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ORIGINAL PAPER

Conceptual Questions and Challenges Associated with the Traditional Risk Assessment Paradigm for Nanomaterials

Jutta Jahnel

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Abstract Risk assessment is an evidence-based analytical framework used to evaluate research findings related to environmental and public health decision-making. Different routines have been adopted for assessing the potential risks posed by substances and products to human health. In general, the traditional paradigm is a hazard-driven approach, based on a monocausal toxicological perspective. Questions have been raised about the applicability of the general chemical risk assessment approach in the specific case of nanomaterials. Most scientists and stakeholders assume that the current standard methods are in principle suitable, but point out that experimental aspects and practical guidelines need specific adaptations. Beyond this laboratory level, risk assessment of nanomaterials also faces a number of substantive and procedural limitations, which are intrinsically attributed to the general orthodoxy of the risk assessment concept. Moreover, the developed formalism used to organize scientific knowledge is closely interlinked with the underlying governance design and the mode of interaction between the two spheres of 'science' and 'decisions'. This contribution will provide a closer look at the evolution of different institutional settings for risk assessment in the context of decision-making. Improved risk governance frameworks with different narratives, process designs and procedural elements will be compared. The question of a general principle of enhanced organization of risk assessment will be discussed taking account of the barriers of substantive and procedural limitations in the special case of nanomaterials.

Keywords Risk assessment · Uncertainty · Decision-making · Risk governance frameworks · Nanomaterials

J. Jahnel (✉)
Institute for Technology Assessment and Systems Analysis (ITAS), Karlsruhe Institute of Technology, Karlstraße 11, 76133 Karlsruhe, Germany
e-mail: Jutta.Jahnel@kit.edu

Introduction

Nanomaterials (NMs) are very diverse in material and form and are generally characterized by their nanosize. They often have significantly different properties than the respective bulk material. For this reason, innovators are particularly interested in using these materials for new or improved products and applications. However, the new properties of NMs may also be accompanied by unwanted biological effects, and this has raised concerns of a number of stakeholders and consumers [1]. Scientists are requested to accurately and rapidly assess possible environmental, health and safety risks, especially against the background of increasing commercial applications. They should provide an evidence base for specific risk management measures to ensure adequate safety for users, workers and the environment. While scientists demand financial support for toxicological and analytical investigations, politicians wonder whether the experts are on the right track and how much support is justified.

The current basis for assessing NMs is the conventional expert-based chemical risk assessment procedure, which was framed by the National Research Council (NRC) in 1983 [2]. In Europe, the bodies responsible for risk assessment are Scientific Committees, such as the Scientific Committee on Health and Environmental Risks (SCHER), the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and the European Food Safety Authority (EFSA). A standard procedure for chemicals was adopted by the Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) [3].

Assessing the potential risks posed by NMs goes beyond applying the standard strategies for assessing conventional chemicals. SCENIHR and EFSA evaluated the current risk assessment procedures and concluded that the methods are, in principle, applicable to NMs, but that specific challenges require further improvements [4, 5]. Risk assessment of NMs is an inherent multidimensional challenge, and limitations become apparent when the traditional paradigm is employed. The entire process is a sequence of data-gathering steps, each with its inherent uncertainty. Despite serious methodological uncertainties, the conventional risk assessment approach is based on confidence in the relevant knowledge and on the possibility to assess and manage uncertainty. In addition, the traditional 'chemical-by-chemical' approach has to be replaced by a detailed 'case-by-case' assessment of all the different forms of NMs, which is an inherently slow and costly process. This leads to decelerated decision-making, sometimes even to a decision-making gridlock. A wider concept for assessing the risks of NMs should allow for a plurality of perspectives, actors and different kinds of knowledge. This kind of approach could take into account both the societal impacts of risks and the need for a broader problem framing, which should be provided by all actors involved.

This contribution describes the different kinds of uncertainty in the assessment of NMs and presents a multilevel perspective for improving the procedure. First of all, there are nano-specific problems. But challenges with regard to the general risk assessment approach and its institutionalization also play an important role for the critical reflection. Hence, additional tools for improving the traditional concept as well as alternative organizational settings of scientific and political deliberations will be described. The elements and process design of different alternative governance models will be compared to identify general principles for a possible redesign of the currently established relation between 'science' and 'decisions'.

For assessing the potential risks of NMs, it is important to link these different levels of detail—the narrow nano-specific level, the broader scientific assessment level and the integration of risk assessment into an overall process of governing technologies [6–8].

The Complex Relation Between Science and Decisions

The role of scientific knowledge and expertise in policymaking has historically evolved in a variety of forms. Three main categories of analytical frameworks and institutional arrangements have been identified and characterized [9].

Decisionist Model (Max Weber, Emile Durkheim)

Industrialized societies could only function with increasingly bureaucratic forms of governance and administration. Weber was the first who proposed a division of labour between experts and politicians. He argued that deliberations of experts should be framed by prior goal-setting policy decisions. This model resonates with the Aristotelian contrast between 'ends' and 'means'. The objectives of policy with the underlying values are the goal-setting 'ends', and the expertise and knowledge are applied for a rationalized choice of the 'means'. Policy decisions can never be based solely on facts since the choice among the 'ends' and the underlying values remain irredeemably subjective [10]. The division of labour is not without its difficulties. It presupposes that officials and experts can identify particular optimal solutions to complex problems. Unfortunately, most risk regulatory contexts are based on uncertain, incomplete and contested evidence.[1] In such circumstances, the division of labour between those that choose the ends of policy and those that select the means becomes increasingly unrealistic. In the face of these difficulties, a positivistic concept gains increasing importance.

[1] Different epistemological meanings of the term 'evidence' have to be considered. In the German context, the term is used for uncontested observations; in the English language, the term is rather synonymous with 'proofs'.

Positivist or Technocratic Model (Henri de Saint-Simon, Auguste Comte)

In this model, objective science is assumed to directly inform policymaking. A fundamental characteristic of this model is an optimistic view of the power of progress and science. It further means that policymaking is based only on 'sound science', and politics is replaced by a scientifically rationalized administration. This narrative is very vulnerable to scientific uncertainties due to incomplete, unreliable or equivocal results. Exclusively evidence-based policymaking also allows the objection that policies include trade-offs regarding the acceptability of risks, based on normative value judgements and not purely factual issues [9].

Inverted Decisionist Model, 'Red Book' Model (National Research Council)

Especially public debates about the health effects of infected bovine tissues in food prior to the recognition of bovine spongiform encephalopathy (BSE) called the purely technocratic narratives into question. Besides scientific factors, socio-political and economic factors are needed in order to inform decision-making in the context of health and environment. The so-called Red Book model of the NRC, published in a red covered book, established the division between scientific aspects (risk assessment) and political aspects (risk management) [2]. Risk management is based on a scientific risk assessment with unidirectional information flow. Risk communication with stakeholders and the public is carried out in a separate step of the risk analysis. This model is the official orthodoxy for risk analysis in the USA, EU, and international organizations like the Organization for Economic Co-operation and Development (OECD) and the World Trade Organization (WTO). In the course of time, the NRC paradigm was further advanced and refined during its application. However, the Risk Commission argued in 2003 that general procedures have not changed significantly in the last three decades [11]. It is the fundamental concept for assessing chemicals or products such as food and has also been applied to NMs. This must be kept in mind when interpreting the challenges in risk assessment of NMs for improving its relevance in decision-making.

General Approach to Risk Assessment of Chemicals in Europe

In general, risk assessment is 'the interpretive and analytical framework used to evaluate research findings related to environmental threats for public health decision making' ([12], p. 1). This means that risk assessment could be seen as a kind of knowledge gathering and organization procedure. In the specific context of risk posed by substances and chemicals, the OECD specifically defined risk assessment as a formalized process intended to 'calculate or estimate the risk to a given target organism, system, or (sub)population, including the identification of attendant 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' ([13], p. 16). While the hazard posed by a substance is defined as its potential to cause harm, the term 'risk' means the likelihood of that harm occurring, taking into account wider considerations of exposure and uncertainty.

The current model of risk assessment maintains the conceptual distinction between risk assessment and risk management according to the 'Red Book' model [2]. Risk assessment is viewed as a solely scientific endeavour and is applied to evaluate risk management options without being influenced by the preferences of risk managers. The theoretical presumption is that risk assessors are neutral, disinterested, independent and objective experts.

The purpose of risk assessment is to identify whether action is needed to control, reduce or prevent exposure on the basis of a soundly based scientific method for identifying and characterizing the risks [14]. Risk management, on the other hand, is based on normative considerations like economic, social, cultural and political factors and involves mandatory and voluntary regulatory options [2]. From a procedural point of view, risk management is a process of 'weighing policy alternatives, in consultation with all interested parties' [15]. Food-related debates in the mid-1990s have resulted in an institutional separation from risk assessment in the EU and in most of the member states [16]. Risk managers in the EU are the European Commission, the European Parliament and the Council of the EU.

The detailed risk assessment procedure for chemicals consists of four steps [13]: hazard identification, hazard characterization, exposure assessment and risk characterization. Exposure assessment means the quantification of possible exposure of individuals and populations to substances as well as the characterization of the nature and size of the exposed population. The investigations include intensity, frequency, route and duration of the exposure. While hazard identification comprises toxicological studies of potentially harmful agents, hazard characterization considers the dose-response relationship. Risk characterization is the final step of the risk assessment procedure and is expressed as the quotient of the actual exposure and the dose level assumed to be without risk.

In general, this four-step process is a chemical-by-chemical approach, focusing on a single substance, a single medium and a single toxic endpoint. Usually, it is a hazard-driven process, which is based on scientific knowledge that can be measured, weighted and monitored. This persuasive power of evidence strengthens the *results-based legitimacy* of the risk assessment concept. With this in mind, the human health risk assessment process depends on using the best data available to inform risk management decisions. Any uncertainty, lack or incompleteness of information must be specified carefully. Uncertainty depends on the quality, quantity and relevance of data, as well as on the reliability and relevance of models and assumptions [6]. In general, uncertainty is any departure from the unachievable ideal of complete determinisms. This includes the lack of knowledge, unknown and unforeseen knowledge [17]. There have recently been improvements in the way that uncertainties are handled and communicated in human health risk assessment [18, 19]. The possibility of public access to scientific data has also increased transparency and openness in assessment processes [20]. In principle, risk practitioners acknowledge that the manner in which uncertainties are addressed is important for stakeholders. The NRC recommended that the extent and detail of the uncertainty and variability analyses should be consistent with the importance and nature of the risk management decision. This may be best achieved by early participation of assessors, managers and stakeholders. To maximize public understanding of and participation in risk-related decision-making, risk assessment should explain the results of the uncertainty analyses in a clear and understandable way to the public and decision makers [6].

In Europe, risk assessment of chemicals is proceduralized by the REACH regulation [3] and the detailed guidance documents provided by the European Chemicals Agency (ECHA). Triggers for regulatory risk assessment are in general the production volume of chemicals; properties such as persistence or bioaccumulation and health effects such as acute and chronic toxicity, reproductive toxicity or carcinogenicity. Thus, the information requirements include different types of data: structural properties that characterize the chemicals, physico-chemical methods that measure data on the relative reactivity of chemical-biological interactions and toxicological tests which are relevant to cellular responses or to an adverse outcome. This well-established and formalized process, the resulting transparent legislation and the possibility of public consultation in risk assessment issues provide the *procedural and social legitimacy* of risk assessment. Providing the public with an independent expert view through scientific analysis, and then explaining and justifying the regulatory actions that are based on these assessments, has been recognized as a major step towards more transparency, accountability and trustworthiness.

Risk Assessment of Nanomaterials: Existing Methods for Specific Questions

Chemical risk assessment has been the standard approach to assessing potential health and environmental risks of conventional bulk chemicals and shall also be used for NMs according to different expert opinions [21–23]. But there are crucial differences between the assessment of NMs and that of ‘conventional chemicals’. The most important challenge is that NMs do not share common characteristics besides the nanoscale size. In addition, NMs consist of multiple forms and variations over their life cycles. Changes in the physico-chemical characteristics, including agglomeration and de-agglomeration, may occur under local environmental conditions and may have an impact on the toxicity of the NMs. Thus, the identification and definition of ‘nanomaterial’ poses the challenge of framing a substance class with high diversity and dynamic properties [24]. An additional challenge is to discriminate between naturally contained, intentionally added and/or engineered NMs and to distinguish them from background particles, especially within complex matrices. Working at the bench with those materials is a complex

task, and even the basics of measurement methods, e.g. applying controls, dosing, dissolution and sensitive detection methods, need careful consideration [25, 26]. Recently, it has been pointed out that the majority of toxicological studies are not based on a proper characterization of material properties. There was a warning against a 'Babylonian diversity' in the applied methods, which are not comparable and often lead to contradictory and even erroneous results [26]. Standardized tests and laboratory quality controls have not been implemented yet, and the development of these procedures will take a long time.

Another specific question is the relationship between physico-chemical properties and potential toxicity of NMs. There is the remaining research question whether the modified behaviour of NMs can be explained with the relevance of different molecular properties at the nanoscale to the overall physico-chemical properties or if there are possibly new and unknown nano-specific effects and modes of action [26]. The described nano-specific challenges lead to higher uncertainty in the assessment process.

There is a general consensus among risk assessors that the classical methods for assessing toxicology, particularly epidemiological studies,[2] in vivo studies with living organisms[3] and in vitro laboratory studies,[4] are in principle applicable to NMs, but that experimental details such as dosing, measurement and detection have to be modified [21]. SCENIHR stated in their opinions on risk assessment of NMs and nanoproducts that the current methodologies are generally likely to be able to identify the hazards associated with the use of NMs. However, they highlighted the need for modifications to the guidance on risk assessment [4, 22]. In its interim review, the 'Working Party on Manufactured Nanomaterials' of the OECD concluded that, just as with traditional chemicals, each NM may pose *specific challenges*, but that in most cases, they can be addressed using the *existing methods*. In some cases, it might be necessary to adapt the methods and test guidelines, but it will not be necessary to develop completely new risk assessment approaches [27]. Following this argumentation, risk assessment of NMs deems to be rather a modified standard chemical approach than a new kind of nano-specific procedure.

In contrast to the 'chemical-by-chemical' approach for substances in bulk, only a more detailed 'case-by-case' assessment could consider the different properties of NMs. However, serious doubts and concerns have been expressed by different stakeholders that a conventional paradigm may not consider all the dimensions of risk which may arise not only from material toxicity but also from interactions with complex biological and environmental systems [28].

Uncertainties in Risk Assessment of Nanomaterials

The concept of risk assessment tends to give the impression that science is a source of certainty. In order to achieve a balanced public debate, it is of great importance that the limits of certainty are better communicated and understood. Several definitions and methodologies have been proposed to describe and assess scientific uncertainty (e.g. [17, 21, 29–32]). In addition to the deficiencies of nanotoxicological studies, these approaches show the limitations of our knowledge about potential effects of the majority of NMs. Exceptions are long and rigid carbon nanotubes inducing severe tissue reactions that may result in tumour formation [26]. In most cases, uncertainty is handled in a qualitative manner by suggesting default factors or a reasonable worst case scenario. This scenario is often based on hazard studies considering pristine NMs at high concentrations. Uncertainty in deterministic risk assessment procedures may cause false negative or false positive predictions of possible effects and indicates the immaturity of quantitative risk assessment. This leads to serious questions regarding the use of traditional risk assessment approaches. Rocks stated that in the case of NMs, 'the key issues for risk analysis relate to methodological issues and knowledge gaps, which have relatively high levels of uncertainty and have important regulatory implications' ([21], p. 49).[5]

Most limitations in physico-chemical characterization result from the lack of suitable technologies and standardized methodologies for measuring the

[2] These studies analyse the patterns of health impacts in a defined human population being exposed to a certain contaminant.

[3] Test animals in in vivo studies are exposed to a controlled dosage of a contaminant, and the toxic responses are monitored.

[4] The toxic effect of a substance on the level of cells are studied isolated from the complex biological processes of whole organisms.

[5] A detailed list of knowledge gaps and methodological uncertainties in the different steps of the risk assessment process for NMs is given in [14, 33].

properties of NMs in complex matrices and at various stages of their life cycle [1, 21, 33–35]. Physico-chemical parameters are best researched for aerosols and airborne NMs. But even in those cases, 'there is no robust set of devices which could be used for monitoring, measuring and characterizing ENP [engineered nanoparticles] in workplace environments' ([35], p. 96). There is a particular need for methods to characterize properties such as agglomeration, aggregation, charge and solubility. However, solubility kinetics, which describes the behaviour to predict transport, fate and impact, also plays an important role [33]. Above all, the important question remains whether the most appropriate parameters have already been identified and whether additional particularly relevant endpoints such as catalytic activity have to be considered. Other critical obstructions are the lack of standard reference materials for NMs and of relevant research to better understand the characteristics of NMs that relate best to their toxicity.

The lack of an instrument and measurement strategy for identifying, monitoring and measuring concentrations of NMs also determines the limitations of exposure assessment. In this risk assessment stage, it is crucial to discriminate engineered NMs from background, natural and incidental NMs. Spatial variability and temporal variability are also important, especially for setting occupational exposure limits [36, 37]. It should be noted that there is not even an agreement about a concept of dose, concentration or metric of NMs in test systems [4, 21, 34, 35]. The standardization of measures of dosage for NMs should make reference to indicators representing the biologically active surface area, e.g. particle number and size distribution, rather than mass. Modelling is a practical way of obtaining predicted first-level concentrations by taking into account the lack of actually measured concentrations. For this purpose, it needs defined input parameters, which at present can only be based on crude assumptions.[6] A few exposure-related studies have been published on occupational scenarios while there are far fewer studies on environmental and consumer exposure and on acute or chronic exposures [23, 38]. Strategies which encourage comparison between workplace air concentration and personal exposure are also recommended. All in all, high-quality exposure data is largely missing.

[6] For a minimum set of items that should be considered in exposure assessment studies, see [37].

Hazard identification deals with critical cause-effect relationships that lead to categorically distinct classifications of substances. In general, a hazard to human health is classified by the main exposure routes (pulmonary, dermal, ingestion) and further broken down into local and systemic effects. According to review articles, most of the toxicity studies are related to the pulmonary exposure to NMs, as this is particularly relevant to occupational safety provisions [26, 35, 38, 39]. Nevertheless, the significance of oral exposure, gastrointestinal absorption and dermal exposure may considerably increase due to innovations in the food and cosmetic sector [35]. In addition, reviewers of the literature on nanotoxicology argued that there are only a few studies dealing with the systemic effects resulting from distribution and translocation of NMs [e.g. 26, 35]. Savolainen et al. [35] stated that '[t]hese findings provide evidence that at least some types of ENM [engineered NMs] can reach the systemic circulation through inhalation' ([35], p. 95), where they could induce their effects in any organ of the body [40, 41]. In particular, the observation that NMs can reach the brain via the blood stream has evoked much concern. However, Krug [26] objected that in most cases, only a very small fraction of the total dose applied actually penetrates into the bloodstream.

In general, it has not been fully understood how NMs interact with living systems, making it impossible to assess the relevant toxicological endpoints and exploring adverse outcomes and diseases. Toxicity studies focus on 'early-stage' effects such as cytotoxicity and inflammation, with few investigations of the long-term effects such as carcinogenicity. Recent reviews have concluded that information on the genotoxicity of NMs is still inadequate for us to draw general conclusions or to make a prediction of carcinogenicity [42, 43]. Moreover, the suitability of the existing in vitro methods for the prediction of in vivo toxicity must be validated [33]. Finally, the use of animal data from in vivo tests for modelling human toxicology is also questionable because the test results often cannot be transferred to humans.

Besides measurement and analytical methods, there is also a need for standardized and validated toxicological test systems as well as appropriate controls. Detailed experimental factors—such as the use of solvents in the case of non-dispersing NMs (e.g. fullerenes) in aqueous media—are not sufficiently addressed in many studies [23, 26, 33, 35, 38]. There is an ongoing debate on the

significance of existing high-dose studies and whether or not the methods are suitable for hazard characterization [44]. On the one hand, high-dose studies are unrealistic and unjustifiable, and on the other hand, they may be viewed as proof-of-principle studies to be validated by appropriately designed follow-up studies using justifiable exposures. In general, studies dealing with high-dose ranges only provide mechanistic insights but are not useful for toxicological assessments. In addition, it has to be considered that even a minor overdose of NMs can lead to erroneous interpretations. The coverage of cells in in vitro experiments, for example, could cause the death of the cells [26].

Moreover, strategies to reduce vertebrate testing and high-throughput screening methods are required [33]. Specifically, modelling approaches such as QSAR (Quantitative Structure-Activity Relationship) and QNAR (Quantitative Nanostructure-Activity Relationship) tools would be useful but are not yet available for NMs. Finally, studies that show no significant (hazardous) effects are usually not published, even though they are crucial to removing from NMs the suspicion of being a hazard [39].

Besides these 'nano-related' uncertainties, general limitations in chemical risk assessment have to be considered. In practice, risk assessors not only determine how experimental studies should be performed but also make decisions about the objects of investigation. Consequently, the same actors determine the means and ends. This is important particularly for the conventional assessment procedure, which is not performed by a plurality of actors, including stakeholders and innovators, and thus results in narrow scientific perspectives and knowledge. On the other hand, scientists have to be aware that their judgements can never be fully neutral and objective, but are influenced by values and tacit forms of knowledge. The choice of impacts to assess and of more or less conservative safety factors inevitably involves non-scientific considerations [45]. These normative factors cannot be strictly separated from scientific knowledge. Both scientific and normative aspects are inextricably linked.

Another constraint, especially for decision-making, is the contradictory experimental data which leads to different scientific interpretations. Risk managers have to deal not only with substantive uncertainty but also with ambiguity, equivocalness and dissent among experts when providing policy options. In general, risk assessment is challenged by the problem of the reliability of data, the huge amount of data and the comparability of the results. Different groups of experts answer different questions and use different pieces of evidence. This questions the evidence-based rationalization of the final risk management step. But also, the procedural legitimacy and the democratic quality of the risk assessment process are questionable, since the detailed technical procedure is complex and difficult to follow for risk managers and laymen. Due to the lack of a common terminology between scientists and decision makers, communication is becoming increasingly challenging. In addition, outsiders to the assessment process doubt about the transparency and trustworthiness in risk analysis [8].

According to the Second Regulatory Review on Nanomaterials [46], substantial modifications of the risk assessment framework for NMs are not envisaged within the next few years. However, minor amendments to REACH annexes, additional guidance by ECHA, market surveillance on consumer products and a web platform for sharing information are expected. In this regard, the OECD undertakes significant activities to provide improved test guidelines for toxicity testing. Based on the results of these activities, the Competent Authorities Subgroup on Nanomaterials (CASG Nano), with members of authorities, industries and NGOs, discusses regulatory improvements. The so-called REACH Implementation Projects on Nanomaterials (RIPoNs) tried to reach consensus among experts on necessary decisions. However, several stakeholders consider the risk assessment procedure according to REACH to be insufficient in the specific case of NMs and advocate the need for a more targeted legislative tool to close existing gaps in information and knowledge [47].

Additional Tools for Improving the Traditional Risk Assessment Concept

From the previous sections, we have learned that the science of risk assessment is becoming increasingly complex. While improved analytical techniques and tools produce more data, questions arise as to how to address issues of multiple risks, life cycle factors and risk communication. Moreover, the disconnect between the available data and the information needs of decision makers is becoming apparent. This means that there is an urgent need to improve the utility and relevance of

risk assessment. Numerous approaches have been developed to improve and facilitate decision-making based upon predicted risk. In principle, there are two different possibilities: either these approaches support the traditional risk assessment framework and try to overcome critical limitations and knowledge gaps by using additional non-conventional and complementary tools or they use alternative conceptual models to redesign the conventional relation of science and decision-making.

Benefits and weaknesses of additional tools for risk assessment were discussed by Jahnel [14]. These attempts include strategies to reduce the testing effort on a 'case-by-case' rationale by grouping and ranking the diverse NMs and synergies from the use of theoretical, computational, and experimental tools [48]. The support of life cycle assessment and value chain assessment was also highlighted [49, 50]. Since most of such additional methods cannot be used alone, it will be necessary to integrate them into a so-called integrated or intelligent testing strategy. The combination of the intelligent testing strategy and a tier-based approach provides toxicity-testing methods with a high throughput. This will probably be quicker, less expensive and more directly relevant to human exposure.

Rodricks and Levy mentioned that, in future, toxicologists will take a new role because risk assessment will expand into other areas such as product life cycle analysis and product design [12]. They also pointed to the changing role of toxicological studies, which may need to be either conducted or interpreted differently. The increased importance of mode of action studies confirms this hypothesis. The mode of action represents an intermediate level of complexity in between molecular mechanisms and physiological outcomes, especially when the exact molecular target has not yet been elucidated or is subject to debate. A strategic vision for future research was introduced 'to promote a shift from toxicity testing primarily in animal models to in vitro assays and in vivo assays using lower model organisms, along with computational modelling, thus enabling the evolution of toxicology from being an observational science into a predictive science' ([51], p. 8). The central part of this future toxicology will be formed by the toxicity pathways, which lead to an understanding of the molecular fundamentals of disease processes and their relationships to environmental factors. The hope is to benefit from modern methods and technologies such as genomics, epigenomics, transcriptomics, metabolomics, proteomics and cell and system biology, together with advanced analytical methods in biostatistics and bioinformatics [51]. Researchers even stress the term 'new' toxicology, also called 'toxicology for the 21st century' [51].

Alternative testing strategies and modelling approaches for the reduction of costs and animal use are closely linked with a change from a 'case-by-case' risk assessment to an approach based on grouping and ranking of NMs [52]. Attributes for the grouping and ranking of NMs could be physico-chemical parameters, biological and toxicological parameters, but also the nature of uncertainty or evidence of assessment data. Some grouping models focus on safety or risk management criteria, which enable a classification of different levels of concern or levels of action for regulatory purposes. The selection of the attributes depends on the specific goals, the different perspectives of the stakeholders involved and the intended addressees [14, 33]. The grouping and ranking of NMs are mostly based on physico-chemical properties, but a defined base set of characteristics and criteria related to risk is an important topic of current research. In addition, the association between material characteristics and subsequent cellular events is not yet well understood. This hampers our understanding of the nano-specific mode of action.

Control banding is another additional and pragmatic tool for risk assessment, derived from work of the pharmaceutical industry. As a heuristic assessment approach in the context of uncertainty, it uses the accepted risk paradigm and grades both hazard and exposure into different levels, usually referred to as 'bands'. The two sets of bands are combined, most often in a matrix, resulting in control or risk bands [53]. In summary, control banding tools designate risk levels associated with recommended levels of control. This approach could be characterized as a risk management strategy oriented to the precautionary principle rather than a classical risk assessment procedure. Control banding strategies, for instance, offer simplified and pragmatic solutions for controlling worker exposures beyond the traditional industrial hygiene [53]. However, the results are strongly influenced by the data and prioritization methods employed and may lead to different interpretations of the risks [54].

We can learn from these additional tools for risk assessment that results are complementary but not comprehensive, particularly because they produce qualitative data for first-tier or preliminary assessments. Moreover, it is obvious that methods for scientific

assessment and risk management are becoming more interlinked and the strict separation between 'science' and 'decisions' is blurring.

The Need for a General Re-appraisal of the Current Risk Assessment Process

A recently published opinion of the non-food Scientific Committees focuses on the new challenges in risk assessment of organic chemicals, including NMs, and describes a vision for an improved future risk assessment methodology in the EU [7]. For a number of reasons, the general procedures used for risk assessment of organic chemicals are anticipated to change substantially over the next few decades. On the one hand, the Scientific Committees realize a change from a rationale based on standard tests to one that is centred on modes of action (science push). On the other hand, there is the political aim to develop alternatives to laboratory animal testing due to a progressive reduction in testing and general ethical concerns (demand pull). Combining both aspects, the general goal should be to replace in vivo animal tests by in vitro tests and to develop new and more sensitive methods for identifying modes of action [7, 55].

Other kinds of anticipated changes in risk assessment are the availability of huge amounts of data from new methodologies, the associated information overload and the lack of an effective process for using this data appropriately (big data). Above all, the study underlines that it is crucial that the public trusts the process of risk assessment and that the findings and implications are understood and provide a sound basis for action where appropriate. For this purpose, a transparent procedure was developed, which shows how data is found, selected and used and how uncertainties should be expressed [18].

Following these changes, the Scientific Committees proposed a general rethinking of the traditional relationship between risk management and risk assessment. Stakeholders, in particular risk managers, should be involved in the risk assessment process without distorting its scientific objectivity. With regard to its usefulness for risk management decisions, the risk assessment process has to take into account the ways in which a risk can be helpfully contextualized. The Scientific Committees argued that '[a]t present, in Europe there is no definition of acceptable risk. Instead, it is often based solely on the application of very conservative, non-scientifically derived default factors. This is an issue that requires a dialogue among all stakeholders since its implications are much more far reaching than the domain of science' ([7], p. 20). Growing stakeholder concerns also force the development of a new paradigm: 'an exposure-driven, flexible, tiered approach, drawing continually on advances in technology and scientific understanding of biology, which meets the needs of stakeholders' ([7], p. 76).

The published scientific opinion was intended to complement the opinion on 'Making Risk Assessment More Relevant for Risk Management' [8], which focuses on improving the utility of risk assessment for risk managers. The motivation for this review was the perception that risk assessment as currently carried out does not adequately inform the risk management process. The starting point was an empirical analysis focusing on the needs of managers and policymakers for effective information. The Scientific Committees concluded that risk assessment results should be expressed in terms of value-relevant impacts rather than 'in terms of technical surrogates'. Indeed, risk assessors should express the likelihood of impact on the basis of evidence, but the impact should be based on entities that matter to people, such as human lifespan, healthy lives or ecosystem services. The Scientific Committees suggested a clear expression of uncertainty, evaluation of different possible scenarios and characterization of the populations and sensitive subpopulations. The background of these recommendations is that current approaches to the assessment of health and environmental risks frequently result in a variety of technical expressions of risk, based on the considered toxicological endpoints, biological responses or other technical parameters. These kinds of expressions are sometimes only indirectly related to the protection objectives pursued by risk managers. On the other hand, risk managers do not always provide an appropriate framework specifying the policy objectives in a manner that would allow usable risk assessment outputs.

In summary, the committees underlined the difficulties in the communication between risk assessors, risk managers and the general public. For example, risk assessors would often try to bridge the gap between technical parameters and the risk managers' interpretation of risk. This could lead to serious misunderstandings.

It is obvious that the presumed division of labour between scientific experts and policymakers in risk governance is commonly invoked, but problematic both conceptually and empirically [9]. Alternative conceptual models involving the redesign of the conventional

relationship between science and decision-making would be more useful to restore public trust and social legitimacy. In particular, the development of more responsive risk governance frameworks with real incorporation of stakeholder perspectives in the risk assessment process is considered a promising approach. This kind of 'opening up' appraisal would consider alternative questions, neglected issues, marginalized perspectives, ignored uncertainties, different possibilities and new options [56]. Its implementation would be possible within open and inclusive frameworks that also take into account the contextual knowledge of stakeholders and the general public [57, 58].

Different Alternative Risk Governance Models

The International Risk Governance Council (IRGC) framework for risk governance of nanotechnology [57] is a model involving a multitude of different actors in a dynamic process with various iterations and feedbacks. This model takes into account the societal impact and societal needs for understanding risk in a broader sense than by scientific experts and acknowledges complexity, uncertainty and ambiguity for risk governance decisions. For this purpose, it integrates a scientific risk-benefit assessment (including environment, health and safety (EHS) as well as ethical, legal and other social issues (ELSI)) with an assessment of risk perception and the societal context of risk, also called 'concern assessment'. In contrast to the linear traditional risk analysis method, the IRGC framework consists of four phases in a circular co-evolutionary process design with iterations and feedback. Some authors describe this governance model as a 'science in policy making' model [9]. The elements of the cycle include a pre-assessment step, followed by the risk appraisal, the tolerability and acceptability judgement phase and the risk management step. The risk appraisal stage is subdivided into a scientific risk assessment, and the above-mentioned concern assessment. The methods for concern assessment derive from the social sciences and include quantitative and qualitative methods. The 'translation' of societal values, concerns and perceptions into concrete measures for risk governance is a difficult challenge and remains an important topic in risk research [59]. This may also be the reason why this abstract model has not been put into practice until now. There is still the limitation that safety regulators are not vested with powers to include societal issues when undertaking risk assessment.

The detailed elements of the IRGC model and the process design in comparison with the conventional risk analysis are presented in Table 1.

Another proposed modification of the traditional risk assessment paradigm refers to the strict and artificial separation of risk assessment and risk management. Scientific considerations alone are not sufficient for the selection of questions to be addressed by experts; these judgements depend on prior, socially variable framing assumptions. The risk-based decision-making framework of the NRC tried to rethink how risk-related problems are identified and formulated and how a broad set of options might be considered [6]. The concept was developed in an NRC study addressing the evaluation and improvement of the traditional risk assessment approach according to the Red Book [6]. The committee suggested a number of improvements regarding the use of scientific knowledge and the utility and relevance for risk management decisions. The central elements of the framework are increased up-front planning, scoping and problem formulation to encourage a wider range of decision options. In this early stage of the process, risk managers, assessors and stakeholders should be involved to determine the major factors and the right questions. According to the idea of responsible innovation, risk and non-risk information will be integrated through the involvement of the business and epistemic community in the early stage of innovation [27]. The framing and problem formulation step, also called 'risk assessment policy', could be characterized as an upstream risk management step. Scientific deliberations are 'sandwiched' between this upstream and the downstream policy deliberation with a bi-directional information flow. Previous science policy was separated from the traditional risk assessment step. In this approach, scientific and policy deliberations are designed in a co-dynamic linear model with reciprocal links between science and policy (see Table 1). It is rather goal-oriented than fact-based [6, 9]. Risk assessment policy should address substantive, procedural and interpretative aspects of risk analysis. Substantive aspects are decisions about evidence, minimum data requirements and the description of the extent and nature of uncertainty and variability. Also, the question of whether cumulative effects have to be considered will be answered. Examples of procedural aspects are decisions about what kind of actors to involve, what kind of

Table 1Narratives, elements and process design of alternative risk governance models in comparison with the traditional Red Book model

	Red Book model	IRGC model	Risk-based decision-making model	Food safety governance model
Narrative	Evidence-based decision-making [2]	Science in policymaking [57]	Transparent model [6]	Precautionary and inclusive governance [16]
Science and decision steps	1. Risk assessment	1. Pre-assessment	1. Problem formulation and scoping	1. Framing
	2. Risk management	2. Risk appraisal	2. Planning and conduct of risk assessment	2. Assessment
		3. Tolerability and acceptability judgement	3. Risk management	3. Evaluation
		4. Risk management		4. Risk management
Assessment step	Conventional risk assessment	Risk assessment, concern assessment	Planning, risk assessment, confirmation of utility	Presumption of prevention, precautionary assessment, concern assessment and conventional risk assessment
Risk communication, stakeholder engagement, public engagement	Separate step in risk analysis	Integrated in the governance process	Integrated in the governance process	Integrated in the governance process
Process design	linear, unidirectional	open, cyclical, iterative, interlinked, co-evolutionary	co-dynamic linear, bi-directional, adaptive	cyclical, iterative, adaptive, inclusive, precautionary

process to apply and how to respond to uncertainties and dissent. Interpretative factors of risk assessment policy deal with judgements and assumptions for data interpretation.

This concept differs from the traditional risk assessment paradigm primarily in its initial problem formulation step in which risk management options and types of technical analyses are identified. This expands the array of the types of impacts assessed beyond individual effects to include broader questions of health status and protection. It provides a formal process for stakeholder involvement throughout all stages but includes time constraints to ensure that decisions are made.

The concept of risk assessment policy was already adopted by the Codex Alimentarius Commission [15]. This international risk management commission was established by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). The goals of the commission are the development of international food standards, guidelines and codes of practice to protect the health of consumers and ensure fair practices in the food trade that are relevant to the World Trade Organization (WTO). Core values of the food codex are the principles of collaboration, inclusiveness, consensus building and transparency. The commission stated that 'risk analysis is an iterative process, and interaction between risk managers and risk assessors is essential for practical application' ([15], p. 113). They proposed risk assessment policy to become 'a specific component of risk management' and recommended that it should be 'established by risk managers in advance of risk assessment, in consultation with risk assessors and all other interested parties' ([15], p. 44). The risk-based decision-making model of the NRC refers to this innovative guideline.

The proposed risk assessment policy is also an important governance impulse in food safety regulation. The general principles and requirements of food law are set out in the European Parliament and Council Regulation 178/2002 [60]. Food safety is based on three pillars: an independent, objective and transparent risk analysis; the application of the precautionary principle in the face of uncertainty and public consultation.

While separate responsibilities for risk assessment and risk management are generally seen as a welcome development, political decision makers, scientists and economic and civil society actors increasingly realize that the institutional separation creates new challenges

in terms of organizing the relationship with risk management. Also the Red Book gives rise to such concern as it states that 'the importance of distinguishing between risk assessment and risk management does not imply that they should be isolated from each other; in practice they interact, and communication in both direction is desirable and should not be disrupted' ([2], p. 6). Interaction is deemed particularly relevant at the beginning of the risk governance process when a problem needs to be defined and the questions for the risk assessors need to be delineated. The stage of framing and setting the terms of reference has also been identified as a critical issue for interaction in food governance [61].

The Food Law EC 178/2002 Explicitly Addresses the Relationship Between Risk Assessment and Precaution in Art. 7 (1): 'In specific circumstances where, following an assessment of available information, the possibility of harmful effects on health is identified but scientific uncertainty persists, provisional risk management measures necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment' [60].

The interpretation and application of the precautionary principle vary across countries and authorities and depend on the regulatory framework, the individual case and the assessors and managers. The identification, characterization and communication of scientific uncertainty and the handling according to the precautionary principle are also case-specific rather than based on guidelines [61]. According to the second pillar of the food law, there should be a more systematic approach to dealing with the challenge of scientific uncertainty.

With regard to public consultation, the question remains how framing in risk assessment could be organized to engage stakeholders and the public and to consider different perspectives in a way that addresses uncertainty and ambiguity. Potential procedural and institutional responses were proposed in the general framework for the precautionary and inclusive governance of food safety [16]. This framework underlines the importance of the framing assumptions in informing risk assessment (see Table 1). Besides risk assessment and risk management, two further steps are deemed to be necessary: firstly, the framing step which relates to risk assessment policy adopted by the Codex Alimentarius Commission, and secondly, a separate evaluation step. The four steps of the cycle are interlinked and involve multi-actor engagement processes. In addition to the conventional risk assessment procedure, assessment within this framework includes the presumption of prevention, a precautionary assessment and a concern assessment [62]. The established linear structure in safety governance is changed into an open, cyclical, iterative and interlinked process, as also outlined by the IRGC [57]. Communication and engagement of stakeholders and the public are seen as integral parts of all steps of the risk governance framework. Risk communication is supposed to contribute to mutual learning in line with the requirements of good governance, including transparency, accountability and legitimacy [62]. This promotes the idea of inclusive governance. In Table 1, the single elements of the three different governance models and the process design are compared with the traditional risk analysis.

Similar patterns and elements for improving the Red Book model have emerged in the presented governance approaches. The linear model has been mostly replaced by a circular procedure [16, 57]. However, Millstone pointed out that circular models have no conspicuous starting point and provide policymakers with less guidance [9]. Therefore, the risk-based decision-making model of the NRC introduced a dynamic linear model which does not start solely from scientific facts.

In all three governance models, framing assumptions are understood as socially variable judgements which should be explicitly separated from the scientific assessment step. It is also generally accepted that the input and participation of risk managers are needed both in preparing an assessment procedure and throughout the whole process [7, 8]. Advantages of this integration are, first, the focus on the scope of the risk assessment process and the increased likelihood that the scientific findings will be better shared by risk managers. Second, it will lead to an improved communication and interaction between the two mutually influenced spheres of science and decisions. The alternative governance models described in Table 1 also acknowledge the integration of stakeholder and public alignment in the knowledge creation phase. This could take place in different governance steps, mostly in the framing or concern assessment part of the concepts, even in the specific scientific risk assessment process. In general, the presented models are useful examples of the transformation of the normative principles of good

governance, in particular towards inclusion, openness, transparency and responsibility [63].

Discussion and Prospects for Risk Assessment of Nanomaterials

The identified challenges in risk assessment of NMs go beyond the multiple nano-specific problems and even question the routines of chemical risk assessment by considering more general governance and institutional issues. Potentially improving the risk assessment process should be interpreted as a multi-level task with multidimensional amendments that need to be harmonized and integrated meaningfully. In general, scientific procedures alone are not sufficient to deal with complex, ambiguous and uncertain issues of risk [64]. Although the traditional risk assessment framework may be powerful for bulk chemicals, its use for estimating the potential risks posed by NMs in the near term is limited. Increased research in broader issues than chemical-based ones, such as decision-making, risk governance and a systematic evaluation of complementary risk assessment tools, is needed [65].

In fact, many complementary tools are currently available to improve conventional assessment. However, most of the additional risk tools serve as preliminary risk screening or research prioritization tools and have not been tested in terms of functionality and limitations over a wider range of applications [33, 66]. Even for experts, it is challenging to decide which one to choose in a given context. This shows that there is an urgent need for guidance in identifying the right instruments but also the right questions and goals for any concrete situation.

For this purpose, the Codex Alimentarius Commission proposed an additional framing step with substantive, procedural and interpretative assumptions established by risk managers in consultation with risk assessors and all interested parties [15]. This so-called risk assessment policy is an important development of scientific and political deliberation that questions the traditional dichotomy of risk assessment and risk management [2]. Risk assessment policies have already been articulated in some risk domains [9]. For example, Scientific Committees recommended that risk assessment and socio-economic analyses should be carried out along separate but parallel tracks, with dialogue between them especially during the initial problem formulation. An extended dialogue with all stakeholders both in initial forums and in final consultations was proposed to clarify issues and ensure increased identification and framing [8]. The Scientific Committees also proposed to establish an independent, multidisciplinary academy of risk assessors that would work with the US National Academy of Sciences and similar bodies in other nations involved in advising on risk assessment [7]. More concrete procedural and institutional responses were proposed in the general framework for the precautionary and inclusive governance of food safety. Specific interface institutions should further improve the interaction of politicians, scientists, economic players and civil society actors [16].

All frameworks presented in Table 1 widely acknowledge the importance of stakeholders besides the scientific routines. This opens the dialogue between actors and prevents any bias resulting from a one-sided perspective. But it also provides a richer repertoire for the policymaking process, practice and outcome. If risk managers can make key dimensions of the framing step explicit, they will readily identify areas of agreement. This will indicate conditions under which science-based policymaking can become democratically and scientifically legitimate.

The question remains whether the presented models are viable and whether political pressures and legal authorities constrain their implementation. This might be the reason for the lack of concrete adaptations of existing regulations so far. Robinson and Levy argued that in the special case of engineered NMs, some elements of a baseline risk assessment may be needed before meaningful regulatory options can be formulated by risk managers. This indicates that some insight may be necessary to design appropriate options. The authors proposed an iterative approach and illustrated the process between the assessment step and the risk management step as a kind of spiral, with several loops of data collection, analysis and evaluation [67]. Iterative, tiered, flexible and adaptive procedures are increasingly recommended. 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’ ([27], p. 47).

According to the growing importance of the European concept of ‘responsible research and innovation’, it is necessary to promote the participation of stakeholders right from the early stage of research and innovation. In fact, the risk assessment frameworks re-

evaluated by the IRGC, NRC and in the food sector proposed additional steps to integrate risk and non-risk information and stakeholder involvement [8, 27]. Also, the expert group of the European Academies Science Advisory Council recommended strengthening the links between science, regulation and the general public to increase efforts towards a common terminology, common needs for data collection and a balanced communication [68]. This would implement Stirling's idea of shifting away from 'stylized analysis/participation contrasts' towards 'opening up analytic and participatory appraisal alike'. Appraisal does not only imply formalized assessment routines. It also includes a wider sociopolitical discourse [56]. Both participation and analysis are specific instances of social appraisal in an 'opening-up mode'. The purpose of this kind of appraisal is to consider ignored uncertainties, to examine different possibilities and to highlight new options, delivering a plural policy advice [56]. However, the translation of inclusion, openness, transparency and responsibility into actual practice is not a trivial undertaking. Until concrete procedures are set in place, 'participation' and 'responsibility' remain empty words.

In most cases, risk assessment policies are decided by expert risk assessors rather than democratically accountable representatives, and alternative risk governance models are developed initially by scholars and policy analysts [9]. The adoption of alternative risk governance models can be observed primarily in the domain of food safety policymaking. Up to now, the only official governance institution acknowledging an inclusive upstream framing step is the Codex Alimentarius Commission. In 2007, all Member States of Codex, including the European Commission, accepted the provisions of the Codex, which means that the co-dynamic model proposed by the NRC has actually been adopted already in food safety practice [15]. Continued research is needed to promote the implementation of those responsive risk governance frameworks to support appropriate decision-making at a regulatory level. This is of particular importance for new and emerging technologies, such as nanotechnology, with a complex, inconsistent and multifactorial risk potential.

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References

1. Fleischer T, Jahnel J, Seitz SB (2012) NanoSafety – risk governance of manufactured nanoparticles. Final Report IP/A/STOA/FWC/2008-096/LOT5/C1/SC3. European Parliament. Directorate General for Internal Policies. Directorate G: Impact Assessment. Science and Technology Options Assessment. PE 482.685. Brussels. http://www.europarl.europa.eu/RegData/etudes/etudes/join/2012/482685/IPOL-JOIN_ET%282012%29482685_EN.pdf. Accessed 23 Oct 2014
2. National Research Council (NRC) (1983) Risk assessment in the federal government: managing the process. The National Academies Press, Washington, DC
3. 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 396:1–849
4. Scientific Committee on Emerging and Newly Identified Health Risks (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. European Commission, Brussels. http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_004c.pdf. Accessed 23 Oct 2014
5. European Food Safety Authority (EFSA) (2011) Scientific opinion: guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain. EFSA J 9(5):2140
6. National Research Council (NRC) (2009) Science and decisions: advancing risk assessment. The National Academies Press, Washington
7. Scientific Committee on Health and Environmental Risks (SCHER), Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Scientific Committee on Consumer Safety (SCCS) (2013) Opinion on addressing the new challenges for risk assessment. European Commission, Brussels. http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_037.pdf. Accessed 23 Oct 2014
8. Scientific Committee on Health and Environmental Risks (SCHER), Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Scientific Committee on Consumer Safety (SCCS) (2013) Opinion on making risk assessment more relevant for risk management. European Commission, Brussels. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_130.pdf. Accessed 23 Oct 2014
9. Millstone E (2010) The evolution of risk assessment paradigms: in theory and in practice. SPRU – Science and Technology Policy Research Report, Sussex. http://pages.ucsd.edu/~aronatas/workshop/Millstone%20Paper%2026April%202010.pdf. Accessed 23 Oct 2014
10. Weber M (1958) Gesammelte Politische Schriften, 2nd edn. J.C.B. Mohr (Paul Siebeck), Tubingen
11. Risk Commission (2003) Ad hoc commission on 'revision of risk analysis procedures and structures as well as of standard setting in the field of environmental health in the Federal Republic of Germany'. Final Report, Berlin

12. Rodricks JV, Levy JI (2013) Science and decisions: advancing toxicology to advance risk assessment. Toxicol Sci 131(1):1–8
13. OECD (2003) OECD series on testing and assessment 44 ENV/JM/MONO 15. OECD, Paris
14. Jahnel J (2015) Addressing the challenges to the risk assessment of nanomaterials. In: Dolez P (ed) Nano engineering: global approaches to health and safety issues. Elsevier, Amsterdam, pp 485–521
15. Codex Alimentarius Commission (2007) 17th edn. World Health Organization, Food and Agriculture Organization of the United Nations, Rome. ftp://ftp.fao.org/codex/publications/ProcManuals/Manual_17e.pdf. Accessed 21 Oct 2014
16. Dreyer M, Renn O (2009) Food safety governance. Integrating science, precaution and public involvement. Springer, Berlin
17. Walker WE, Harremoës P, Rotmans J, van der Sluijs JP, van Asselt MBA, Janssen P, Krayer von Krauss MP (2003) Defining uncertainty: a conceptual basis for uncertainty management in model-based decision support. Integr Asses 4(1): 5–17
18. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) (2012) Opinion on the Memorandum on the use of the scientific literature for human health risk assessment purposes – weighing of evidence and expression of uncertainty. European Commission, Brussels. http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_s_001.pdf. Accessed 23 Oct 2014
19. European Food Safety Authority (EFSA) (2009) Guidance of the Scientific Committee on Transparency in the Scientific Aspects of Risk Assessments carried out by EFSA. Part 2: general principles. EFSA J 1051:1–22
20. European Commission (2009) Rules of procedure of the scientific committees on consumer safety, health and environmental risks and emerging and newly identified health risks. Directorate-General for Health & Consumers, adopted on 18 December 2009, Brussels. http://ec.europa.eu/health/scientific_committees/docs/rules_procedure_en.pdf. Accessed 23 Oct 2014
21. Rocks S, Pollard S, Dorey R, Levy L, Harrison P, Handy R (2008) Comparison of risk assessment approaches for manufactured nanomaterials. Final Report. Defra, London
22. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) (2009) Opinion on risk assessment of products of nanotechnologies. European Commission, Brussels. http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf. Accessed 23 Oct 2014
23. Aschberger K, Micheletti C, Sokull-Kluttgen B, Christensen FM (2011) Analysis of currently available data for characterising the risk of engineered nanomaterials to the environment and human health—lessons learned from four case studies. Environ Int 37(6):1143–1156
24. Commission Recommendation 2011/696/EU of 18 October 2011 on the definition of nanomaterial. OJ L 275:38–41
25. Handy RD, van den Brink N, Chappell M, Mühling M, Behra R, Dusinska M, Simpson P, Ahtiainen J, Jha AN, Seiter J, Bednar A, Kennedy A, Fernandes TF, Riediker M (2012) Practical considerations for conducting ecotoxicity test methods with manufactured nanomaterials: what have we learnt so far? Ecotoxicology 21:933–972
26. Krug HF (2014) Nanosafety research—are we on the right track? Angew Chem Int Ed 53:2–18
27. OECD (2012) OECD series on the safety of manufactured nanomaterials 33 ENV/JM/MONO 8. OECD, Paris
28. Maynard AD, Aitken RJ, Butz T, Colvin V, Donaldson K, Oberdörster G, Philbert MA, Ryan J, Seaton A, Stone V (2006) Safe handling of nanotechnology. Nature 444(7117): 267–269
29. Stirling A (2001) On science and precaution in the management of technological risk. European Commission Joint Research Centre publication 19056/EN/2. JRC, Ispra
30. Refsgaard JC, van der Sluijs JP, Højberg AL, Vanrolleghem PA (2007) Uncertainty in the environmental modeling process—a framework and guidance. Environ Model Softw 22(11):1543–1556
31. Grieger KD, Hansen SF, Baun A (2009) The known unknowns of nanomaterials. Describing and characterizing uncertainty with environmental, health and safety risks. Nanotoxicology 3:222–233
32. Hunt G, Riediker M (2011) Building expert consensus on problems of uncertainty and complexity in nanomaterial safety. Nanotechnol Percept 7:82–98
33. StoneV, Pozzi-Mucelli S, Tran L, Aschberger K, Sabella S, Vogel U, Poland C, Balharry D, Fernandes T, Gottardo S, Hankin S, Hartl M, Hartmann N, Hristozov D, Hund-Rinke K, Johnston H, Marcomini A, Panzer O, Roncato D, Saber AT, Wallin H, Scott-Fordsmand JJ (2013) Research prioritization to deliver an intelligent testing strategy for the human and environmental safety of nanomaterials. Final report of the project ITS-NANO (FP7/2007-2013 grant agreement no. 290589). http://www.its-nano.eu. Accessed 23 Oct 2014
34. Oberdörster G (2010) Safety assessment for nanotechnology and nanomedicine: concepts of nanotoxicology. J Intern Med 267(1):89–105
35. Savolainen K, Aleniusa H, Norppaa H, Pylkkänena L, Tuomia T, Kasperb G (2010) Risk assessment of engineered nanomaterials and nanotechnologies—a review. Toxicology 269:92–104
36. Bergamaschi E (2009) Occupational exposure to nanomaterials: present knowledge and future development. Nanotoxicology 3(3):194–201
37. Clark K, van Tongeren M, Christensen F, Brouwer D, Nowack B, Gottschalk F, Micheletti C, Schmid K, Gerritsen R, Aitken R, Vaquero C, Gkanis V, Housiadas C, de Ipina JML, Riediker M (2012) Limitations and information needs for engineered nanomaterials-specific exposure estimation and scenarios: recommendations for improved reporting practices. J Nanoparticle Res 14:970–983
38. ENRHES (2010) Engineered nanoparticles: review of health and environmental safety. An international collaborative review involving researchers from Edinburgh Napier University, the Institute of Occupational Medicine, the Technical University of Denmark, the Institute for Health and Consumer Protection of the European Commission's Joint Research Centre, and the Institute of Nanotechnology. Project Report. http://www.nanowerk.com/nanotechnology/reports/reportpdf/report133.pdf. Accessed 23 Oct 2014
39. Krug HF, Wick P (2011) Nanotoxicology: an interdisciplinary challenge. Angew Chem Int Ed 50(6):1260–1278
40. Kreyling WG, Semmler M, Erbe F, Mayer P, Takenaka S, Schulz H, Oberdörster G, Ziesenis A (2002) Translocation of

ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. J Toxicol Environ Health A 65:1513–1530
41. Elder A, Gelein R, Silva V, Feikert T, Opanashuk L, Carter J, Potter R, Maynard A, Ito Y, Finkelstein J, Oberdörster G (2006) Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environ Health Perspect 114:1172–1178
42. Gonzalez L, Lison D, Kirsch-Volders M (2008) Genotoxicity of engineered nanomaterials: a critical review. Nanotoxicology 2:252–273
43. Landsiedel R, Kapp MD, Schulz M, Wiensch K, Oesch F (2009) Genotoxicity investigations on nanomaterials: methods, preparation and characterization of test materials, potential artifacts and limitations—many questions, some answers. Mutat Res 681:241–258
44. Oberdörster G (2010) Concepts of nanotoxicology. NanoAgri 2010 Conference. http://www.nanoagri2010.com/fao_mini_papers_extra_files.pdf. Accessed 23 Oct 2014
45. Millstone E, van Zwanenberg P, Marris C, Levidow I, Torgersen H (2004) Science in trade disputes related to potential risks: comparative case studies. Institute for Prospective Technological Studies, Seville
46. Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee: Second Regulatory Review on Nanomaterials. COM (2012) 572 final, Brussels, 3.10.2012
47. Stakeholders' Response to the Communication on the Second Regulatory Review on Nanomaterials (2012). http://www.beuc.org/publications/2012-00667-01-e.pdf. Accessed 23 Oct 2014
48. European Union (2013) Safety Evaluation Ultimately Replacing Animal Testing (SEURAT-1). http://www.seurat-1.eu. Accessed 23 Oct 2014
49. Grieger KD, Laurent A, Miseljic M, Christensen F, Baun A, Olsen SI (2012) Analysis of current research addressing complementary use of life-cycle assessment and risk assessment for engineered nanomaterials: have lessons been learned from previous experience with chemicals? J Nanoparticle Res 14: 958–981
50. Robinson DKR (2011) Value chains as a linking-pin framework for exploring governance and innovation in nano-involved sectors: illustrated for nanotechnologies and the food packaging sector. EJLT 2(3):1–28
51. Savolainen K, Backman U, Brouwer D, Fadeel B, Fernandes T, Kuhlbusch T, Landsiedel R, Lynch I, Pylkkänen L (2013) Nanosafety in Europe 2015-2025: Towards safe and sustainable nanomaterials and nanotechnology innovations. Finnish Institute of Occupational Health, Helsinki. www.ttl.fi/en/publications/electronic_publications/pages/default.aspx. Accessed 23 Oct 2014
52. Oomen AG (2013) Concern-driven integrated approaches to nanomaterial testing and assessment—report of the NanoSafety Cluster Working Group 10. Nanotoxicology. doi:10.3109/17435390.2013.802387]
53. Paik SY, Zalk DM, Swuste P (2008) Application of a pilot control banding tool for risk level assessment and control of nanoparticle exposures. Ann Occup Hyg 52(6):419–428
54. Brouwer DR (2012) Control banding approaches for nanomaterials. Ann Occup Hyg 56:506–514
55. U.S. Environmental Protection Agency (EPA) (2013) Next generation risk assessment: Incorporation of Recent Advances in Molecular, Computational, and Systems Biology (External Review Draft). EPA/600/R-13/214A, Washington, DC. http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=259936. Accessed 23 Oct 2014
56. Stirling A (2008) 'Opening up' and 'closing down': power, participation, and pluralism in the social appraisal of technology. Sci Technol Hum Values 33(2): 262–294
57. IRGC (2006) White paper on nanotechnology risk governance. International Risk Governance Council, Geneva
58. Fleischer T, Jahnel J, Seitz S (2014) Technology assessment beyond toxicology. In: Arnaldi S, Ferrari A, Magaudda P, Marin F (eds) Responsibility in nanotechnology development. Springer, Berlin, pp 75–91
59. Fleischer T, Haslinger J, Jahnel J, Seitz SB (2012) Focus group discussions inform concern assessment and support scientific policy advice for the risk governance of nanomaterials. IJETS 10:79–95
60. 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 31:1–24
61. Ely A, Stirling A, Dreyer M, Renn O, Vos E, Wendler F (2009) The need for change. In: Dreyer M, Renn O (eds) Food safety governance. Integrating science, precaution and public involvement. Springer, Berlin, pp 11–29
62. Ely A, Stirling A, Dreyer M, Renn O, Vos E, Wendler F (2009) Overview of the general framework. In: Dreyer M, Renn O (eds) Food safety governance. Integrating science, precaution and public involvement. Springer, Berlin, pp 29–47
63. Commission of the European Communities (CEC) (2001) European Governance. A White Paper. COM 428 final, Brussels, 25.07.2001
64. Funtowicz S, Ravetz JR (1992) Three types of risk assessment and the emergence of post-normal science. In: Krimsky S, Golding D (eds) Social theories of risk. Praeger, Westport, pp 251–273
65. Grieger KD, Baun A, Olsen R (2010) Redefining risk research priorities for nanomaterials. J Nanoparticle Res 12:383–392
66. Riediker M, Ostiguy C, Triolet J, Troisfontaine P, Vernez D, Bourdel G, Thieriet N, Cadène A (2012) Development of a control banding tool for nanomaterials. J Nanomater 2012:1–8
67. Robinson LA, Levy J (2011) The [R]evolving relationship between risk assessment and risk management. Risk Anal 31(9):1334–1344
68. European Academies Science Advisory Council (EASAC) and European Commission Joint Research Centre (JRC) (2011) Impact of engineered nanomaterials on health: considerations for benefit-risk assessment. JRC Reference Report EUR 24847 EN. European Union, Luxembourg