NANOREG HIGHLIGHTS: CURRENT ACHIEVEMENTS AND FURTHER CHALLENGES IN RISK ASSESSMENT AND RISK MANAGEMENT OF MANUFACTURED NANOMATERIALS

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Abstract

The immense beneficial potential of manufactured nanomaterials (MNM) may be threatened by limits of MNM environmental, health and safety (EHS) aspects understanding. Despite the extensive research in the field of nanotoxicology and exposure to MNM, comprehensive knowledge for regulation is still missing. NANoREG is the first FP7 project looking for answers needed by authorities on EHS by linking them to a scientific evaluation of data and test methods. It aims to provide a tool box of relevant instruments for reasonable risk assessment and management of MNM.

There is already number of achievements behind NANoREG project. The questions and needs of regulatory relevance have been identified and grouped within three knowledge gaps: hazard related characteristics of MNM, standardized methods to determine them, nano-specific risk assessment approaches. Nevertheless, standard operation procedures for some MNM characterization, toxicity testing and exposure measurements were developed. Critical exposure scenarios for MNM within the key value chains were identified. Toxicity testing focused on long-term inhalation toxicity, genotoxicity and immunotoxicity have been carried out. The Czech Republic actively participates at in vitro screening methodology development to evaluate toxicity by inhalation, at harmonization of genotoxicity protocols, exposure measurements and modelling and development of decision tree for risk assessment.

Despite the progress achieved since now, there are still many challenges regarding safety aspects of NMs which have to be addressed in further research

Keywords: Manufactured nanomaterials, risk assessment, risk management, regulation

1. INTRODUCTION

Nanotechnology, which is in EU strategies [1] considered to be KET - “key enabling technology” brings exceptional potential to economy growth and society benefits, but as any other development jump may bring also new threats. In the case of nanotechnology, the question is possible impact to human health and environment due to new aspects of hazard, new ways of transport, caused and accompanied by possibilities of nanoparticles self-assembling behaviour, transformation and accumulation. Even if materials, understood today as engineered nanomaterials, had been used for centuries in certain industrial domains as pigments, ceramics and metallurgy, the concept of nanotechnology was introduced in 1959 by Richard Feynman [2] and the real boom of nanotechnologies started in this millennium, when its importance was recognized by industrial and societal leaders. The consequence of such a tremendous development is that nanomaterials have moved from R&D laboratories to industrial applications and to products. Today, 300 to 400 thousands of workers are involved in EU nanotechnology production sphere [3] and multiple numbers in processing of material involving nanostructured objects. Soon, every consumer will be exposed to certain types of intentionally produced nanomaterials. And this is why the question arises, whether nanomaterials exhibit new hazards and provoke new risks for human health and environment.

These considerations comprise both health and environment concerns as well as possible societal and economic impact of undesirable neglecting, as expressed by the US President’s Council of Advisors on

Science and Technology [4]: “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 European Union documents, e.g. in the Second Regulatory Review on Nanomaterials [5] or in the research strategy on nanotechnology safety prepared by Nanosafety Cluster [6], and nanotechnology safety is widely involved in research program of EU FP7 and Horizon 2020.

The goal of this contribution is to provide an analysis of the state-of-the-art in the nanotechnology risk management with special focus on regulatory aspects.

2. NANOMATERIALS SAFETY MANAGEMENT AND ITS GAPS

2.1. Nano-safety

Due to the fact, that the highest probability to be exposed to the risk of nanomaterials is nowadays in nanotechnology industry, the concern is focused mainly on nano-OHS, which is one from specific applications of OHS management and should respect general rules of safety management and OHS principles. It means that such rules, as principles described in the OHSAS 18000 or in the ISO 31000, are appropriate guidelines.

Significantly, the most important are health and environment hazards. Nanomaterials have been (and are) developed for their new functionalities and these novelties may bring new situations in toxicology, as well as new types of environment fate, new types of transport, accumulation and transformation. This is why numerous nanotechnology safety oriented projects have been launched. As mentioned in the overview done by European NanoSafety cluster [6], more than thirty projects concentrated on nanomaterial safety have been financed throw Framework Programme FP7.

The position of European Commission is [5], despite of the specificity of nanomaterials, the preference to adapt existing legislation to nanomaterials and not to create completely new one. The REACH directive and other related legislation (dealing with cosmetics, pesticides etc.) give sufficient base and paradigms are with the high probability applicable to the nanosafety as well. Nevertheless, nano-specific regulation is needed. The process has started already, e.g. specific affix “nano-” can be used for nanomaterials. In 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 has been used in (experimental) studies. The manual also refers to the “Guidance updates for nanomaterials” and links to REACH Implementation Projects on Nanomaterials (RIP-oNs) and the OECD Working Party on Manufactured Nanomaterials (WPMN). In October 2014, ECHA organized the Topical Scientific Workshop Regulatory Challenges in Risk Assessment of Nanomaterials. The workshop participants concluded that even if considerable progress has been accomplished, important gaps still exist in nanotechnology safety knowledge and practice. Some of those gaps are listed in following paragraphs.

2.2. What is nanomaterial?

The regulation is based on well-defined subjects to be regulated: what has to be surveyed, controlled and regulated. For it the unambiguous and comprehensible definition with measurable (by technically and economically viable methods) parameters should be agreed. Nowadays, at least eight institutions (European Commission, CEN, ISO, SCENHIR, American Chemistry Council, ICCR, ICCA and German Chemistry Association) and seven states (Australia, China, France, USA, South Korea, Switzerland and Thai-wan) have issued various definitions of nanomaterial. In addition, at least 4 European regulatory acts use the definition of nanomaterial different from EC recommendation (European Union Cosmetic Product 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). The only parameter, 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 by derogation, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials [7]. On the other hand, in the bibliography, the size of particles over 100 nm is frequently exceeded and SCENHIR (Scientific Committee on Emerging and Newly Identified Health Risks) recommends in its report [8] to use tiered approach covering in three tiers whole nanoscale 1 - 999 nm.

Another set question arises when considering such questions as agglomeration, surface treatment, corona effects etc.

2.3. Interaction with living systems and hazard

In the most of tests, substances toxicity is studied in their molecular form, i.e. in solutions. Nanoparticles toxicity differs from substances in solution by many aspects:

- Nanoparticles move in environment and in organisms as particles, i.e. by different type of mobility than molecules. Nevertheless, nanoparticles may pass cell membranes and other biological barriers, eventually enter to the cells and accumulate in organs.
- Nanoparticles of various sizes may exhibit different toxicological effects [9].
- Nanoparticles toxicity is influenced by the surface properties, including the “corona”. Then, during the life cycle of nanoparticles or due to the coating, the toxicity may change.
- Nanomaterials are self-assembling, which leads to the agglomeration, deposition and formation of secondary structures.
- As result of physico-chemical behaviour, dose-effect dependences sometimes show local maximum, i.e. in certain range increasing dose leads to decreasing effect, what makes risk assessment and modelling tricky.
- The proper metric of dose is uncertain. As WHO Workshop on Nanotechnology and Human Health [10] has concluded, it is evident, that the toxicity of nanoparticles is not only mass-dependent but might also dependent on physical and chemical properties that are not routinely considered in today’s toxicity studies.

2.4. Exposure

Risk in toxicology is composed from hazard and exposure part and then, the control of exposure is a basic tool of occupational health and safety. We face to several problems in exposure assessment. The metric is not sure; without knowing which dose metric is principal to express toxicity hazard (number or mass concentration, active surface…) it is difficult to assess exposure. There is a need to elaborate typical situations and to prepare the library of exposure scenarios, which will be harmonized between countries and enables sharing of experience and transfer of data and knowledge. Such libraries are prepared in various research projects and thus, the harmonisation becomes to be principal problems.

For exposure assessment, the inventory of nanomaterials use is necessary. Some countries, e.g. France, introduced the specific legislation for inventory of nanomaterials, nevertheless in the majority of countries, no legislation demanding inventory of exposure exists yet and generally, industry hesitates to release information.

2.5. Risk assessment and risk modelling

As has been shown above, both principal parts of risk assessment, i.e. hazard identification and exposure assessment are in the nanosafety still not equipped by 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 high and growing number of existing nanomaterials and extremely high number of potential combinations of various nanomaterial properties makes case-by-case risk assessment of nanomaterials so demanding as to be impracticable.

Contemporary situation is that we still have not yet verified models and input data are accompanied by important uncertainty. Rather than risk assessment, we can provide risk characterization, which has to be supplemented by risk communication.

2.6. Regulatory aspects

The regulation in chemical safety is based on principles of risk management as system of interlinked steps. In the nanotechnology safety, we face to high degree of uncertainty and to the lack of information transferrable from one scientific discipline to another. The overview of situation including the flow-chart diagram is described in literature [11]. What is an important result is that for sound nano-risk management, the communication among wide spectrum of disciplines, i.e. nanomaterial characterization, physical and chemical properties of them, interaction between nanoparticles and living systems, human toxicology, exposure assessment, environmental fate, life cycle analysis and risk modelling are necessary for valuable risk assessment. Interlinks between risk assessment and risk control, including regulation, must be set up, based on mutual understanding and acceptance of needs and gaps of involved disciplines.

The analyse of research projects oriented to nanotechnology safety shows, that most of them are both narrow-oriented and focused on scientific answer only, thus not bringing answers to regulatory needs. This is why, in the framework of EU FP7, of the first project was launched in European context, which uses bottom-up approach and concentrates on bringing answers given by regulators more than on science-only oriented research.

3. NANOREG PROJECT

3.1. Project background

This project with acronym NANoREG (see www.nanoreg.eu), unifies nearly 70 partners, together with government representatives of participating countries, which cooperate to eliminate uncertainties in nano-risk management. All “old” EU member countries, Czech Republic, Brazil and South Korea participate. The project aims to identify the EHS aspects that are most relevant from a regulatory point of view. It will provide tools for testing the EHS aspects and the assessment and management of the risks to the regulators and other stakeholders. To assure that the final results of the project can be implemented in an efficient and effective way, industry and regulators are strongly involved in the project.

NANoREG aims at reducing the uncertainty in judging the environmental, health and safety (EHS) aspects of nanomaterials in a regulatory context. It will analyse the applicability of current testing and assessment instruments to manufactured nanomaterials, suggest an overall framework for their testing and assessment, as well as provide regulators with a tool box and other instruments to implement the framework. In order to do so, it is important that the project focuses on providing „Scientific answers to regulatory issues“, i.e. NANoREG must stay focused on the issues and questions that regulatory authorities are facing and on the information they need when assessing the risk of nanomaterials and deciding on risk management measures. Despite the concentrated and concerted effort of wide spectrum of project participants, project consortium has found, that today’s knowledge yet does not allow direct application of regulation and together with knowledge building, we have to use “soft” techniques, mainly based on voluntary basis.

3.2. Risk control, decision making and regulation

Working in high degree of uncertainty together with still existing gaps in knowledge demands to use rather soft instruments than strict regulation, e.g. exposure limits. For sound regulation, relatively high degree of certainty and evidence based decision making are crucial and this is why we cannot expect the consolidated

nanomaterials-specific regulation probably sooner than after a decade. On the other hand, the effort of regulatory bodies is significant and step-by-step progress expectable. Till covering all important gaps, EHS concerns should be solved by applying voluntary tools and precautionary principle.

Already existing voluntary tool, applicable to the nanomaterials in occupational safety, is the control banding, already standardized by ISO/TS 12901-2 [12]. Technical specification focuses on inhalation control of risks associated with occupational exposures to nanomaterials, even if knowledge regarding their toxicity and quantitative exposure estimations is limited or even lacking.

Generally, the voluntary risk control in nanosafety is developing dynamically and we can expected, that it will become the inherent part of responsible care in industry. The precautionary principles have been already implemented in some countries, e.g. Swiss [13].

3.3. Communication

There is an important set of gaps in communication among interested groups of nanosafety. Somehow, the real communication, it means bi- or multilateral information exchange leading to changes in views, positions or approaches, is very limited outside of each stakeholders group. Each side is talking its own language and not interested enough whether others are able to understand their messages or not. Their positions are different; beside of regulators, which position is difficult due to the lack of “hard” data and methods, we meet other important stakeholders as well:

Customers: Are asking simple question: “Should we be afraid of those nano-something? How much?” or “Can we be sure that you protect us enough, you guys doctors, scientists, governments…?” Unfortunately, the reactions are either silence or talking highly scientific topics and not answer those questions. The understandable reaction is, that people may lose the confidence to government and to science and they might be sensible to any well given information, even to the negative propaganda. This is the big threat for nanotechnology development due to the risk of credibility loss.

Toxicologists are driven by their common language and procedures and by the metric of their success expressed in scientometry, for which is nanotoxicology good field. They are rarely interested by decision making process to create realistic safety measures of people/environment protection, so they still provide information not fitted for decision making and regulation.

Industry is in difficult position, moving in unpredictable environment. Afraid of easy change from societal nano-enthusiasm to nearly nano-scepticism (see “customers”), industry which some years ago showed nanomaterials as an attractive attribute of their products, today hesitates or even hides the information of nanomaterials content in products. The same is their position with respect of OHS - it is very difficult to get reliable information about exposure.

NGO and other activists, some politicians. Because of non-transparent environment and lack of open and comprehensible communication, the conditions bring risk to be favourable for misusing nanotechnology as “public enemy” and “easy target” and to build up popularity by creating the synthetic campaign of fear. On the other hand, NGOs have today no possibility to get serious, true and understandable information what the situation is, so it is easy to declare that something is wrong with nanosafety.

Safety managers. Their talk is frequently “we wait for right data and regulation and then we will do everything perfectly” what sounds badly to customers and workers, who feel be unprotected and abandoned. Safety managers should effort to be the “translators between disciplines” and to communicate with thinking on information receiver.

4. CONCLUSIONS

Nanotechnologies bring new needs and new challenges in safety. The science, regulatory bodies and whole society made remarkable progress in nanomaterial-specific part of environment protection, health and safety,

but they still exist important gaps in knowledge and new techniques have to be developed. The paradigms of chemical safety are still applicable, even if certain will be probably modified. The NANoREG project brings new insight by using bottom-up approach and being developed to bring scientific answers to the regulators according their needs.

The nanotechnology safety demands parallel development of regulation and use of "soft" tools as precautionary principle or control banding. The crucial problem of safety management and regulation development is in communication among scientific disciplines, regulator and other stakeholders.

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