Risk Assessment of Engineered Nanomaterials: A Survey of Industrial Approaches

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Engineered nanomaterials pose many new questions on risk assessmentthat are not yet completely answered. Thus, voluntary industrial risk assessment initiatives can be considered vital to the environmental health and safety issues associated with engineered nanomaterials. We present an overview of the general properties of nanomaterial products in the market, and how industry, in general, approaches issues of nanomaterial risk and safety based on a written survey of 40 companies working with nanomaterials in Germany and Switzerland. It was found that the nanomaterials in this sample exhibited such a diversity of properties that a categorization according to risk and material issues could not be made. Twenty-six companies (65%) indicated that they did not perform any risk assessment of their nanomaterials and 13 companies (32.5%) performed risk assessments sometimes or always. Fate of nanomaterials in the use and disposal stage received little attention by industry and the majority of companies did not foresee unintentional release of nanomaterials throughout the life cycle. The development of risk and safety decision frameworks in industry seems therefore necessary to ensure that the potential risks of engineered nanomaterials are taken into consideration.

Introduction

Zurich.

The introduction of nanoparticulate materials (NPM) into more and more applications will inevitably also result in their introduction into environmental compartments and ecosystems. It is therefore likely that also an exposure of the human body to NPM will take place. NPM, defined here as engineered materials with one or more dimensions below 100 nanometers, have large surface areas per unit of volume and novel electrical and magnetic properties that differ from

conventional materials (*1*). NPM can generally be divided into bulk NPM, typically produced in the chemical or the polymer industry in metric tons (e.g., titanium dioxide and carbon black), and novel NPM with targeted properties fulfilling specific functions (e.g., carbon nanotubes and quantum dots) (*2*). There are already many products containing NPM in the market today, and the unique properties of NPM have raised expectations for more applications ranging from lightweight materials, drug-delivery systems, and catalytic converters to usage in food, cosmetics, and leisure products.

However, NPM possess unique properties that may have toxic potential (*3–6*) and implications for their environmental fate (*7–10*). Therefore, various stakeholders have called for action to ensure the workplace, consumer, and environmental safety of NPM production and products (*2*). NPM may fall under different regulations depending on the application, but the regulations are currently found to be inadequate in dealing with the unique properties of NPM (*11*). For example, material safety data sheets (MSDS) treat NPM as bulk material, and therefore fullerene (C_{60}) is often represented by the MSDS of carbon black (*12*). As a result, there is an ongoing discussion regarding assessing and managing the risks derived from NPM properties, the methodological challenges involved, and the data needed for conducting such risk assessments (*1, 2, 5, 6, 12–15*).

Industry, scientists, governmental bodies, and environmental advocacy groups find regulatory interventions useful, but they are of different opinions as to whether regulations should be evidence-oriented or precaution-oriented, voluntary or top-down controlled (*2*). Voluntary initiatives have been under consultation in the United States and the UK (*1, 16*). At the moment, regulatory bodies do not know to which extent they should regulate this area. Improved scientific knowledge on the potential hazards and risks of NPM is needed to determine the type and extent of regulations (*2*). Regulations often demand that certain risk assessment activities or precautionary measures are conducted by industry, such as the Toxic Substances Control Act for regulating chemicals in the United States (*11*). However, given that NPM may cause harm (*3–6*) and that there are currently no regulations that take the specific properties of NPM into account, the responsibility for safe production and products is mostly left with industry. Risk assessment procedures and precautionary measures initiated by industry are therefore vital to managing the environmental health and safety of NPM. It is therefore of utmost importance to investigate industrial initiatives in this area, but to the best of our knowledge no such investigations were publicly available at the time of this study.

The objectives of this study were to explore what properties the NPM have that are currently available on the market, and how industry responds to these properties in terms of risk assessment procedures and precautionary measures. To this end, we conducted a written survey of the representative industries involved in NPM production and application in Germany and Switzerland. Through the responses collected from various companies we are able to present an overview of the general properties of NPM products in the market and to gain insights into how industry in general approaches issues of NPM risk and safety.

Methods

In order to investigate what properties the NPM on the market have and what companies have done with regard to

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FIGURE 1. Industry sectors involved in NPM production or application.

risk assessment procedures, we conducted a written survey. The data were collected in Germany and Switzerland between December 2005 and February 2006. The sample consisted of a total of 135 companies: 48 of them were from Switzerland and 87 were from Germany. The companies were identified through websites, literature reviews, and personal contacts (see Supporting Information). A prerequisite for company selection was that the company had to have NPM-based products available on the market. A total of 40 companies filled out the questionnaire, which represents a response rate of 29.6%. We asked for the person responsible for risk assessment or for nanomaterials in the company to complete the survey: 16 of the responding persons had worked for less than 5 years at the company, 13 persons had worked there between 5 and 10 years, and 10 persons had worked there for more than 10 years. One person did not fill out this question.

Figure 1 gives an overview of the industrial sectors of all companies in the sample compared with the responding companies, and shows that the responding companies give a representative picture of the sample. The two largest industrial sectors were "chemicals and materials" and "consumer goods" and the most common application fields for NPM within these industrial sectors were coating and thin films for different materials (e.g., glass, wood, and textile), medical applications, and electronic products. Twenty of the participating companies were from Switzerland and 20 were German companies. Twenty-five companies had less than 100 employees, 8 companies had between 100 and 1000 employees, 6 companies had more than 1000 employees, and 1 company did not answer this question. Fourteen companies reported that they were "primary producers" of NPM, 21 companies were "downstream users" working with purchased NPM for their applications, 2 companies produced and purchased NPM for their applications, and 3 companies did not answer this question.

Design of the Questionnaire. The questionnaire started with a product description, since NPM may be used either as a pure chemical substance (or a mixture of substances) and/or incorporated as a component of a product. We specified that we were referring to the NPM product with the greatest production volume in the company, be it a pure NPM or a product containing NPM, and the respondent was asked always to refer to this product when answering the questions. Although the company might also handle other NPMs with various toxicity profiles, focusing only on one NPM was a necessary, although not ideal, limitation in order to simplify the questionnaire and thereby increase the probability of a successful response. The minimum size of the NPM also had to be below 100 nanometers (nm), according to the NPM definition. Additionally, as different situations could occur where information was not available for the respondent, for example, if a primary producer conducted tests of which the secondary producer was

TABLE 1. **Design of the NPM Questionnaire**

Material Properties

- Please give a short description of your product and its application.
- Do you produce, buy, or buy and refine the nanoparticulate material?
- What are the mean particle diameter and the particle size distribution of the nanoparticulate material in your product?
- What form/shape does the nanoparticulate material take?
- What is the chemical composition of the nanoparticulate material?
- Has the surface of the nanoparticulate material been modified in order to present specific reactivity properties?
- What is the surface charge of the nanoparticulate material in pure water at pH 7?
- Does this nanoparticulate material have an adsorbing capacity?
- Does the size distribution of the nanoparticulate material change in the following environments (water, soil or atmosphere)?
- Which of the following processes describes the degradation of the nanoparticulate material?

Exposure and hazard assessment related procedures

- Are there possible unintentional releases of the NPM into the following systems (water, soil, air, human body) during production, consumption, or disposal in your country?
- Have you evaluated the possible uptake of the NPM by the following organisms (aquatic, soil, humans, other organisms) during the different stages of the product life cycle?
- Against which toxicities has the NPM been tested?

Risk assessment procedures

- Does your company conduct risk assessments where NPM are involved?
- What was the result of your risk assessment?
- Have measures been taken based on these risk assessments?
- Has your company introduced maximal exposure times and exposure concentrations for workers while handling nanoparticulate materials?

unaware, the respondent had the options in the case of all questions of answering "not aware", "unknown", or "not evaluated".

The questionnaire was then divided into three main sections: (1) material properties, (2) exposure and hazard assessment, and (3) risk assessment. The questions can be found in Table 1. In the Results section the number (*n*) is given in parenthesis indicating the number of survey answers for this question.

Material Properties. The specifications of the physical and chemical properties of the NPM are crucial for assessing the hazards (ecological and toxicological) and exposure. Based on the published literature and proceedings from

scientific conferences (see, e.g., *1, 3–5, 7–11, 13–20*), the following appear to be the most important properties suggested for risk assessments.

• Size. A reduction in size, resulting in an increase in surface-to-volume ratio and an enhanced toxicity per unit of mass compared to larger particles of the same substance, has been observed (*5*). NPM are, for example, more likely than larger sized particles to penetrate deeper into the lungs, may translocate from the lungs into the body resulting in exposure to internal organs, and may be able to pass the blood–brain barrier (*5*).

• Shape. This may prove to be an important factor. Fibrous shaped NPM provide an example in relation to inhalation where length and biopersistency seem to determine inflammatory potential (*19*).

• Chemical Composition. The intrinsic toxicological properties of the chemical are of importance for the toxicity of NPM (*13*). The effects of carbon black have, for example, been shown to be more severe than those of TiO₂ (20).

• Surface Modifications and Charge. The much greater surface area of the particle and, consequently, the greater potential reactivity of both passive surface layers and active surface agents may enhance the intrinsic toxicity of the NPM (*13*). The enhanced surface area is seen as a possible driver for inflammation of tissue. Studies have shown that NPM surface modification may result in diminishing cytoxicity such as by functionalization of carbon nanotubes (*17*) or coating of iron oxide NPM (*18*).

• Adsorbing Capacity. Other substances of concern might be adsorbed onto the NPM. For example, carbon-based NPM have been proven efficient in adsorbing polycyclic aromatic hydrocarbons (*9*).

• Solubility and Persistence. Materials with low solubility or degradability could persist in biological systems for long durations. Through active functionalization or adding surfactants to the NPM the solubility can be modified to differ from that of the bulk chemical agent (*13*).

Exposure and Hazard Assessment Related Procedures. The chemical properties (e.g., surface chemistry, reactivity, surface coatings, or adsorbed species), particle size range and distribution, and other physical characteristics (e.g., shape, density, surface charge, solubility, etc.) determine the form in which the NPM may be released.

In this part of the questionnaire we were interested in finding out which exposure- and hazard-related procedures had been conducted by the company. The three questions asked in this part addressed releases, uptake by organisms, and toxicity of NPM.

Risk Assessment Procedures. NPM have different characteristics depending on the material, product, and life cycle stage in consideration, and currently toxicity has to be evaluated case by case (*21*). The current risk assessment approaches used for chemicals are generally assumed to be applicable to NPM (*1, 13*) and a generic risk assessment can be useful as a starting point of the case-specific assessment. The questionnaire did not specify the term "risk assessment" and the individual companies were therefore free to interpret which procedures qualify as a risk assessment. The questions were asked in this way as there are no best practices for NPM risk assessments developed at the moment. Furthermore, we were interested to know which precautionary measures the companies had taken and whether these were based on a conducted risk assessment.

Results

Nanomaterial-Related Properties. The NPM in our sample had a wide size distribution, as seen in Table 2, but with 54.2% ($n = 13$) cases reporting a maximum size below 100 nm. However, only 24 out of 40 companies gave complete information on the size distribution of their NPM. The majority of nanomaterials produced had a spherical shape (62.5%, $n = 25$), 20.0% ($n = 8$) were reported as engineered with a sheet-like structure, and 5.0% ($n = 2$) were fibrous shaped. The majority of the NPM were composed of metal oxides and nitrides (55.0%, $n = 22$); fewer were composed of carbon (10.0%, $n = 4$) or organic compounds (10.0%, $n =$ 4). The NPM were surface modified in 60.0% of the cases (*n* $=$ 24). In 35.0% of the cases ($n = 14$) they had a positive or negative surface charge in water at pH 7; 5 of these 14 companies reported that their NPM had multiple charges. The adsorption tendency indicates that in the majority of cases ($n = 12, 30.0\%$ vs. $n = 9, 22.5\%$) the NPM tend to attach themselves to surfaces. In 15 cases (37.5%) the nanomaterials could be degraded by chemical processes, often in combination with other processes (4 cases photolytic, 2 cases biological); however in 11 cases (27.5%) the NPM were reported as nondegradable, a possible indication of persistency. As seen in Table 3, only in 9, 6, and 7 cases (22.5%, 15.0%, 17.5%) aggregation in water, soil, and air, respectively, was reported, whereas in 13, 12, and 14 cases (32.5%, 30.0%, 35.0%) the size distribution of the NPM remained stable in contact with water, soil, and air, respectively. In 8 of the 12 cases which in all environments reported no size changes, the NPM had additionally been surface modified (functionalized or coated). We ran several analyses (crosstabulations and cluster analyses) of the NPM properties (size, shape, chemical composition, adsorption capacity, surface modifications, surface charge, size distribution changes, and degradability) to investigate whether the NPM could be assigned into different categories with regard to properties important for determining a potential risk. However, the NPM in our sample exhibited such a diversity of property combinations that a division into categories was not deemed reasonable.

Exposure and Hazard Assessment Related Procedures. The potential release of NPM throughout the life cycle (production, consumption, and disposal) into environmental media (water, air, soil) or a direct exposure to humans was reported possible only in 5–10 cases (see Table SI-2 in the Supporting Information). It is also noteworthy that a majority $(50.0-67.5\%, n=20-27)$ of companies felt sure that no release could take place throughout the life cycle. This finding is interesting considering the small number of companies which had undertaken investigations of potential uptake of the NPM by different organisms throughout the life cycle (see Table SI-3, Supporting Information). Only 4 companies reported investigating the potential uptake by organisms of NPM released from the production site or from the product: one company investigated the potential uptake by both aquatic and soil organisms and three companies investigated human uptake. There were around 30 cases where no investigations were reported in the production or use phase. At the disposal stage no investigations of potential uptake were reported. In comparison, more companies have conducted toxicity tests. Among those 10 companies (25.0%) which reported conducting toxicity tests, there were 9 acute toxicity tests conducted, whereas more long-term tests were less frequent, occurring in the following order: mutagenicity $(n = 5)$ carcinogenicity $(n=4)$ > immune toxicity $(n=3)$ > hormone activity $(n = 1)$. Eighteen companies (45.0%) reported no such tests conducted, and 7 company representatives (17.5%) were not aware of any tests conducted, whereas 5 companies (12.5%) did not answer the question.

Risk Assessment Procedures and Precautionary Measures. In response to the question "Does your company conduct risk assessments where nanoparticulate materials are involved?" 26 companies (65.0%) indicated that they did not perform any risk assessments, 13 companies (32.5%) performed risk assessments sometimes or always, and 1 company (2.5%) did not answer the question.

TABLE 2. **NPM Characteristics in Sample**

TABLE 3. **Response to the Question: "Does the size distribution of the NPM change in the following environments?"**

Of the 13 companies conducting risk assessments, 8 companies reported that a conclusive evaluation was possible and 5 reported that it was not possible. Although no further information was given by the companies, a majority of the companies perceived their current risk assessment procedures as sufficient to evaluate NPM risk, even though no standardized procedures for NPM exist. Furthermore, existing safety measures were stated to be sufficient in 7 companies, whereas in 5 companies additional measures had been taken (1 company did not answer this question). More information on their risk assessment procedures was requested, but companies did not respond any further. On a separate question "Has your company introduced maximal exposure times and exposure concentrations for workers while handling NPM?" 9 **(**22.5%) companies answered yes, 29 (72.5%)

answered no, and 2 (5.0%) companies did not answer the question at all.

After initial analysis of the data, the general impression was that it seemed quite arbitrary which companies conducted toxicity tests and risk assessments, and which companies took precautionary measures at the production stage. Therefore, further analyses of the correlations between different variables in this study, utilizing cluster analyses, crosstabulations, and chi-square tests, were conducted to investigate whether explanatory variables for a company's likelihood of conducting risk assessment could be found. However, there were no significant differences in the response patterns for companies which produced or for companies which purchased the NPM or in the response clusters regarding material properties that may serve as early warnings

FIGURE 2. Relationship of company size and conducted risk assessments.

for potential risks (life cycle release, size changes, and degradability). Furthermore, no differences were found in the responses comparing risk assessment with toxicity tests, uptake tests, or maximal worker exposure times. For example, only 3 of the companies that reported as conducting risk assessments have also introduced maximal exposure times and concentrations for their workers. By cross-tabulating the responses concerning the evaluation of uptake, testing toxicity, and performing risk assessment, 11 companies were found not to be conducting any such procedures, whereas 1 company conducted all three procedures.

When analyzing company size, see Figure 2, it was found that only 7 of the small companies and 1 medium-sized company performed risk assessments. Four of the 6 large companies reported as performing risk assessments, indicating that these companies may have greater access to resources for performing assessments. Two companies did not fill out the related questions. However, the association between size of industry and risk assessment was not statistically significant ($\chi^2_{(2)} = 4.54$, $p = 0.104$).

Discussion

Since our survey could not find any relationship between NPM characteristics, risk assessment procedures, and precautionary measures, the current situation causes some concern about worker, consumer, and environmental safety. The companies in this survey seemed in general not to give high priority to risk assessment of NPM and our analysis reveals that there is a lack of a general industrial framework for evaluating NPM risks, among these companies. This consideration is strengthened as these companies were selfreporting a lack of risk assessments. Considering the relatively high response rate and that Germany and Switzerland have NPM industries similar to many other industrialized countries, our findings may also reflect the current situation in various countries.

NPM Characteristics, Risk Assessment, and Precautionary Measures in Industry. A nanoparticle 10 nm in diameter has 20% surface atoms, whereas a nanoparticle of 1 nm in diameter has 100% surface atoms (*22*), which makes it extremely important to keep surface chemistry in mind. Surface modifications are essential for agglomerate control, dispersion, and stabilization of NPM. The small sizes and the great surface area of NPM imply higher biological activity per given mass compared to larger particulate forms, which may lead to enhanced toxicity should they be taken up into living organisms (5) . For example, TiO₂ has been found to be more toxic in nanoparticulate form than in larger particulate form (*5*). However, keeping NPM as single particles as long as possible during production is essential for a high quality of many NPM based applications, and one of the main challenges of industrial production is to overcome the interparticle forces that make an effective dispersion and

coating of nanoparticles difficult (*22*). It seems therefore reasonable that a large majority of the NPM in our sample were reported coated or functionalized, and our results suggest that this may also be one reason why up to one-third of the NPM were reported to stay in the nanometer size range also in contact with water, air, or soil. Exposure in nanoparticulate form may therefore be possible in various environmental media. However, it is very hard to estimate NPM behavior without performing measurements. Therefore, we question whether as many companies as reported in Table 3 can know how their NPM will behave in, for example, soil. The reason for this is 2-fold: first, the scientific knowledge base is very limited in this area (*23*) and, second, many of the companies were unaware of their NPM surface charge as seen in Table 2. The surface charge is considered to have a strong influence on the behavior of NPM in soil or water (*14*). It seems therefore rational to assume that NPM may be available for uptake by organisms after release to indoor air or to the environment, especially as NPM were reported as being nondegradable in almost one-third of the cases, indicating a longer half-life and thus a longer presence in the environment. This assumption contrasts with the findings in Table 4, where the majority of the industry representatives in this survey expressed their opinion that no release, or subsequent uptake, was possible throughout the life cycle of their products. Furthermore, very few companies evaluated the potential uptake by different organisms and only one in four companies conducted any toxicity tests at all. This is interesting as no criteria for what would qualify as a release, uptake, or toxicity test were given in the questionnaire and any procedure, regardless of quality, could therefore have been reported.

Our survey did not specify any definitions of the term "risk assessment" or of procedures such as evaluating NPM release, NPM uptake, or NPM toxicity. For all these aspects it was possible on the questionnaire to mark "not aware" or "unknown", by which we intended to prevent the respondent from guessing. Accordingly, the respondent could subjectively interpret these terms. It is therefore an interesting finding that only about one-third of the companies reported conducting risk assessments, although they were able to include any activities they considered appropriate there. The potential bias the companies may have for reporting a higher level of risk assessment activities than in reality may therefore have been limited in this survey. Even if we assume that all of the 95 nonresponding companies in the sample might be conducting risk assessments, there would still be about one out of five (26/135) companies not conducting any risk assessment. In other words, there would still be a significant fraction of companies not conducting risk assessment procedures, regardless of the response rate. However, the sample size in this study was limited, especially larger companies were underrepresented, and for some specific questions regarding material properties there were missing responses or the respondents marked the question with "unknown". This may have influenced the results of the crossvariable analyses. Nevertheless, the overall results indicate that industry, in general, does not have a systemic approach to assessing NPM risks. Although many NPM may not constitute a high risk potential, the limited focus on risk assessment procedures may have the consequence that industry underestimates the toxic potential and probability of exposure of some important NPM, and, consequently, does not take enough precautions to minimize risks to workers, consumers, or ecosystems. The industry may also profit from initiating risk assessments. This is because lay people perceive higher risks associated with nanotechnology than experts (*24*). If public concerns are not sufficiently addressed, the public trust in the industry may be reduced and some applications may therefore have difficulty finding acceptance in the market.

NPM Risk Assessment and Industrial Sectors. In this survey we found that about one-third of the companies were primary producers of nanoparticles and nanotubes and that most of the downstream users applied NPM for coating and in paints, thin films, and electronic products. However, the statistical analysis found no difference in the responses between primary producers and downstream appliers as to whether they conducted risk assessment procedures. A survey of nanotechnology in the United States' manufacturing industry found NPM product trends similar to those in our survey (*25*). Furthermore, Figure 1 indicates little difference between the industrial structure of the responding companies and the nonresponding companies. The findings in this study seem therefore to be relevant and potentially representative also for other countries. Based on our results, an interesting aspect for further research would be to investigate whether industrial risk assessments for NPM are more or less prevalent than for other critical compounds or manufacturing sectors.

Industrial Risk Management of NPM Production and Products: What To Do? We found no relationship between the responses to the question on risk assessment with the responses to the questions on other procedures (toxicity testing, uptake evaluations, worker exposure limits). However, we found that eleven companies conducted neither risk assessment nor toxicity tests, nor did they evaluate NPM uptake by organisms, whereas one company conducted all three procedures. Furthermore, we found no visible response pattern related to selected material properties, or difference of primary producers versus downstream users of NPM. An interesting question for further research is whether the precautionary measures and the level of risk assessment initiatives within the company may depend on the safety culture of the individual company.

In this survey no significant link was found between those companies conducting risk assessments and the company size. However, the sample size was small and we may therefore not have been able to find such a difference, should one exist. The majority of companies that participated in this survey were small and medium enterprises. Many large companies in this survey declined our request for participation in letter form. The representatives wrote that risk assessment was an important topic for their companies, but they did not provide any further information. Because of the limited response from large companies, it is difficult to evaluate how high questions of risk and safety may rank on the corporate agenda of the large corporations involved with NPM.

In this survey, we found that the majority of companies did not perform any form of risk assessment. Furthermore, no factors were identified that could provide any explanation of why some companies conducted risk assessment and why others did not. Our results may have detected a lack of any systemic approach among industry players in regard to assessing NPM risks. Although most NPM applications may indeed be quite safe, there is still the issue of concern that consumers may be exposed to unassessed risks. Developing proactive risk management strategies appears to be an urgent task for minimizing the risk of harm to the environment and the public health. How much responsibility the individual firm should take in a globalized market is an issue of considerable debate in policy (*26*). Nevertheless, it may be necessary for regulators to take measures to ensure that NPM risks are properly assessed by industry. A first step could be to initiate an NPM database with information on the properties of the different NPM produced and handled in industry. Such a database would assist in categorizing NPM with respect to, e.g., chemical properties, toxicity, and consumer use. The database could have an international scope such as the European Union. The voluntary reporting scheme in place in the UK has received very few contributions from industry (*16*). A legally enforced information duty of NPM producers seems therefore to be the most effective solution to ensure quality and coverage. Actively initiating risk management strategies may also help industry address any public concern related to the possible risks of NPM.

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Supporting Information Available

Description of the methodology used for data gathering, table of websites used to identify companies, table of the response to the question "Are there possible unintentional releases of the NPM into the following systems?", and table describing the number of companies evaluating potential uptake by organisms throughout the NPM product life cycle. This material is available free of charge via the Internet at http:// pubs.acs.org.

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