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Chapter 17

FINE AND ULTRAFINE PARTICLE RISK MANAGEMENT: PROBLEMS TO BE SOLVED

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ABSTRACT

Recent studies have elucidated some hazardous properties of fine and ultrafine (nano-sized) substances and particles. Thus, to avoid the risks associated with these small particles, especially for nanoparticles (NPs), research aims to reduce NP exposure and examine the relationship between the physicochemical characteristics of NPs and their hazards. The engineering of less hazardous nanomaterials for industrial use has also been a focus. Due to the emergence of hazard concerns and the accumulation of basic research data regarding the potential health effects of NPs, action has been taken to regulate the usage of engineered nanomaterials. Recent discussions on policies for nanomaterial risk evaluation, management and governance have concentrated on problems to be solved.

In order to reduce their associated risks, a method to assess the level of the adverse effects of NPs, including engineered nanomaterials, has been a major focus of current research efforts, as has the design and implementation of a risk assessment and management scheme. The present chapter will describe the problems that will need to be resolved in order to establish a nanomaterial risk management program and summarize the current status of these issues to consider effective risk prevention measures that could be implemented in the future. Finally, the issue of communication techniques for risk information, when uncertainty and unsolved problems remain, is discussed.

Keywords: environmental ultrafine particle, engineered nanomaterial, detection technology, exposure scenario, risk communication

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DEFINITION OF THE INTENDED TARGETS OF NANO-REGULATION

The toxicity of fine and ultrafine (nano-sized) particles has been a major issue in the toxicology and public health fields. Research has elucidated that nanoparticles (NPs) represent a larger hazard than bulk particle matter and shown the potential hazards and risks of engineered nanomaterials in industrial use. The level of adverse effects from exposure during the production, consumption, and disposal of nanomaterials remains unclear and has been the subject of intense debate. The design of less hazardous nanomaterials with useful functions and the reduction of the amount of nanomaterials to which humans are exposed are the main strategies for their safe use.

The nanomaterials targeted for regulation were initially defined as "objects measuring 1-100 nm in at least one plane of dimension." Under this definition, a communication on preventive responses against exposure to nanomaterials was published in March 2009 by Japan's Labor Standards Bureau, Ministry of Health, Labour and Welfare. The document discussed methods to suppress NP exposure with the goal of reducing risks on human health associated with exposure.

In reality, however, nanomaterials are particle aggregates that vary in size and consequently the initial nanomaterial regulations were difficult to apply under the original definition. The European Commission defined "nanomaterials" based on these indications in 2011 as "a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50% (European Union, 2011)".

Nevertheless, this definition may be revised in the near future because it has several issues in regards to measurement of nanomaterials and risk prevention. First, if particles measuring 1-100 nm in diameter account for less than 50% of the aggregates, the regulations pertaining to nanomaterials do not apply. Thus it is essential to perform evaluations to determine whether these NPs are safe. If they are found to be unsafe, counter-proposals for the definition of NPs will be required. In addition, the European Commission recommended that the primary particle diameter be included in the definition of nanomaterials; however, such a measurement would be impossible using current techniques. The measurement of primary particle diameters currently relies on transmission or scanning electron microscopy, neither of which allows for quantitative analysis of particle size distribution. Furthermore, measurement of particle size distribution based on physical phenomena, such as particle motion or sedimentation velocity and light scattering, do not allow for the measurement of the primary particle diameter within aggregates because the aggregated particles behave in an integrated manner.

The major challenges in nanomaterial risk management are thus: how to define substances which pose a risk, and the means by which risk management should be evaluated. The issue of the definition as to what would be regulated is similar to that which is applied to environmental ultrafine particles; it should be shown in combination with the measurement method.

RE-CONSIDERING THE MECHANISM OF NANOPARTICLE-INDUCED TOXICITY FOR ITS REGULATION

The major concern regarding NPs is that airborne nano-sized particles may have significant health effects. As a result, these particles have been a major research focus. An epidemiological prospective cohort study published by researchers from the Harvard School of Public Health, which followed up of 8,111 adults for 14-16 years, was conducted in six US cities and controlled for individual risk factors, revealed that mortality was most strongly associated with fine particulate air pollution (PM2.5) (Dockery et al. 1993).

Furthermore, a previous report revealed that after intratracheal administration of low-solubility fine and ultrafine particles with different diameters but the same mass, inflammation was greater when smaller particle sizes were present (Oberdörster et al. 2000). These data have caused increased concern regarding the hazards associated with ultrafine particles in the environment and engineered nanomaterials.

There are two primary NP-specific toxicity mechanisms. The first proposed mechanism suggests that NPs have high reactivity due to their large specific surface area. The high reactivity of NPs facilitates oxidation-reduction reactions on the particle surface, thereby inducing *in vivo* toxicity via oxidative stress (Nel et al. 2006). The second mechanism suggests that NPs have unique pharmacokinetics due to their small diameter. Previous reports have shown that when NPs are inhaled they reach deep into the lungs, where they are likely to accumulate (Oberdörster et al. 2005). As shown in rodent models, NPs may further migrate, in small amounts, from the lungs to the extra-pulmonary organs (Kreyling et al. 2002; Oberdörster et al. 2002). It has also been shown that if NPs enter into circulation in the pregnant body, they may pass through the placenta and accumulate in the major organs of newborn offspring (Takeda et al. 2009).

The transfer property of NPs through the placenta was demonstrated using an *ex vivo* human placental perfusion model (Wick et al. 2010). The permeability of the blood-tissue barrier by NPs, including their ability to pass through the placenta, is not related to passive diffusion. Previous reports have shown that when NPs (10-100 nm) enter the body, they are difficult to eliminate, and thus remain for extended periods of time (Choi et al. 2010). Within the blood-tissue barrier, there is a system that eliminates uptaken substances (rather than inhibits substance incorporation). The size of NPs permits their uptake by cells, making them less susceptible to clearance. This could serve as a basis for the regulation of NPs.

Assuming that the toxicity of NPs is related to their pharmacokinetics, aggregate diameter is a critical measurement for the determination of toxicity risk. Furthermore, given that the toxicity of NPs is proportional to their high reactivity, which is further dependent on surface area, the primary particle diameter should also be taken into consideration. The mechanisms of NP toxicity must be clarified through toxicological research in order to optimize NP regulation and to define the regulatory targets.

ESTABLISHING A METHOD FOR ASSESSMENT OF ADVERSE EFFECT LEVEL

Before conducting a nanomaterial risk assessment, it is necessary to establish a more appropriate adverse effect level assessment index. This will help to estimate and categorize tolerable levels of exposure and acceptable applications for each nanomaterial.

Instead of using fixed methods and tests that are limited to assessment indices, the adverse effects of chemical substances and materials must be assessed using a research process that simultaneously optimizes the employed methods and assessment indices. In 2011, a report on the risk assessment of nanomaterials, including carbon nanotubes, fullerene, and titanium dioxide NPs, was produced and published in Japan by the NEDO Project, entitled "Research and Development of Nanoparticle Characterization Methods" (2006−2011; P06041). Studies have shown that the above materials showed no-observed-adverse-effect level (NOAEL). However, the adverse effect level assessment index that was used as the basis for calculating the NOAEL in this risk assessment study was limited. On the basis of this point, the researchers of the risk assessment for the project stated that the assessment would be revised within 10 years, in line with future scientific findings.

It is actually difficult to determine whether risk assessment should be conducted based on the data on the developmental toxicity of nanomaterials (see Chapter 13). The reason for this is that it is not clear whether the next-generation effects of nanomaterials (developmental toxicity) are detected under conditions in which the toxicity was not identified in the exposed parent organism (Ema et al. 2010). To put it another way, if the reproductive and developmental toxicities are only expressed under exposure conditions in which a nanomaterial can be detected via general toxicity tests, then it may be sufficient for a risk assessment to only take into account a NOAEL result from general toxicity tests.

However, if the developmental toxicity is generated under conditions whereby general toxicity is not expressed, then risk management should be based on the developmental toxicity data for NPs to which pregnant women may be exposed. The present challenge for studies on developmental toxicity caused by nanomaterials is to identify the correct approach.

DEVELOPING A HIGHLY SENSITIVE AND QUANTITATIVE DETECTION TECHNOLOGY FOR NANOMATERIALS

The obastacle to realizing the appropriate assessment of nanomaterial risk is a lack of technology that would allow for the quantitative detection of small quantities of nanomaterials distributed in the tissues of living organisms. To conduct nanomaterial risk assessment, in addition to exposure assessment, it would be desirable to assess the absorption rate, distribution, and clearance of the material in the exposed organism. To achieve these goals, it is essential to detect nanomaterials in biospecimens in a way that is both highly sensitive and quantitative.

However, the technologies that are considered capable of assessing nanomaterial distribution quantitatively, namely inductively-coupled plasma mass spectrometry (Sewell et al. 2011) and fluorescence detection (Burns et al. 2009; Mota et al. 2013), may not be at a level that permits detection of the biodistribution of the extremely small quantities of

nanomaterials that result from low levels of exposure. Moreover, if a nanomaterial consists of an element that naturally exists in the body in large quantities (e.g., carbon), then it would be very difficult to quantitatively analyze its biodistribution.

On the other hand, with electron microscopic observation, which permits the highly sensitive detection of single nanomaterials in biospecimens, it is extremely difficult to quantitatively analyze nanomaterial distribution. Radioactive nanomaterials can be traced and detected in biological tissues with a high sensitivity (Meiring et al. 2005; Singh et al. 2006); however, non-radioactive materials cannot be detected by this principle.

As previously mentioned, some nano-sized particles/materials are associated with health problems because, despite their small mass, they are capable of exerting considerable adverse effects on human health. It is necessary to quantitatively detect the distribution of these extremely small quantities of NPs in the body. It is imperative that the technological development required for overcoming this problem is encouraged from the point of view of guaranteeing the safety of nanomaterial-related technological innovation.

DISTINGUISHING EXPOSURE SCENARIOS FOR EACH TYPE OF NANOPARTICLE

A discussion of nanomaterial risk should address the question of the exposure scenarios to be applied to each type of nanomaterial. It is necessary to distinguish "the scenario" in which an individual is exposed to the nanomaterial, "the amount" of the material to which they are exposed, and "how" they are exposed. Although setting such exposure scenarios should be carried out when discussing the risk assessment of chemical substances and materials, in reality, many discussions have continued without sufficiently addressing this distinction. For example, in the case of materials that are applied in the medical field in drug delivery systems with systemic administration (Davis et al. 2010; Lee et al. 2012) or inhalation (Dames et al. 2007), safety issues are reviewed when the material is administered to a limited number of eligible patients. The safe use of medically applied materials is specially governed by the Pharmaceutical Affairs Act. In contrast, when nanomaterials are contained in commercial products and used in such a way that the consumer is not exposed, safety issues are related to the occurrence of adverse effects resulting from industrial/ occupational exposure (Abbott and Maynard 2010; Lee et al. 2011; Koivisto et al. 2012; Nowack et al. 2013), particularly during production/manufacturing and analysis.

If nanomaterials in commercial products are in a form in which the consumer may also be exposed, it will be necessary to implement a risk assessment that considers that possibility (Abbott and Maynard 2010; Chen et al. 2010; Nowack et al. 2013).

Although these factors are all included under the generic term, "nanomaterial", the types of material used are different, as are the predicted exposure levels. Furthermore, considerable individual differences are present among the people who may be exposed.

Any discussion of nanomaterial risk assessment must consider this point. However, if the consideration of exposure scenarios and risk assessment procedures based on such scenarios becomes too complicated, then it might actually jeopardize the realization of risk management.

To maximize the potential of nanomaterials after risk assessment, it would be effective to create a template and an assisting web-based tool, like that of Van Duuren-Stuurman et al. (2012), which allows the user to easily calculate the predicted exposure based on exposure scenarios for each nanomaterial. A testing method should be established to estimate the hazard and tolerable level of exposure for each NP, in order to categorize acceptable applications.

ARE NANOPARTICLES "UNKNOWN ENCOUNTERS"?

Exposure to NPs has increased since industrial development, although many maintain that NPs do not represent novel risks, because they have long been present in the environment. Fullerenes and carbon nanotubes, for example, are generated by combustion and have been present in the environment since ancient times. In addition, water on the surface of soluble silver NPs can ionize them to reform NPs smaller (approximately 10 nm in diameter) than those found in nature (Glover et al. 2011). Thus, NPs can occur spontaneously when bulk ("non-nano") materials are soluble, forming the basis of the argument that NPs have existed since ancient times and that their associated risks have not inreased.

Caution is required when interpreting data because NPs in the liquid or gas phase can easily aggregate, resulting in a large secondary particle diameter. This is clearly reflected in the correlation between the concentration of fine and ultrafine particles in the environment and the distance from the source of emission. Diesel engines are an important source of the particles, emitting ultrafine (nano-sized) particles and PM2.5 in large amounts on roads with heavy traffic. The Health Effects Institute of the United States, which supports research on the health effects of air pollution, previously mentioned that they found no inverse correlation between the amount of PM2.5 and the distance from the source of emission, whereas a significant inverse correlation was found between the concentrations of ultrafine particles and the distance from the source of emission.

We also measured the particle number concentration in the atmosphere (which is a strong indicator of the concentration of NPs), using CPC3007 (TSI Co., US), which measures the particle concentration suspended in the gas phase with a secondary particle diameter of 20-1000 nm. Our results confirmed that high concentrations of ultrafine particles were found on the sidewalk of a main road, but were not observed at distance 200 meters from the road without any significant obstacles.

Given that localized sites with high NP concentrations are present in the environment, highway workers, for example, may be exposed to a highly localized risk. Likewise, for engineered nanomaterials, the exposure levels must be evaluated at various sites of production, analysis, and waste disposal, and caution must be taken in areas in which there is a high risks of locally elevated concentrations. Thus, the focus of risk management should be narrowed to geographical points where NPs are likely to be present in higher concentrations than in the environment.

SECURING THE INDEPENDENCE OF RISK MANAGERS

Measures designed to tackle the problems associated with the risks of substances and materials released into the environment often entail difficulty. The scientific data generated from the assessment of adverse effects and risks are filled with uncertainties that arise from interspecific differences, individual differences, and test design (Hendren et al. 2013).

Scientific data are indispensable when judging the degree of risk, but it is essential to keep in mind that the data were obtained in accordance with the test design, and that the results were obtained under the conditions of that test. It is also essential to bear in mind that even if the test design was appropriate, the data that can be viewed are only measured values or representative values. Therefore, the point at which it is acceptable to implement risk management, i.e., the level of detail required for the risk assessment and the amount of scientific evidence that is required before implementing a risk management scheme are aspects that should be ultimately entrusted to decision-makers (risk managers). Decisions on risk management do not only involve scientific evidence but also policy judgments (Joffe and Mindell 2002). This is one of the major reasons for the difficulties that are encountered when measures against environmental risk are applied.

Therefore, while risk managers are required to avoid exerting any influence upon the aforementioned risk assessments, risk evaluators are required to conduct scientific analyses without being deterred by any factors that could affect the decision making (policy judgement) process of risk managers. It is therefore essential that both of the parties (risk evaluators and risk managers) involved in the development of risk management schemes independently fulfill their respective roles.

DEVELOPMENT OF RISK COMMUNICATION PATTERNS TO REDUCE COMMUNICATOR ANXIETY - A WORKSHOP STUDY

Given that each private citizen will probably become an NP “risk manager”, there will be an increase in cases where the risk of NPs must be communicated. Especially with regard to engineered nanomaterials, where regulations such as “nano-labelling” and the “registration of nano-products” have been promoted. However, since the risk evaluation of NPs remains unresolved, attention should be paid to the process of communicating the risks and hazards of nanomaterials. While atmospheric fine and ultrafine particles pose various risks, so to do other environmental factors. To effectively address environmental risks, decisions must be made by effectively conveying and communicating information which describes the risks.

In particular, environmental and health issues and the social acceptance of emerging technologies has led to increasing social debates, which can pose problems in part due to the presence of a plenty of diverse stakeholders. Therefore, this issue must be addressed carefully.

Since the Fukushima Daiichi nuclear power plant accident in March 2011, the problem of risk communication has been emphasized in Japan. In the past, the term “risk communication” was associated with specialized technical terms used by government and corporation officials;

however, today it is used when addressing the public. Similar to the Fukushima accident, risk communication is carried out by the government and mass media.

However, in many cases, risk communication has not been successful, reflecting issues in understanding the conflicts associated with risks that exist in society. Improved communication could resolve this source of controversy. In particular, while previous studies have evaluated risk communication, they have not developed practical and functional methods for real-world implementation. Previous studies have demonstrated an association between risk communication techniques and the level of participant satisfaction (Haynes et al. 2011) and consideration for stakeholders (Sanderson et al. 2006). Nevertheless, the process of information dissemination by scientists during risk communication and the literacy of the communicator have never been studied. Anxiety levels in the communicator could be an obstacle to effective risk communication. Thus, the anxiety and concerns resulting from limitations in communicator literacy when conducting risk communication were examined.

The study was particularly focused on situations in which adopting a communication technique resulted in advantages and disadvantages and in which it was difficult to deal with anxiety and fear. These situations were called "dilemmas". Uncertainty regarding the future contributes to anxiety and fear. Converting this pattern into visible information is effective in achieving communication that surpasses the hindrances caused by anxiety and fear.

Our study aimed to change the communicator's dilemma regarding empirical and implicit knowledge into formalized knowledge (visible information) using a pattern language approach. In addition, a workshop was held to give participants an opportunity to experience a risk communication dilemma with accumulated in-group empirical and implicit knowledge, and to convert it into formalized knowledge. As a result, we developed a prototype process for collecting risk communication patterns from various perspectives for all purposes and challenges.

In our study, "risk communication", was defined as a situation in which scientific information related to risks, including uncertainty and probabilistic logic, was provided while an interactive exchange of opinions was conducted. A "dilemma," was defined as a situation in which the existence of both advantages and disadvantages could be envisioned among the results when a risk communicator used a certain method to communicate a risk. "Pattern language," was defined as "structures which appeared repeatedly when describing a certain event (patterns), and which were collected and assembled together as a single form". The pattern language was designed based on attempts to create a pattern language for the transformation of practical knowledge into a common language, and which was based on a description method (Alexander, et al., 1977).

There are two processes for the creation of pattern languages: the partial development approach, which was used in our study, and the general construction approach. Thus, the stance used in this study was one in which meaningful patterns were assembled together, even if they only accounted for one part of the entire ensemble.

For the conversion of dilemma situations likely to be encountered by risk communicators in dilemma situations into formalized knowledge, a three-day workshop was conducted in August 2012 at Waseda University Graduate School in collaboration with students attending journalism courses and participants in an intensive summer workshop conducted by the Science Media Centre of Japan.

In this study, the following patterns were extracted for the purpose of enumeration.

- Typological universal issues and dilemma situations which are likely to occur repeatedly during risk communication.
- Characteristics:
  - Problem-solving is rarely easy to achieve.
  - Commonalities exist between different specialties.
  - Each problem-solving method has its own advantages and disadvantages.

In addition, a set of contexts, problematic issues, and proposed countermeasures, which are defined below, was extracted as a pattern of dilemma situations during risk communication.

- Contexts
  - Prerequisite conditions defining a context of risk communication.
  - "To what does the risk relate?" "Who is the source of information regarding the risk?" etc.
- Problematic issues
  - Various problematic issues, which can occur under the contexts listed above, and from the perspective of the communicator in charge of risk communication.
- Proposed countermeasures
  - Proposed countermeasures aimed at solving or alleviating problematic issues.
  - Advantages and disadvantages envisioned to occur as a result of adopting the proposed countermeasures.

As a result, 51 patterns were extracted and categorized into the 10 groups listed below.

- The communicator is unable to get the audience to understand the message.
- The communicator is unable to respond to misinformation caused by mass media.
- People question the communicator's role in society.
- People question the communicator's opinions and judgment.
- The communicator is worried about the technique used for communicating information.
- Problematic issues on the communicator's side.
- Problematic issues pertaining to relationships of mutual trust.
- The information is difficult to handle.
- Information about the risks is given at the time of an emergency.
- A dilemma situation which is dependent on the content.

An example is shown in the next page (Table 1).

During the workshop, the participants worked together to extract dilemma situations that were likely to occur during risk communication based on their own experiences and from various perspectives. The participants discussed scenarios with each other and shared their

own experiences and thoughts. They were successful in converting and categorizing dilemma situations and implicit knowledge into formalized knowledge.

By understanding this classification, the participants could find dilemma situations that resembled the problems they faced and better understand how to address them. Next, the participants could determine the optimal communication technique by evaluating the proposed countermeasures along with the problematic issues. In addition, the advantages and disadvantages of adopting a proposed countermeasure were mentioned in the list of patterns. Thus, the participants could understand the likely results of using a proposed communication technique.

Moreover, when a risk information provider examines the pattern list, they are able to acquire systematic information regarding problems that may occur while providing information, the proposed countermeasures, and potential outcomes when the communicator provides a certain explanation or adopts a particular behavior. The "problem/proposed countermeasure" sets in risk communication may become more refined by repeatedly extracting dilemma situations using various organizations and communities.

Table 1. Problematic issues likely to be encountered while communicating information pertaining to the risks associated with nanoparticles and proposed countermeasures

Problematic issues	Proposed countermeasure
Issues suggesting an association between existing substances and diseases	Such information should be handled carefully.
The problem of bringing potential risks to the surface	The advantages of conducting risk management should be explained clearly.
Issues pertaining to the presence or absence of a relationship of trust	Understand the knowledge of the recipients (their background, current situation, and level of understanding). Listen to the claims and requests of "the other party."
The issue of how to use and communicate statistical data, numerical data, and technical terms.	Distribute supplementary explanations on a separate sheet of paper.
The issue of who determines the presence or absence of risks, and who takes responsibility.	Specify clearly that the person who evaluates the risks, the person who determines what to do, and the person who takes responsibility are all different people.
The possibility of giving an excessive impression of risks by publicly presenting data on the harmful effects of a substance while the research study is still under development.	Initially specify (as much as possible) the rank of importance and degree of influence of other factors

CONCLUSION

This chapter discussed findings on the adverse effects of NPs and the challenges associated with implementing risk assessment and risk management schemes. If the NP risk problem is perceived as an environmental risk problem, then it can be said that although the risk to individuals may be small, it remains a problem that affects a large number of individuals. Further, the assessment and management of such a risk is no easy task. Risk management is, however, something that should be implemented as a preventative approach to adverse health effects.

Further accumulation of precise scientific data and continued constructive discussions on the implemention of fine and ultrafine (NP) risk management schemes are necessary. The main challenges include the establishment of developmental mechanisms and protection methods for the potential adverse effects of novel technologies/materials/ substances; the resolving of concerns about health and environmental problems, and the building of a foundation upon which the new technologies can be used sustainably and effectively. Improved risk communication, with respect to communicator anxiety, will also contribute to the establishment of an effective risk management scheme for the use of engineered nanomaterials and a reduction in exposure to environmental fine and ultrafine particles.

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