Risk assessment of nanomaterials and nanoproducts – adaptation of traditional approaches

J Jahnel, T Fleischer, S B Seitz
Karlsruhe Institute of Technology, Institute for Technology Assessment and Systems Analysis (ITAS), Karlstrasse 11, 76133 Karlsruhe, Germany
E-mail: jutta.jahnel@kit.edu

Abstract. Different approaches have been adopted for assessing the potential risks of conventional chemicals and products for human health. In general, the traditional paradigm is a toxicological-driven chemical-by-chemical approach, focusing on single toxic endpoints. Scope and responsibilities for the development and implementation of a risk assessment concept vary across sectors and areas and depends on the specific regulatory environment and the specific protection goals. Thus, risk assessment implication is a complex task based not only on science based knowledge but also on the regulatory context involving different parties and stakeholders. Questions have been raised whether standard paradigms for conventional chemicals would be applicable and adequate for new materials, products and applications of nanotechnology. Most scientists and stakeholders assume that current standard methods are in principle applicable to nanomaterials, but specific aspects require further development. The paper presents additional technical improvements like the complementary use of the life cycle methodology and the support of risk-based classification systems. But also aspects improving the utility of risk assessment with regard to societal impacts on risk governance are discussed.

1. Introduction
Nanomaterials are substances with a high diversity commonly characterized by its nano-size. Their properties differ significantly from those of larger particles of the same material. This makes them suitable for new or improved applications in areas, such as in medicine, environment and energy production. However, these new properties are just the same as those which concern scientists, policy makers, a number of stakeholders and parts of the general public. These concerns have to be taken seriously because experiences of the past showed that new materials may be a source of new threat for human health and the environment [1]. Moreover there is a need for a responsible approach to ensure that potential safety issues are being addressed carefully because nanomaterials are already used in a number of commercial applications. The scientific community – in particular the toxicologists – is requested to answer the question whether nanomaterials pose environmental, health and safety (EHS) risks or not, and to provide policy makers with the appropriate knowledge to perform risk assessment (RA) as a prerequisite for science-based risk management. The current concept for assessing nanospecific risks is the conventional expert-based chemical RA procedure. This is a well-established process which is specified with the Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) [2].

A nanospecific RA goes beyond present standard strategies for conventional chemicals. EU committees like the Scientific Committee on Emerging and Newly Identified Health Risks
SCENIHR and the European Food Safety Authority (EFSA) evaluated the current RA procedures and concluded that the methods are in principle applicable to nanomaterials, but specific aspects require further development [3, 4]. SCENIHR proposed additional technical tools for the improvement of the standardized RA procedure like the use of the life cycle methodology [5] or the support of preliminary classification systems [6].

Moreover, the traditional exposure-response paradigm arises from a narrow toxicological perspective and will not consider adequately societal impacts and societal needs for understanding risk in a broader sense than experts. Despite of serious methodological uncertainties the conventional RA approach is based on confidence in the knowledge used and the possibility of assessing and managing uncertainty as described by SCENIHR [7]. Accordingly, a wider concept is needed which allows for a plurality in perspectives, actors and different kinds of knowledge. In addition, regulation based on quantitative RA is an inherently slow governance process which is not intended to facilitate decision-making. The paper highlights the challenges and strategies for improving RA of nanomaterials in the context of risk and innovation governance.

2. The traditional risk assessment paradigm

The classical RA is a well-established and formalized process intended to “calculate or estimate the risk to a given target organism, system or (sub)population, including the identification of uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system” [8]. While the hazard of a substance is its potential to cause harm whereas risk is the likelihood of that harm occurring, taking into account wider considerations of exposure and uncertainty. The RA process consists of four steps: hazard identification, hazard characterization including dose-response assessment, exposure assessment, and risk characterization.

According to the Risk Commission [9], the scientific RA process primarily deals with consequences of the effects of noxious agents to human health quantifying the probability of a harmful effect to individuals or populations. The framework was developed for conventional chemicals as an information and decision supporting tool for regulations in the context of safety and sustainability. Associated uncertainty in the progress is managed by the application of safety factors. In general, the traditional approach is a chemical-by-chemical approach, focusing on a single substance, a single media and a single toxic endpoint. In cases where the risk of adverse effects at exposures below a safe level is expected to be practically zero, the Margin of Exposure can be calculated to describe the quotient between expected exposure and the No-Observed-Adverse-Effect-Level. Thus, the output of RA is based on a substance specific quotient produced on an absolute basis.

Triggers for chemical RA are in general the quantities of a chemical, the properties like persistence or bioaccumulation and the effects like acute and chronic toxicity, sensitization, genotoxicity, reproductive toxicity or carcinogenicity. Thus, information requirements include physicochemical properties, toxicological and ecotoxicological information. Chemical RA has been the standard approach for assessing the potential health and environmental risks of bulk chemicals and subsequently has been applied to nanomaterials in recent years [10-12]. In Europe this process is defined for chemicals by the EU chemicals policy REACH (Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals) [2] and the detailed guidance documents provided by the European Chemicals Agency (ECHA).

As a decision support tool RA uses the weight of evidence approach: This process is based on the totality of data in a holistic manner and facilitates transparency and quantification in decision-making. The data provided by toxicology are ranked and scored considering the varying quality, relevance and consistency. This results in the so-called strength of evidence, which is inversely related to the degree
of uncertainty. In addition individual data are clustered in evidence lines. Complementary and contradictory evidence of varying strengths and evidence lines are considered in the weight of evidence process. SCENIHR stated that this weighing of evidence is important as a guideline for preliminary RA and for determining the priority for further assessments [7].

Accordingly, classical RA privilege scientific knowledge that can be measured, weighted and monitored. But also values, ethics and tacit forms of knowledge are important factors. There are several inherent value judgments in RA and questions raised if value-based decisions should be left to political decision-makers [13].

RA for products considers the matrix in which the chemical or substance is delivered to the end-user. Scope and responsibilities for the development and implementation of RA for a concrete product and risk management context vary across sectors and areas and depends on the specific regulatory environment. For example RA of nanoproducts falls under the specific regulations for foods, novel food, cosmetics or biocidal products. With regard to RA purposes the assessment of the hazard potential of nanomaterials “as manufactured” has to be complemented by an assessment of nanomaterials “as consumed”. As an example, the nanospecific RA for foods proposed by EFSA follows a comparative approach using the data of a relevant comparator like a non-novel material or the corresponding bulk material. With the aid of special criteria like solubility, persistence and translocation it will be decided whether a specific toxicological assessment is required. A tiered weight of evidence approach divided the toxicological assessment into an initial toxicological profiling and supportive studies. Finally, nanomaterials “as used” in its intended food matrix will be evaluated [4, 14].

3. Challenges for a nanospecific risk assessment

Nanotoxicology emerged from the classical toxicology and studies in particular the biological effects of engineered nanomaterials on living organisms and in ecosystems [15]. There is a consensus that the classical measures of toxicology are in principle applicable to nanomaterials, but standard procedures of RA have to be modified [10]. SCENIHR stated in their opinions on RA of nanomaterials and nanoproducts that the current methodologies are generally likely to be able to identify the hazards associated with the use of nanomaterials. However, they highlighted the need for modifications of the guidance on the assessment of risks [3, 11]. In its interim review the Working Party on Manufactured Nanomaterials of the OECD concluded as with traditional chemicals, it is clear that each nanomaterial may pose specific challenges, but in most instances, they can be addressed with existing methods. In some cases, it might be necessary to adapt methods and test guidelines. But it will not be necessary to develop completely new RA approaches [16]. The adaptation of regulations like REACH and its detailed guidance is an ongoing process [17]. However, serious doubts and concerns are expressed that a conventional paradigm may not be sufficient to capture all the dimensions of risk which may arise not only from its material toxicity but also from its interactions with complex biological and environmental systems [18]. The main limitations of current procedures for the RA of nanomaterials are summarized with the following points:

- The identification and definition of the term “nanomaterial” poses a challenge for framing a “substance class” with a high diversity [19].
- Equipment and methods for characterization and detection of nanomaterials are often not appropriate and need further optimization. It is still an analytical challenge to detect nanomaterials in biological matrices. Furthermore there is still no agreement about a concept for the dose or concentration of nanomaterials in test systems [10, 18, 20].
- High quality exposure data is also largely missing. Many exposure related studies are published on occupational scenarios while much fewer studies are published on environmental and consumer exposure as well as about both acute and chronic exposures [12, 21].
There is still a need of standardized toxicological methods as well as appropriate controls. Detailed experimental factors - such as surface functionalization, dispersing behavior in biological media or the use of solvents in case of non-dispersing nanoparticles (e.g. fullerenes) in aqueous media are not addressed sufficiently in many studies [12, 21].

Studies that showed no significant (hazardous) effects are usually not published, even though they are crucial to relive nanomaterials from the suspicion of hazard [22].

There is an ongoing debate on the significance of high-dose in vitro or in vivo studies conducted so far and whether or not the used methods are suitable for hazard characterization [23].

For eco-toxicological studies it is in general difficult to simulate real environmental scenarios [12, 21].

Besides the described knowledge gaps and methodological uncertainties the most important challenge is the fact that nanomaterials share no common characteristics besides the nano-scale size. In the nanotoxicology community it is consensus that only a “case-by-case” assessment is responsible and sound. Thus, RA requires the full dataset for each and every kind of nanomaterial. This makes the progress of gathering the relevant data extremely slow. Therefore, a complete RA is only possible for a small selection of high abundant nanomaterials [12, 22].

4. Strategies for improving nanospecific risk assessment

4.1. Combining life cycle methodology with the risk assessment procedure

Life cycle assessment (LCA) is a systematic assessment of the potential environmental impacts of a defined good or service throughout all life cycle stages, contributing to the production of the product under investigation, its use and disposal [24]. LCA is a most extensively developed and standardized methodology. The assessment typically covers a broad range of environmental impacts, such as climate change, resource depletion, and toxicity on human health caused by releases of chemical agents. In contrast to RA the results of LCA are normally presented on a relative or comparative basis, such as the comparison of two alternative solutions for product development, to make informed decisions regarding the relative environmental sustainability of products. The LCA inventory is a mass-based accounting system that does not take into account spatial, temporal, dose–response, and threshold information. Hence, this assessment tool could be helpful to quantify potential impacts of nanoproducts across different life cycle stages. In excess of the traditional chemical RA the manufacturing aspect but also consumption and disposal aspects are addressed. However, nanospecific LCA has its own challenges and limitations. There is a lack of robust data regarding emissions and exposures related to the production, use and disposal of nanomaterials and products containing them and subsequently a need to establish a database which includes the most common production pathways. As discussed already for RA knowledge about the environmental fate, behaviour, and toxicological impacts of nanomaterials are generally limited. The unclear metrics used in these assessments, the inconsistencies in viable data sources and the challenge of proper identification and characterization of nanomaterials results in serious methodological uncertainties.

Formulating strategies to use LCA and RA together for the assessment of chemicals has been pursued in a range of research efforts for more than a decade, and remains a topic of on-going work. Some proposed approaches range from the use of the same data, the complementary use of the results as well as efforts to integrate these two tools into one [5]. The proposed integrative approaches could be allocated to a more traditional RA approach applied in a life cycle perspective (“LCA-based RA”) or to the more conventional LCA supplemented by RA in specific life cycle steps (“RA-complemented LCA”) [5]. However, the full integration into one tool is considered neither desirable nor meaningful as the two tools answer different questions and have different system boundaries. For example the two methods have differing scopes, aims, and end results: while LCA assesses a wide variety of
environmental impacts of a product or system related to the functional unit, RA deals with the health and environmental risks of a single substance at a particular point in the chemical’s life cycle. As these different systems have their own meanings of terms like “life cycle” or “characterization” it may be more beneficial to use these two technical tools in a complementary manner. The following approaches were proposed:

- The performance of RA at each or selected stages of a product’s life cycle.
- The identification of potential health issues on a system-wide and hypothetical basis by LCA which is followed by a detailed RA.
- LCA as a strategic tool to prioritize data which is needed to complete by RA.

Obviously, both LCA and RA methods require substantial amounts of technical data and strong expert knowledge. Both methods have been criticised for not being able to effectively handle uncertainties or the lack of data adequately [5].

4.2. The support of risk-based classification systems

Despite of advances in frameworks and assessment methodologies, a comprehensive characterization of predictive properties for all nanomaterials is far from complete. Thus, some authors proposed a preliminary relative risk ranking or risk classification of nanomaterials. Zuin et al. [25] used physico-chemical and toxicity data for a relative ranking of the hazard potential of quantum dots, fullerenes, single-walled carbon nanotubes and carbon black. The classification system of Olson and Gurian [26] is based on the properties persistence and toxicity. They recommended that persistence should be characterized first because this determine the burden of proof for non-toxicity. Tervonen et al. [7] described a classification system for nanomaterials based on a set of performance metrics that measure both the toxicity and physico-chemical characteristics as well as the expected environmental impacts through the product life cycle. The parameters included properties of nanomaterials like agglomeration, aggregation, reactivity, charge, critical functional groups, size, bioavailability, bioaccumulation and the toxic potential. In addition a relative ranking of the exposure potential of selected nanoparticles were proposed using different transport and persistence properties in the aquatic environment [27].

The various nanomaterials will be clustered in different risk categories with the aid of the weight of evidence method, a formal decision analysis or expert judgments. The purpose of the proposed classification and categorization systems is not to select a single best alternative, but to preliminarily rank or group the alternatives through a structured process. The results are important for prioritizing further studies or management measures. A detailed RA may be reserved for nanomaterials found to be both persistent and toxic and for high exposure scenarios [7].

An example for a classification system was introduced by the German NanoKommission. This stakeholder commission on nanotechnologies was established by the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) and presented a key dialogue panel within the German Federal Government’s Nano-Initiative. A proposed preliminary assessment tool structures nanomaterials in three categories, the so-called ‘levels of concerns’ and combined them with voluntary measures for risk management in the following way:
1. Probably hazardous – concern level high:
   - Criteria: Exposure occurs; materials have high mobility, reactivity, persistence or toxicity of the materials.
   - Measure: A concept is required for measures to minimise exposure or to avoid certain applications.

2. Possibly hazardous – concern level medium:
   - Criteria: Exposure cannot be ruled out; materials have unknown agglomeration or deagglomeration behaviour; too little is known about materials' solubility and biodegradability; the possibilities for release not of nanoparticles from matrices have not yet been explored.
   - Measure: A concept is required for measures to reduce exposure of humans and the environment.

3. Probably hazardous – concern level low:
   - Criteria: Exposure can largely be ruled out; materials are soluble or biodegradable; materials are bound in matrices; materials form stable aggregates or agglomerates.
   - Measure: No measures in addition to those for "good work safety practice" (or "hygiene practice") are required.

The criteria for the different categories are based on current studies and need to be refined if further specific assessments in the area of health and environmental protection become available [20].

Another example is the Swiss ‘Precautionary Matrix for Synthetic Nanomaterials’. This approach was introduced as a key element under the Swiss Action Plan for synthetic nanomaterials and was revised on the basis of users’ experience at the beginning of 2010. The precautionary matrix ‘provides a structured method to assess the "nanospecific precautionary need" of workers, consumers and the environment arising from the production and use of synthetic nanomaterials. Upon entering a limited selection of nanomaterial-specific and application-specific parameters into an electronic form (size of the particles, reactivity and stability, their release potential, the amount of particles) the matrix provides a simple risk classification:

   - Class A: risks specific to nanomaterials are low, no further clarification necessary.
   - Class B: possible risks, further clarification and/or risk reduction needed.

The Precautionary Matrix may be regarded as an instrument that supports companies. It is to be used in the context of duty of care and industry self-supervision. The approach functions simultaneously as a differentiation aid, a detector of gaps in knowledge and an early warning system but should not in any way replace a quantitative RA process [20, 28].

4.3. The role of the social context: concern assessment
In order to consider societal impacts and societal needs for understanding risk in a broader sense than experts, the classical toxicological-driven RA paradigm should be widened for more plurality in actors and different kinds of knowledge. Actors in the RA process are the industry and manufacturers which have to ensure that substances brought on the European market do not adversely affect human health or the environment. On the other hand scientists like toxicologists, and legislators as well as scientific committees, European and national agencies and politicians are also engaged in assessment procedures. Classical RA however overemphasises the role of technical experts and scientific knowledge that can be measured and weighted. It is also important to consider the contextual information from the general public and the civil society organisations. The IRGC framework for the risk governance of nanotechnology [29] is a sophisticated risk management model involving a
multitude of different actors in a dynamic process with various iterations and feedbacks. It acknowledges that risk governance decisions have to be taken in instances of complexity, uncertainty and ambiguity. Therefore, strategies should be based on a corrective and adaptive approach and take into account the level and extent of available knowledge and a societal balancing of the predicted risks and benefits. The framework includes two concepts for the governance of manufactured particulate nanomaterials:

It integrates a scientific risk-benefit assessment (including environment, health, and safety (EHS) and ethical, legal, and other social issues (ELSI)), with an assessment of risk perception and the societal context of risk, called “concern assessment”. The IRGC framework is a cyclical process and consists of four phases:

1. “Pre-Assessment”: trigger or initiator of the whole assessment and management process
2. “Risk Appraisal”: comprises two elements: risk assessment and concern assessment.
3. “Tolerability and Acceptability Judgment”: brings together the classic risk characterization and risk evaluation as a new element.
4. “Risk Management”: has to react not only to new scientific results regarding a hazard or an exposure to it. It also reacts to changing societal or cultural factors like altering expectations on risk reduction procedures, new judgments about tolerability and acceptability of risks, developing value systems or shifting risk perceptions of different actors.

Some authors criticised this framework because public participation is still perceived as a factual input, as part of an expert-driven process, rather than a real empowerment of citizens. The risk appraisal stage is subdivided into the traditional RA and concern assessment without a concrete inclusive concept. This might only be tempting, “if not intended to fall into the trap of identifying the former as legitimate (i.e. scientific), while the latter could be viewed as ‘political’, hence of a different sort of legitimacy” [13].

In detail, Renn and Walker defined concern assessment as “a social science activity aimed at providing sound insights and a comprehensive diagnosis of concerns, expectations and perceptions that individuals, groups or different cultures may link to the hazard” [30]. The perception of technological risks depends on psychological factors such as perceived threat, familiarity, personal control options and positive risk-benefit ratio. But also political and cultural factors such as perceived equity and justice, visions about future developments and effects on personal interests and values are important. A systematic assessment of the concerns and preferences of the various actor groups and the public at large, a systematic feedback of its results to the related regulatory and legislative processes are necessary prerequisites to improve our understanding of the likely societal responses to the developments in nanomaterials and nanotechnology.

While chemical RA can build upon a long tradition of methodological development, concern assessment is still in its early stages. Among a set of well-established methods that social science uses to study perceptions of nanotechnology’s benefits and risks within individuals, groups or the society as a whole are quantitative and qualitative methods. Each of them has its own pros and cons. Quantitative methods – including surveys which are designed to ascertain large and therefore representative datasets as well as experimental studies using non-probability samples – for example, allow for testing and revising existing hypothesis, and making statements about defined groups of people. Typical examples are large, standardized polls within a representative sample of a population. In contrast, qualitative methods are rather designed to gain insights into individual arguments, ideas or values and to explore new aspects of an issue. Thus, they are designed rather open (not standardized) to capture even unexpected facts. Beside in-depth interviews, focus groups are typical examples of qualitative methods. The results of focus group discussions can broaden the perspective of various actors.
involved in risk governance but a simple interpretation of the participants’ positions voiced as stable attitudes would be misleading [20, 31, 32]. The ‘translation’ of societal values, concerns and perceptions into concrete measures for risk governance is still a subject of debate.

5. Recommendations for risk assessment in the context of risk governance

Although the traditional RA framework is a powerful approach for bulk chemicals, its use for estimating potential risks of nanomaterials in the near-term may be limited due to a kind of “paralysis by analysis” problem. An improvement of research in broader issues than chemical-based aspects such as decision-making, risk governance and a systematic evaluation of complementary RA tools is needed and was increasingly stipulated [33]. In general, RA should support timely decisions and it should be transparent and open to inspection by all. In addition iterative, tiered, flexible and adaptive procedures are recommended which also consider improved social and cultural aspects. According to the OECD “adaptive management” means that “the substance is produced and used under a certain set of conditions based on a preliminary assessment, while additional data are collected to periodically evaluate the initial assessment and to modify the conditions as needed to ensure health and safety” [16]. Incorporating product life cycle considerations into this tiered process may prioritize RA needs.

On the other hand the precautionary principle should support decisions in the absence of scientific certainty. The precautionary principle is embedded in the EU law and applies especially within EU product authorization procedures. The principle runs through legislation for example in the “no data, no market” idea of REACH or the pre-market authorization in special food regulations. This principle allows governmental bodies to intervene with risk management decisions like case-by-case decisions whenever necessary. In the general food law framework (EC 178/2002) [34] it is acknowledged that “scientific risk assessment alone cannot provide the full basis for risk management decisions”—leaving open that risk management decisions could be partly based on ethical principles or particular consumer interests. According to the idea of responsible innovation it is also necessary to promote the participation of stakeholders since the early stage of innovation through the involvement of the business and epistemic community.

The recently re-evaluated traditional RA framework by the National Research Council goes in this direction: additional steps were proposed to integrate risk and non-risk information and stakeholder involvement [16]. In addition, various elements like iterative RA and stakeholder engagement are currently implemented in REACH. Thus, adaptation of traditional RA is a necessary and ongoing process which should not only consider preliminary tools but also serve for facilitating regulatory measures. In this context the question remains whether the compatibility of RA with the precautionary principle will need a further paradigm shift.

References

[1] Oberdörster G, Oberdörster E and Oberdörster J 2005 Environ Health Perspect, 113(7) 823-839
[2] Regulation EC/1907/2006 of the European Parliament and the Council of 18 December 2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH). OJ L 396/1, 30.12.2006
[3] SCENIHR 2007 Opinion on the appropriateness of the risk assessment methodology in accordance with the technical guidance documents for new and existing substances for assessing the risk of nanomaterials (Brussels: European Commission) http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_010.pdf
[4] EFSA 2011 EFSA Journal 9 2140
[5] Grieger K D, Laurent A, Miseljic M, Christensen F, Baun A, Olsen S I 2012 J Nanopart Res 14 958-981
[6] Tervonen I, Linkov J, Figueira J Steeves J, Chappell M and Merad M 2009 J Nanopart Res 11
Governance Council

[30] Renn O and Walker K 2008 Global Risk Governance: Concept and Practice Using the IRGC Framework (Dordrecht: Springer)

[31] Fleischer T and Quendt C 2007 Wissenschaftliche Berichte FZKA 7337.

[32] Fleischer T, Haslinger J, Jahnel J and Seitz S B 2012 International Journal of Emerging Technologies and Society 10 (2012) 79-95

[33] Grieger K D, Baun A and Olsen R 2010 J Nanopart Res 12 383-392

[34] Regulation EC 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31/1, 1.2.2002