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Toward the Development of Decision Supporting Tools That Can Be Used for Safe Production and Use of Nanomaterials

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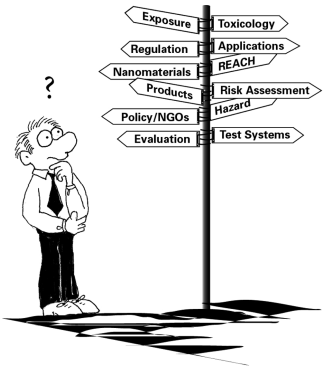
CONSPECTUS

Although researchers have intentionally produced and used nanomaterials for more than a century, nanotechnology has made its mark in most areas of daily life in the past 20 years. Now thousands of products contain nanoparticles, nanofibers, or nanostructured parts. Because some chemical products have caused severe problems to human health and to the environment, we should consider the overall biological and toxicological effects of nanomaterials as we decide whether to use them in various products. We should also reflect on the mechanisms for making these decisions, which may greatly influence the development, production, and use of such products.



The preselection of appropriate materials during the early product design state should allow industry and applied researchers to mitigate the risks of these new materials. However, currently the human and ecological risks of the applied nanomaterials during their life cycle are unknown. A large set of physicochemical characteristics can determine the potential human and environmental exposure to and hazards from nanomaterials. Thus, researchers will need many years to gather and analyze all the data to perform a comprehensive risk assessment for engineered nanomaterials and to develop a sound decision making process. The ideal risk assessment approach would include cost-effective screening processes to target resources toward the risks of greatest concern.

The outcome of the risk assessment is only as good as the quality of the data used. Unfortunately, the actual review process of most journals that publish on nanotoxicology focuses on "mechanistic studies and results" rather than a toxicologically relevant outcome. For example, journals often do not include studies that show no effect as worthy of publication ("no-effect-studies" dilemma), which can lead to misleading interpretations of toxicological data for hazard identification.

However, even with insufficient data sets, researchers can produce a preliminary comparable risk assessment ("approximate" risk assessment). Researchers have already performed risk-based evaluations of nanomaterials grounded on the comparison of exposure concentrations with no-effect levels (as required for chemical risk assessment), examining generic nanomaterials such as "nano-TiO_2" but not specific forms or modifications. Even though these data sets on hazard and exposure are incomplete, they already provide the basis to illustrate the current state of knowledge and uncertainties. Therefore industry and applied researchers can calculate the probability that an adverse effect might occur and begin to balance the benefits and potential risks of an innovation. Based on the increasing numbers of nanotoxicology publications and funding programs, this Account reviews the decision support approaches that already exist to safely implement engineered nanomaterials during an early phase of innovation.

Introduction

Engineered nanomaterials (ENM) have special characteristics, and they are therefore investigated intensively by academic and industrial scientists with the aim to improve existing functions in products or to implement new ones. However, these special characteristics of ENM can also be a challenge because of new or different implications for human health and environmental safety compared with conventional chemicals. Decision makers in industry and applied research have to select the right nanomaterial to achieve a specific function for their products. Apart from the technical performance of the product, the question is what nanomaterial they should implement in order to reduce the risk for the environment and human health. It is estimated

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that the initial design of a product determines 70% of the cost of a product's development, manufacture, and use.[1] These costs are influenced not only by the production equipment but also by the safety issues during production processes (occupational health) and human and environmental risks (consumer acceptance). "The maximum degrees of freedom for managing a new technology occur at the design and development phases".[2] Thus, it seems prudent for industry and applied research to mitigate the risks during early design stages by preselecting the "appropriate" nanomaterials. Currently, the key challenge for industry and applied research are the unknown human and ecological risks of the applied nanomaterials during their life cycle.

Based on past experiences with chemicals or materials, the potential risks of nanomaterials are in the focus of media, consumer groups, and authorities. Consequently, from the perspective of risk assessment the risks of nanomaterials might be too much emphasized in relation to the risks of other known or new substances. However, it is reasonable that in the context of nanotechnological research, many international and national initiatives have been launched earlier in the innovation cycle than in the past to obtain data about the safety and risks of these new materials in the US (e.g., refs 3 and 4) and the EU.[5]

However, it will take its time to gather and analyze all the data required to perform a comprehensive risk assessment for ENM to support a sound decision making process.[6−9] This is due to (1) high variety of ENM of the same composition (size, morphology/structure, surface, impurities), (2) their possible high surface reactivity, (3) sparse and limited equipment and methodology to monitor time and space resolved particle concentration, and consequently (4) the high requirements for human health and environmental hazard studies (standardization) and the experimental concepts. In a perfect world, each individual ENM should be investigated in relation to its physicochemical properties and its effects on numerous biological end points. Due to time and cost restraints, this is currently not feasible. Hence, there is a need to facilitate near-term decisions by "alternative" risk assessment approaches in the context of high uncertainties.

In the first part of this Account, we will give a short review on alternative approaches for an "approximate" risk assessment. These approaches aim to support decision makers in research and industry in the near term to safely implement ENM during an early phase of innovation. These alternative approaches are a balancing act, because they all suffer from a lack of data about exposure and hazard and a lack of consensus about the relevant indicators and about the correct

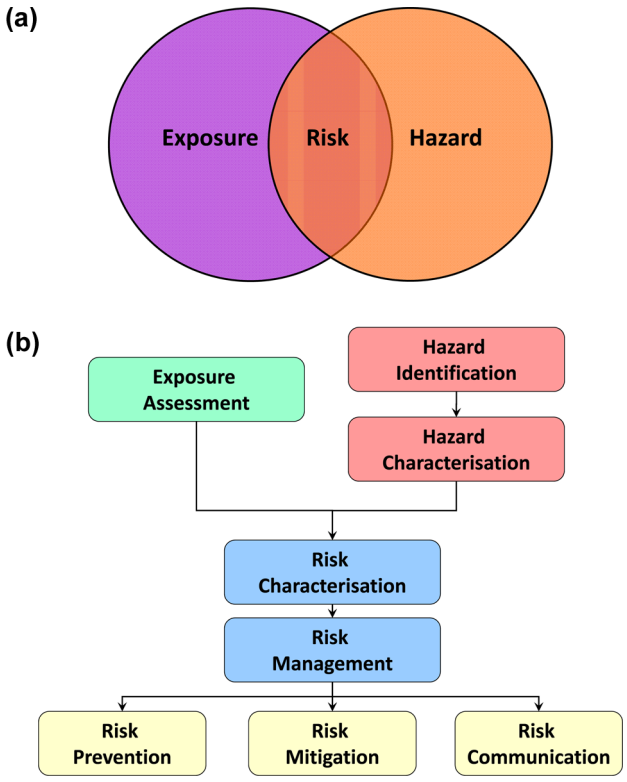

FIGURE 1. (a) Risk as a function of hazard and exposure, if there is no hazard or no exposure, there will be no risk. (b) Risk assessment and risk management regarding possible adverse substances or materials (adapted from ref 11).

metrics inter alia. Even if these approaches do not fully guarantee the avoidance of false negatives (underestimated risks) or false positives (overestimated risks), they are a good starting point for a "comprehensive" risk assessment. In the second part of this Account, we illustrate approaches for a preliminary comprehensive risk assessment with focus on data generation. In the third part, we discuss intelligent testing strategies and modeling, which may facilitate accelerated data generation and the relevance of data quality management.

Risk analysis and uncertainties

Risk is a function of hazard (for human health or the environment) and the probability of exposure (Figure 1a). Risk analysis is classically composed of risk assessment and risk management.[10] The risk assessment includes hazard identification and characterization, exposure assessment, and risk characterization, which is then integrated into the risk management, where either prevention, mitigation, or communication strategies are developed to implement the technology in a safe and sustainable way (Figure 1b).

For a safe implementation of an innovation, a careful risk analysis is mandatory within the conventional risk assessment.

In the conventional risk assessment, the chemical composition of a material governs the human and environmental hazards. For ENM, in contrast, a large set of physicochemical characteristics seems to determine the potential human and environmental hazard and exposure.[12] Thus, the implementation of an innovation in the field of nanotechnology is challenging because established knowledge or regulatory decision tools cannot be fully applied and have to be discussed and adapted case by case.

In any situation of uncertainty, characterized by the lack of hazard or exposure data or both, decision makers in industry or research need and demand approaches that facilitate near-term decisions.[9,13−16] During the early phase of innovation, the development pathways of new materials and products can be influenced easily; later the influence is hampered by several socio-economic irreversibilities such as the return of investments.

A complete risk assessment for an individual ENM is not yet possible due to extensive uncertainties,[17] which may be the result of different reasons, such as a lack of data on potential human health and environmental hazards and exposure, contradictory experimental data, uncertainty about the physicochemical properties of the ENM that may be responsible for any specific toxicity or hazard,[18] uncertainty about the dose metric for the ENM,[19−21] or a lack of data on toxicokinetics of the ENM.

Grieger et al.[22] have analyzed the uncertainties and assume that most of them are "either partially or wholly epistemic" and, thus, may be "reduced with further research efforts". To gain a specific function within a new product, material scientists or industrial decision makers have to decide first to achieve this by use of ENMs or "conventional" materials. Second the kind or type of ENM has to be selected. Third they have to conclude whether there is sufficient information for hazard and exposure in order to achieve a sound risk assessment.

Alternative Approaches for Near-Term Decisions

Numerous alternative approaches that facilitate near-term decisions in the context of insufficient data for ENMs have evolved during recent years. Such approaches are also called "control banding",[23] complementary tools, or approximative risk assessments and have been developed as pragmatic tools to manage the risks resulting from exposure to potentially hazardous compounds in the absence of validated toxicological and exposure information.[8,24−27] Insufficient data can mean that (i) no experimental studies or models are available, (ii) data are numerous but contradictory, or (iii) data are of insufficient quality. In order to support decision making, these approaches attempt to approximate or rank potential hazard, exposure, or risks of ENM and to give structure to the state of knowledge and uncertainty. So far all these nanospecific alternative approaches seem to follow the conventional risk assessment procedure (see Figure 1b). Some of these approaches focus on specific phases of the product life cycle, while others take into consideration the whole product life cycle. They differ also in assessing specific ENM categories and products. The results of these approaches are (1) approximation of hazard, exposure, and risks (e.g., refs 25 and 28), (2) relative ranking of hazards or of risks (e.g., ref 29), (3) ranking of fields of priority for risk research (e.g., refs 17 and 18), and (4) ranking of fields of precautionary actions (e.g., ref 30).

All these alternative approaches are based on peer reviewed hazard and exposure studies or on data of parent or bulk material of the ENM. Based on the interpretation of the data of these studies and assumptions, experts identified preliminary relations between the physicochemical properties of ENMs and potential hazard or exposure and established algorithms in the form of decision trees or decision matrices or assigned scores to hazard parameters. Many of these decision trees integrate additional information such as production volumes of ENMs. These decision trees can be used in order to rank hazard (Figure 2), exposure (Figure 3), and risks of ENMs roughly and to derive priority areas for risk research.[8,17,18,25,31,32]

Höck and colleagues[30] developed a tool that supports the identification of precautionary action fields. Here the decision makers insert the requested data and receive information about priority fields for precautionary actions. Whenever a piece of required information is not available, the highest priority value must be used. Stoffenmanager nano 1.0[34] and NanoSafer[35] are also tools that facilitate the relative evaluation of occupational risks and recommend risk reduction measures. The approaches of Höck and colleagues[30] and SRU[25] focus on data requirements that are easily ascertained. The following properties of an ENM seem to be critical for exposure and hazard assessment: small size, high surface reactivity, high aspect ratio, no agglomeration, no or slow dissolution, not firmly integrated into matrix material. The experience has shown that manufacturers have difficulty obtaining information on these and other physicochemical properties of ENMs from suppliers. Furthermore there is no broad scientific consensus of how these properties, especially in combination, generally affect human health and the environment.

There are some alternative approaches that provide valuable information on hazard and risk ranking for specific

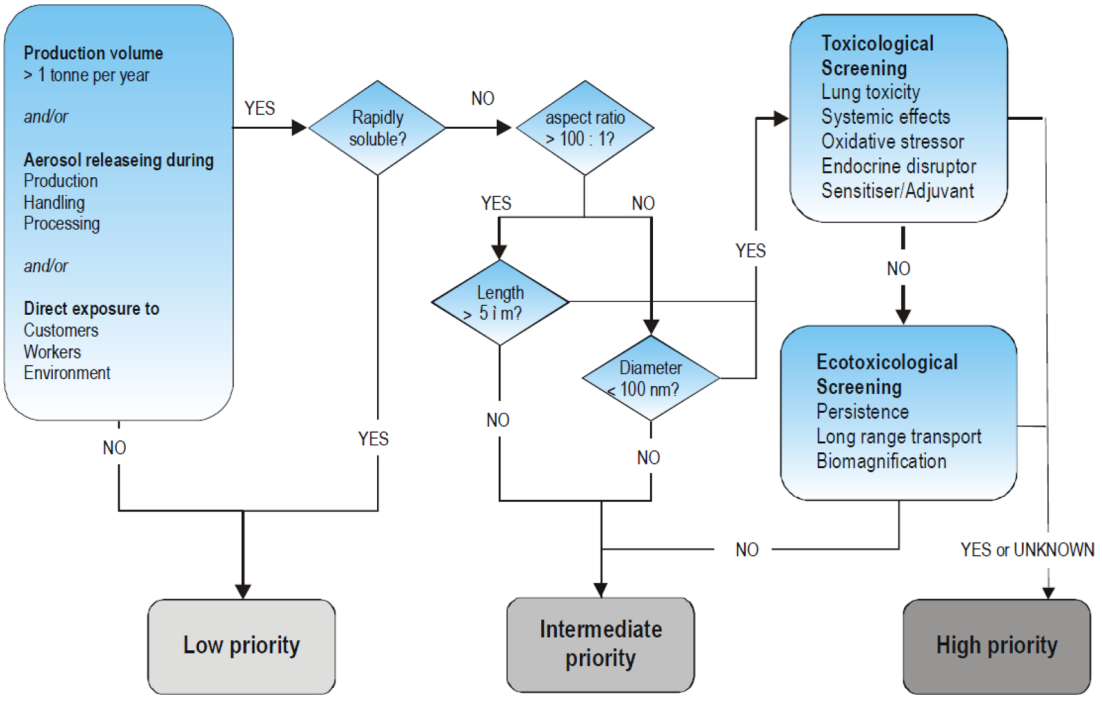

FIGURE 2. Preliminary scheme (decision tree) for the hazard characterization of ENMs.[33]

ENM categories or an approximate risk assessment of specific ENMs and products. SRU[25] presents a preliminary risk assessment of selected nanoproducts. These products are ranked in three risk categories: products of low risk, "sufficient" data, or both, products of medium risk, medium uncertainties, or both, and products of high risk, high uncertainties, or both.

Tervonen et al.[29] proposed a decision support system for classifying nanomaterials into different risk categories. A stochastic multicriteria acceptability analysis was used as the basis. Five nanomaterials were classified based on a set of performance metrics for toxicity, physicochemical properties, and expected environmental impacts. The authors stress that this classification is a starting point for a more thorough follow-up analysis. Zuin et al.[28] used the "Weight of Evidence (WoE)" approach and expert judgment for a relative hazard ranking of four materials on the basis of the integration of their physicochemical properties and toxicological effects.

Another study assessed the ENM effects on human health and the environment for eight different ENMs used for the façade coating and textile industry.[36] This work was a first attempt to differentiate ENM categories with respect to relevant environmental, biological, and technical end points. Interestingly, some ENMs may affect the environment less severely than they may affect human health, whereas the case for others is reversed. This is especially true for CNTs, which are interpreted as "rather safe" for the environment and "uncertain" for human health.

The results of the alternative approaches are not always conclusive. In areas with no sufficient data, the border between facts and assumptions is fluid. Thus, the results are strongly influenced by the selection of data, scientific methods, and assumptions and consequently may lead to different interpretations of the risks.

The alternative approaches circumvent the lack of data needed for a comprehensive (traditional) risk assessment by taking additional information into account.[16] For example in order to evaluate exposure, the product life cycle and the product design have to be taken into account.[37,38] The design of a product, for example, the location, the photocatalytic activity, the bonding, and the concentration levels of the ENM in a product, determine in what quantities and forms ENMs might be unintentionally released during the product life cycle.[36,39,40] Further added avenues for evaluation include inter alia the anticipated global volumes of ENM production.[41]

Added Values of Alternative Approaches

The results and information provided by these approaches should comprise support for or against the decision to go ahead with an innovation with a specific ENM. Alternative approaches do not necessarily prevent false negatives or false positives and should not be seen as substitute for a

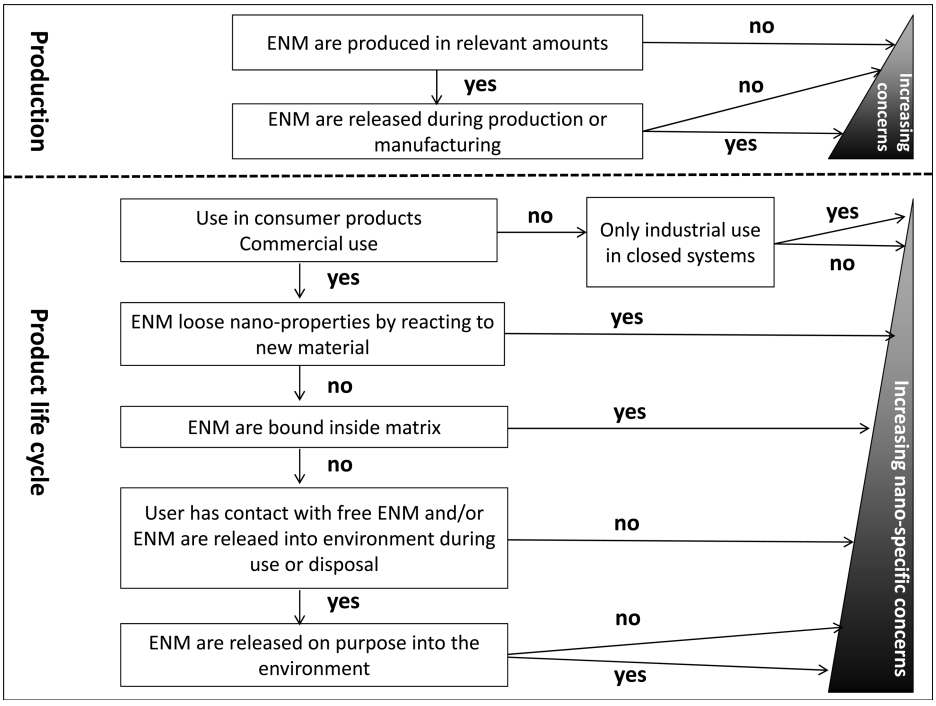

FIGURE 3. Scheme (decision tree) for the prioritization of ENMs following exposure criteria (adapted from ref 25).

comprehensive risk assessment, but rather as a first step toward it. However, these approaches may provide valuable information to the decision makers so that they are better informed to select or to avoid the application of a specific ENM. For example, a product that during its life cycle may unintentionally release ENMs to natural waters (e.g., coating for boats and houses) should not contain ENMs that increase toxicity in the presence of aquatic organisms and could enter the environment in relevant concentrations. Thus, we encourage industries and material researchers to take into consideration information from these alternative approaches, in order to minimize risks by selecting appropriate nanomaterials for specific products. Moreover, these alternative approaches are appreciated by industrial decision makers in order to improve the communication within the value chain.

Requirements That Alternative Approaches Should Fulfill

As nanotechnologies are evolving, new exposure and hazard information will be generated constantly. Therefore, the alternative approaches must be able to accommodate new data in order to enable a most accurate risk assessment on an ENM.[42] The approaches should incorporate any information on the product design and all stages of the product life cycle. Additionally, the whole life cycle of the ENM should be considered, for example, also the behavior of the ENM in the technosphere such as wastewater treatment facilities, recycling facilities, and incineration plants.

These alternative approaches carry uncertainties with them. Apart from the state of knowledge, the state of uncertainty also has to be characterized and illustrated in order to reinforce decision-making. With growing knowledge about the relationship between physicochemical properties and hazard and exposure, the alternative approaches have to be refined, and ENM categories have to be split into subcategories.

The alternative approaches should be combined with other elements of the well described comprehensive frameworks[25,43,44] and strategies,[45,46] where also the evaluation of benefits (cost–benefit analysis) and the comparison of ENMs with alternative materials are propagated. Last but not least, the results can only be as good as the quality of the data applied. Thus, the selection of data to be considered in the approach is crucial.

First Comprehensive Risk Assessments for ENMs

Several authors have already tried to follow a risk-based evaluation of ENMs for the environment based on the comparison of predicted environmental concentrations (PECs) and predicted no effect concentrations (PNECs), following the approach used for conventional chemicals.[47] One major conclusion was that in principle the approach

TABLE 1. Relative Risk Rankings for ENM in the Environment and for Human Exposure Based on Alternative and Comprehensive Risk Assessments[a]

reference	assessment type	environment	human
Zuin et al., 2011[28]	alternative		QD ≫ C_{60} > SWCNT > CB
Tervonen et al., 2009[29]	alternative	CdSe > Ag > MWCNT > C_{60} > Al	
Mueller and Nowack, 2008[49]	comprehensive	TiO_2 > Ag > CNT	
Gottschalk et al., 2009[50]	comprehensive	Ag > ZnO > TiO_2 ≫ CNT = C_{60}	
Aschberger et al., 2011[51]	comprehensive	ZnO ≫ Ag > TiO_2 > MWCNT = C_{60}	Ag > MWCNT > C_{60} > TiO_2
O'Brien and Cummins, 2010[52]	comprehensive	TiO_2 > Ag > CeO_2	

[a]Abbreviations: QD, quantum dots; SWCNT, single-walled CNT; MWCNT, multiwalled CNT; CB, carbon black.

used by REACH in the EU is also suitable if only limited data is available.[26] Meanwhile several studies supported this statement by illustrating that the information available is sufficient to draw first quantitative conclusions. These approaches rely heavily on models to estimate environmental concentrations because no trace analytical methods are available to selectively quantify ENMs in environmental matrices.[48] Mueller and Nowack[49] used a simple material flow modeling to derive PEC values for ENMs for Switzerland. The modeling was based on estimates of ENM production and followed the life-cycle of the ENM-containing products. The release into technical and environmental compartments was estimated, and mass flows to water, air, and soil were calculated and transformed to regional environmental concentrations based on established procedures.

This approach was further extended by Gottschalk et al.[50] by using a probabilistic approach and incorporation of additional environmental processes, for example, sedimentation. The general approach was also based on the whole life cycle of ENM-containing products. Risk quotients were calculated for air, surface water, sewage treatment effluents, soil, and sludge-treated soil.

Aschberger et al.[51] performed an environmental risk assessment for four types of nanomaterials. The employed risk assessment methodology was that of a regulatory risk assessment under REACH,[47] with modifications to adapt to the limited available data. If possible, environmental no-effect concentrations were established from relevant studies by applying assessment factors in line with the REACH guidance and compared with available exposure data. To indicate the uncertainties associated with the derived values and make clear that they should not be used for any regulatory purposes, the authors decided to use the terms indicative no-effect concentrations (INECs) instead of PNECs. Also O'Brien and Cummins[52] used an equivalent approach and estimated environmental concentrations and evaluated the ecotoxicological literature to derive benchmark dose lower confidence limits (BMDL) for ENMs.

A similar approach of comparing predicted environmental concentrations and health limits was also applied to derive human health risks. Aschberger et al.[51] estimated indicative human no-effect levels (INECs) and compared them to available exposure data. The main risks for human health were found to arise from chronic occupational inhalation exposure. The information on consumer exposure was considered to be too scarce to attempt a quantitative risk characterization. Using a similar method O'Brien and Cummins[52] concluded that the toxicological risks for human uptake of ENMs from drinking water were of very low concern.

The results obtained so far are to some extent comparable to each other but show of course some differences in the relative ranking of the ENM (see Table 1). A major issue is that in all approaches a generic ENM is evaluated (e.g., nano-TiO_2) and not a specific material (e.g., anatase-TiO_2 with AlOOH coating and siloxane functionalization). The risk assessments therefore have to deal with a wide variety of different reactivities and properties of all the different forms of one ENM-type.

Data Quality Management: The Base for Reliable Risk Assessment

Over the past decade, national and international research programs in nanoscience and nanotechnology generated among new inventions and applications also a broad spectrum of methodologies, data, and overviews addressing nanosafety aspects of specific nanomaterials.[53] Depending on the economic interest in certain nanomaterials, the amount and quality of data available can be different. Depending on the application, exposure and potential hazard of the same nanomaterial may be very different; thus, only case-by-case assessment is possible. A careful life cycle evaluation of the product delivers the specific need for information about exposure and hazard, which will be necessary to assess the nanomaterial (applied in the innovation) of interest. This critical process may need the support of designated experts.

The quality of published data is crucial for the process of risk assessment and peer-reviewed studies are the major

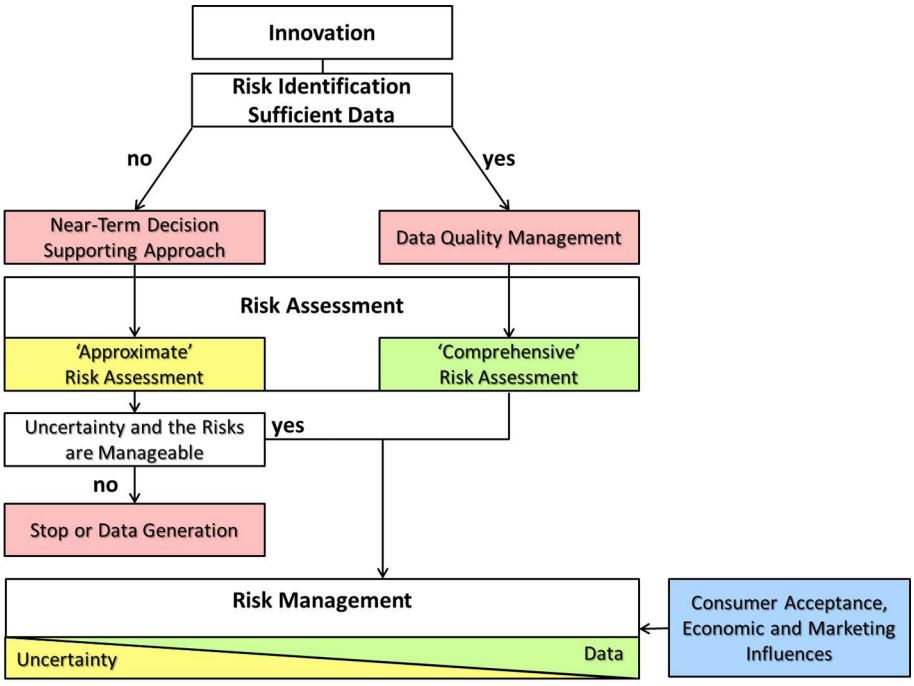

FIGURE 4. Decision supporting chart for safe implementation of nanomaterials.

source for such data. But these highly scientifically based publications assessed by experts are difficult to follow for nonscientific readers. Important for a high quality hazard study is the inclusion of a detailed and comprehensive material characterization as demanded by different experts,[54] a realistic dose–response relationship according to good laboratory practice, appropriate controls, and a multievidence-based methodological setup. Within the knowledge base for nanomaterials presented on the website www.nanoobjects.info, a criteria checklist has been published which is used to select those studies that include sufficient information about these important points in their publications (download available at http://www.nanoobjects.info/cms/lang/en/Wissensbasis/kriterienkatalog). Unfortunately the peer-review process is not able to avoid fully weak or doubtful studies in terms of reliability or significance.[11] Evidence maps, a transparent and fact based characterization tool of scientific evidence of reported results, increase the reliability of the current knowledge and help nonexperts to come to an informed judgment.[55] Other sources of reground knowledge are reviews summarizing the current knowledge and in the best cases including a hazard ranking of selected nanomaterials.[36]

The increasing number of nanomaterials developed will require alternative testing strategies replacing the time and cost intensive case-by-case studies. A tier-based approach using high throughput systems would improve the output.[24,55,56] However, such intelligent test strategies are still under development and not validated or standardized for nanomaterials. An alternative and promising way to get fundamental data, without increasing the experimental work is considering quantitative structure–activity relationship (QSAR)[57] or modeling.

Time and space resolved exposure measurement and carefully conducted release studies are rare or even not existent but crucial for the risk assessment. The ongoing development of portable devices[58] and further development of methodology to detect, identify, and quantify nanoparticles in the different environmental compartments (as done in ref 59) will help to reduce uncertainty of the exposure and release data. To overcome today's lack of data, modeling of potential exposure is an alternative approach to define at least minimum or maximum levels.[16]

In certain cases, the benefit of an innovation is clearly identified, but the near-term decision evaluation has identified uncertainties and knowledge gaps; thus, the generation of data is required. In particular to identify a hazard, the specific properties of the ENM require additional attention in assessing their potential biological effects: uptake and biodistribution, surface effects, and material properties (such as shape, agglomeration status, contaminants) as discussed recently.[11] If the near-term decision models predict a verifiable risk and the benefit of the innovation is not obvious, the development toward the market should be stopped. Finally, the decision makers have to decide whether the risks and

the uncertainties are acceptable and manageable and the consumers will accept a product under these circumstances.

Conclusions

Actually there is a highly innovative environment for nanotechnological developments, but on the other hand, questions about the possible consequences for human health and environmental safety grow steadily. Based on experience we had with several chemicals and materials during past decades, the discussion about new technologies and materials came up earlier in the phase of development. With regard to nanotechnology, the safety aspects are within the focus of the public since the real manipulation on the atomic scale started in the mid-1980s.

Although there is uncertainty and lack of knowledge about specific aspects and possible risks of ENMs, there is already enough information available to draw first conclusions.[60] Nevertheless, most results obtained so far are only to some extent comparable to each other and are not always conclusive and show sometimes remarkable differences in the relative ranking of the ENM. In areas with insufficient data, the border between facts and assumptions is fluid. Thus, the resulting evaluation is strongly influenced by the quality of the selected data or the scientific methods.

To establish a product with ENM on the market, one of the first and most important steps is data quality management (Figure 4). We can follow two different approaches when evaluating new compounds, the "comprehensive risk assessment" approach when enough data are available and the "approximate risk assessment" when few or contrasting data are available. This means that with insufficient data sets a comparable risk assessment in the sense of an approximate risk assessment is possible and can lead to suitable risk management, which includes measures to balance benefits and potential risks of an innovation by calculating the chance of occurrence of probable effects. The final decision is not only dependent on the scientific risk ranking but also on soft criteria such as economic considerations, consumer acceptance, and entrepreneurial spirit or other market influences.

In this context the decision support approaches presented and discussed in this Account fulfill several important roles with respect to nanomaterials:

- They are able to steer the innovation process in an early phase in industry and academia.
- They can support decisions when following the precautionary approach.
- They can be used as an intermediate approach when some data are available but not sufficient for the comprehensive risk assessment.

Inadequate studies may result in false-positive or false-negative outputs; thus, the specialty of the ENM in biological assays should be taken into account. Scientists in an academic environment are dependent on publications as one of the evaluation indicators, hence provoking a "positive" outcome from their projects. But toxicological validation is based on standardized methods with comparable experimental setups and realistic parameters for the treatment of biological systems (cells or animals). Because "no-effect-studies" have nearly no chance to be published, the picture of nanotoxicology is distorted, probably leading in the wrong direction for decisions.[11] Moreover, far too high exposure concentrations have been used in many toxicological studies during the past years, and these studies have been cited preferably by newspapers and other public media, guiding the public debate probably in the wrong direction. For the sustainable production and use of ENMs in innovative products, we need an objective discussion observing the principles of toxicology and following established rules for assessing the risks (considering both effects and exposure). As we have shown in this Account, performing such risk assessments is already possible, using both alternative and comprehensive approaches.

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BIOGRAPHICAL INFORMATION

Claudia Som is a senior scientist working on system analytical tools for decision support for the development of new technologies. She got her diploma degree in biology at the University of Zurich. Since 1992, she established cooperative arrangements on the sustainability of technologies with industrial associations. Her current interest is to contribute to sustainable innovation in industry.

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Harald Krug received his Ph.D. in Animal Physiology from the Georg-August University in Göttingen (1982). In 1996, he was appointed as Professor at the Technical University of Karlsruhe (Environmental Toxicology) and in 2008 at the University of Berne (Switzerland). He heads the Department *Materials meet Life* at the Federal Institute for Materials Science and Technology (Switzerland) and is a member of the board of directors. His main focus is nanomaterials and their possible interaction with living organisms.

Peter Wick heads the research laboratory for Materials-Biology Interactions at the Federal Laboratories for Materials Science and Technologies, Empa, in St. Gallen since 2010. He studied and received his Ph.D. (2002) in cell and molecular biology at the University in Fribourg (Switzerland). His interest is to establish the methodology and scientific knowledge for a comprehensive understanding of how engineered nanomaterials influence human health. He is a member of the advisory board of the Swiss Action Plan on Nanomaterials and Precautionary matrix as well as Editorial Board Member of *Nanotoxicology*.

FOOTNOTES

The authors declare no competing financial interest.

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