Nanoparticles are transported in a form of particles in the environment and in organisms, and as such they may exhibit specific types of mobility. Nanoparticles may pass biological barriers including cell membranes, enter the cells as well as accumulate in certain organs.
- Nanoparticles of various sizes may exhibit different toxicological effects. For example, for titanium dioxide

nanoparticles it has been shown that particles in the size range from 20 to 30 nm are considerably more toxic when it comes to respiratory health effects than their microparticle (>100 nm) counterpart [13].

- Toxicity of nanomaterials is substantially influenced by their surface, including the "corona" of molecules formed in biological fluids. Corona determines the biological activity and fate of the nanomaterials. Resulting situation is that during the life cycle of nanoparticles, the toxicity may change significantly and that surface modification (coating) of nanoparticles may influence resulting toxicity.
- Typical behaviour of nanomaterials is self-assembling which leads to agglomeration, deposition and formation of secondary structures. This brings principal problem to the toxicity testing - to reach reproducible results, tests with well-dispersed pristine nanoparticles are preferred but their effects may significantly differ from real exposure situations.
- Another effect probably linked to the self-assembling and agglomeration is that in many cases, dose-effect dependence shows local maximum, i.e. in certain region increasing dose leads to decreasing effect which makes risk assessment and modelling tricky.
- The proper dose metric is uncertain. As WHO Workshop on Nanotechnology and Human Health [14] has concluded, it is evident that the toxicity of nanoparticles is not only mass-dependent but might also be dependent on physical and chemical properties that are not routinely considered in today's toxicity studies. Some studies found that particle number was the best dose metric; in others, toxicity was related to the surface area or to the number of functional groups on the surface of nanoparticles.
- Besides the "chemical" effect of nanomaterial caused by dissolved species (e.g. Ag^+ ions in the case of nanosilver), two typical interlinked toxic effects of nanoparticles are observed: inflammation (caused typically by oxidative stress) and genotoxicity. Some nanoparticles as single-wall nanotubes are suspicious to be potential carcinogens.

3.5. Exposure

As risk in toxicology is composed of hazard and exposure part, the control of exposure is considered a basic tool of occupational health and safety. Nevertheless, we face several problems when dealing with exposure assessment of nanomaterials. First of all, the metric is not clear; without knowing which dose metric is the most relevant to express toxicity hazard (number or mass concentration, surface area, reactivity of the surface, etc.), it is difficult to assess the exposure. Techniques and instrumentation for field measurements are rather complicated and expensive. Simple, low-cost and robust measurement techniques need to be developed. Moreover, it is not easy to distinguish between background (natural, incidental) nanoparticles and their engineered counterparts. Under the circumstances, we need to work with typical situations and to prepare the library of exposure scenarios which will be harmonized across countries and will enable sharing of experience and transfer of data and knowledge. Such libraries are being prepared in various research projects (e.g. NANEX, MARINA, GUIDEnano, SUN) and thus, the harmonisation emerges as the principal problem.

For exposure assessment, an inventory of production and use of nanomaterials is necessary. Some countries, e.g. France, introduced the specific legislation for reporting of nanomaterials. Nevertheless, in most countries, no legislation demanding inventories of nanomaterials and exposure exists yet and generally, industry is naturally unwilling to release information unless being obliged by law.

3.6. Risk assessment and modelling

As has been shown above, both principal parts of risk assessment, i.e. hazard identification and exposure assessment, are not yet equipped with necessary instruments and important gaps in knowledge and tools lead to the fact that we have to work with the high degree of uncertainty. Nevertheless, the risk assessment rules are generally valid in nanoscience and at least basic risk assessment can be done in individual cases.

On the other hand, the huge and continuously growing number of existing nanomaterials and the extremely high number of potential combinations of various nanomaterial properties make the case-by-case risk assessment of nanomaterials so demanding that impracticable, unless the key specific properties driving the critical outcome of interest are well known [14]. For instance, it has been estimated that there are up to 50,000 potential combinations of single-walled carbon nanotubes, depending on their structure, dimensions, manufacturing processes and surface coatings. Furthermore, there are many other nanomaterials, such as quantum dots, fullerenes, metal and metal oxide nanoparticles, resulting in practically countless types of nanomaterials, which may pose different risks.

Contemporary state-of-the-art of the nanomaterial risk assessment and modelling is that we still do not have verified models and input data are accompanied by significant uncertainty. Rather than risk assessment, we can provide risk characterisation, which has to be supplemented by risk communication.

3.7. Risk control, decision making and regulation

The high degree of uncertainty and existing gaps in knowledge require the use of rather soft regulation instruments than simple limits. For sound regulation, relatively high degree of certainty and evidence based decision making are crucial. This is why we

cannot expect the consolidated nanomaterial-specific regulation in occupational health and safety sooner than after at least 10 years. Meanwhile, OHS concerns should be solved by applying voluntary tools and the precautionary principle.

A useful tool, applicable to the nano-specific OHS, is the control banding. This technique, which fitted better for voluntary than for regulatory purposes, has been already standardized by ISO/TS 12901-2 [15]. This standard focuses on inhalation control of the risks associated with occupational exposures to nanomaterials, even if knowledge regarding their toxicity and quantitative exposure estimations is limited or lacking.

The uncertainty in nanosafety brings the necessity to use precautionary principle, well-known from environmental issues. Switzerland was the first country introducing the precautionary principle to the nanosafety in 2008 [16], in the form of the precautionary matrix applicable for synthetic nanomaterials.

Generally, the risk control in nanosafety is developing dynamically and we can expect that it will become the inherent part of the Responsible Care, the voluntary initiative of the industry.

4. Conclusions

Nanotechnologies bring new opportunities and benefits in countless fields of science and technology. On the other hand they also introduce new challenges in OHS. The science, regulatory bodies and whole society have made remarkable progress in nanomaterial-specific part of OHS, but important gaps in knowledge still exist and new techniques have to be developed. The general principles of chemical safety are still applicable, even if certain paradigms are probably to be modified. The nanotechnology safety assurance demands parallel development of regulation and use of "soft" tools such as the precautionary principle or control banding.

Acknowledgement

This presentation was supported by the Czech Ministry of Education, Youth and Sports (COST.CZ, LD14041 NANOEXPO) and by the COST Action TD 1204 Modelling Nanomaterial Toxicity (MODENA).

References

[1] FENMAN, R.P.: *There is a Plenty of Room at a Bottom*, http://www.pa.msu.edu/~yang/RFeynman_plentySpace.pdf, cit. 18.11.2014
[2] http://ec.europa.eu/enterprise/sectors/ict/key_technologies/kets_high_level_group_en.htm, cit. 18.11.2014[3] FP7 NMP Work Programme 2013, European Commission C(2012) 4536 of 09 July 2012, p. 15
[4] http://ec.europa.eu/enterprise/sectors/ict/files/kets/hlg_report_final_en.pdf, s.13, cit. 18.11.2014
[5] Report to the President and Congress on the Third Assessment of the National Nanotechnology Initiative, US President's Council of Advisors on Science and Technology, Washington 2010
[6] *Second Regulatory Review on Nanomaterials*, COM (2012) 572 final, Brussels, 3.10.2012
[7] http://www.nanosafetycluster.eu/news/83/66/Nanosafety-in-Europe-2015–2025.html, cit. 18.11.2014
[8] http://www.csb.gov/csb-releases-final-investigation-report-on-three-accidents-at-the-hoeganaes-iron-powder-facility-in-gallatin-tennessee/, cit. 18.11.2014
[9] *Compendium of Projects in the European NanoSafety Cluster*, ed. by M. Riediker and G. Katalagarianakis, Institute for Work and Health, Lausanne, Switzerland 2012, available at http://www.nanosafetycluster.eu/uploads/files/pdf/2014_NSC_Compendium.pdf
[10] DANIHELKA, P., POLEDNAK, P.: Risk analysis - General approach. *Communications - Scientific Letters of the University of Zilina*, 10 (1), pp. 20-23, 2008
[11] RAUSCHER, H., ROEBBEN,G.(editors): *Towards a Review of the EC Recommendation for a Definition of the Term "Nanomaterial"*, Science and Policy Report by the Joint Research Centre of the European Commission, European Union 2014, ISBN 978-92-79-36600-0, doi:10.2788/36237
[12] Scientific Committee on Emerging and Newly Identified Health Risks, *Scientific Basis for the Definition of the Term "Nanomaterial"*, http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_032.pdf, 2010
[13] VOGEL, U.: *Pulmonary and Reproductive Effects of Nanoparticles.* WHO Workshop on Nanotechnology and Human Health: Scientific Evidence and Risk Governance. Bonn, December 2012.
[14] *Nanotechnology and Human Health: Scientific Evidence and Risk Governance*. Report of the WHO expert meeting, December 2012, Bonn: Copenhagen: WHO Regional Office for Europe, 2013
[15] ISO/TS 12901-2: 2014, Nanotechnologies - Occupational Risk Management Applied to Engineered Nanomaterials - Part 2: Use of the Control Banding Approach
[16] HOCK, J., HOFMANN, H., KRUG, H., LORENZ, C., LIMBACH, L., NOWACK, B., RIEDIKER, M., SCHIRMER, K., SOM, C., STARK, W., STUDER, C., VON GOTZ, N., WENGERT, S., WICK, P.: *Precautionary Matrix for Synthetic Nanomaterials*. Federal Office for Public Health and Federal Office for the Environment, Berne 2008.