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Risk Characterization for Nanotechnology

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Nanotechnology is a broad term that encompasses materials, structures, or processes that utilize engineered nanomaterials, which can be defined as materials intentionally designed to have one or more dimensions between 1 and 100 nm. Historically, risk characterization has been viewed as the final phase of a risk assessment process that integrates hazard identification, dose-response assessment, and exposure assessment. The novelty and diversity of materials, structures, and tools that are covered by above-defined "nanotechnology" raise substantial methodological issues and pose significant challenges for each of these phases of risk assessment. These issues and challenges culminate in the risk characterization phase of the risk assessment process, and this article discusses several of these key issues and approaches to developing risk characterization results and their implications for risk management decision making that are specific to nanotechnology.

KEY WORDS: Nanotechnology; risk; risk assessment; risk-benefit tradeoff; risk characterization; risk management

1. RISK ASSESSMENT STEPS

Risk characterization has been defined in the 1996 report "Understanding Risk: Informing Decisions in a Democratic Society" as: "A synthesis and summary of information about a hazard that addresses the needs and interests of decision makers and of interested and affected parties. Risk characterization is a prelude to decision making and depends on an iterative, analytic-deliberative process."(1) That is to say, how risk will ultimately be characterized should be driven by the process itself. It is not a just a summary of the results of several studies; it drives questions that the research will answer. Risk characterization must contain, at a minimum, key information from the hazard identification, exposure assessment, and the potency (dose-response) stages of the risk assessment. From the hazard identification step, risk characterization should report the kind of data used for the analysis, normally human (epidemiology) or animal tests. It should discuss the quality of these data and any ancillary information used such as pharmacokinetics[1] and the approach used to assess the scientific evidence (e.g., weight of evidence).[2]

From the exposure assessment, there should be a description of the concentration of the hazardous substance (nanomaterials) in the product, human intake on a body–weight basis, the route(s) of exposure (i.e., oral, inhalation, absorption), and the frequency and duration of exposure. It should discuss which populations were studied, including populations that are highly exposed. Finally, it should discuss whether there are reasons to be concerned about aggregate or cumulative exposures, as well as synergistic or antagonistic effects.

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[1] Pharmacokinetics is the study of the bodily absorption, distribution, metabolism, and excretion of drugs.

[2] A weight-of-evidence evaluation takes into account the strengths and weaknesses of different measurement methods when determining whether the results show that a stressor has caused, or could cause, a harmful environmental effect. Massachusetts Weight of Evidence Workgroup, 1995.

Epidemiological data are normally considered superior to the other primary option, animal data, for calculating exposure and potency (dose response). Epidemiological data provide information on health effects observed in human populations from "real-world" exposure levels. Animal data are generally used for risk assessments for the thousands of chemicals for which no epidemiological data exist (including nanomaterials), for compounds that have not yet entered into the market, or where toxicity prohibits human testing in clinical studies.

Describing nanoproduct potency (dose response) presents special challenges. For chemicals, this discussion is largely about the development and outcome of a dose-response function. Risk characterization is largely driven by a discussion of the key data and the model(s) used to develop this function. Nanotechnology presents a specific challenge in this area as dose may not be as important as other parameters, such as the shape of the compound (which will determine the surface area and, potentially, its chemistry) or its surface charge or coating. It is also important to note the potential for differing potencies for various subpopulations—as is the case for many chemicals and environmental pollutants, the young or elderly, for example, may be more sensitive to adverse effects from nanoscale products.

The classic outcome of a risk characterization is the probability and severity of the hazard, with discussion of the uncertainties associated with each of these components. For example, risk could be described as a one in 1,000 chance of a worker developing a particular kind of tumor from exposure to a toxicant in a factory with 10,000 workers. This might mean that 10 people are expected to develop the tumor over a lifetime of exposure, but it could be as few as 0 and as many as 20 people depending on the uncertainties associated with calculating this risk estimate. Generally, in the case of nanotechnology, there are insufficient data or experience on which to formulate reliable probability or severity estimates. Without such baseline estimates uncertainty bounds have little practical meaning.

In the context of nanotechnology risks, probability will need to be considered in a risk-risk tradeoff framework—that is, the likelihood that a particular adverse outcome will either be caused by the production and consumption of nanotechnology products or will fail to be prevented because these products have not been produced. For classical risk assessment, this refers to a single or range of probabilities of health effects that are predicted to affect some portion of the population or adversely affect some portion of the environment. It is equally important to describe, however, the probability of health benefits associated with the manufacture of a nano-based product that is intended to reduce risk, for example, a system that will enable targeting cancer cells to deliver a kill dose more efficiently without affecting the surrounding tissue.

The probability of risk must be applied to the population that is likely to be affected as probability estimates can confuse stakeholders and decisionmakers if used out of context. Thus, risk probability numbers in any risk characterization should be described in the context of the scope of the assumed exposed, or potentially exposed, populations. For nanotechnology this includes workers in associated research and production facilities, consumers of nanotechnology products, and those potentially exposed to nanoparticles that make their way into the environment.

The risk characterization should also include some discussion of the severity of the outcomes assessed, for example, cancer or a disruption of an ecosystem of some kind. For instance, it may be that certain types of cancer are caused by the manufacture of nanoparticles, and it is important to distinguish which types of cancer, what are the likely symptoms, what is the recovery rate, and other effects that are associated with a particular technology.

Finally, the risk characterization should consider the time periods involved in exposure before effects are likely to be produced, and the time before the effects of exposure are observed. For example, a person may experience an obvious allergic reaction immediately upon exposure to a particular nanomaterial, but that reaction may abate with no permanent effect once the exposure is removed. On the other hand, another individual may experience no immediate symptoms from exposure to the nanomaterials, but suffer adverse health effects at some point in the future from either the single exposure or repeated exposures to the nanomaterial. The relative novelty of nanotechnology means that there are not yet sufficient data on exposure and effects processes on which to base such time period analysis.

2. RISK MANAGEMENT DECISIONS AND RISK CHARACTERIZATION

There are two distinct approaches to risk management of any new activity or technology. The "precautionary approach" forbids the activity or

technology to go forward until its safety has been demonstrated with some specified degree of certainty, while the "risk-based approach" monitors its impact after introduction into commerce, regulating it if it is found to be unsafe. The U.S. regulatory structure treats new drugs and new food and color additives with a precautionary approach. This includes nanotechnology products like some sunscreen lotions. The risk-based approach applies to a broad range of other nanotechnology products, from fabrics to paints and sports equipment. When risks are uncovered after a product or technology is introduced to the market, new regulations seek to mitigate them through information dissemination, standard setting, or bans. In some cases, remedies and new incentives arise from tort markets. These issues are largely untested in the case of nanotechnology. Depending on which approach is taken with a new technology, different risk management questions and data will drive the risk analysis process and, ultimately, risk characterization.

As noted earlier, a key aspect for nanotechnology risk characterization is the potential for both significant risks and risk-reduction possibilities. Ohanian *et al.* discussed the idea of considering risk-reducing benefits in a 1997 article in which they noted:

> A good risk characterization addresses both the "present situation" (i.e., candidate for risk reduction) and the range of reasonable options or alternatives. In addition to quantifying potential benefits (i.e., risk reductions), such discussions provide valuable insight on the potential consequences that would be expected to arise from exercising each of the alternatives (i.e., "substitution risks"). . . .The principle is generalizable to most risk assessment and management situations.[2]

For some products and technologies, the precautionary approach does not guarantee that society will be safer overall for some types of risks. This is particularly the case when new technologies or products not only improve our overall well-being but, more specifically, reduce existing risks. Such may be the case for nanotechnologies that can directly reduce existing risks by replacing a riskier substitute or by helping to improve health outcomes in *ex post* health care. Think here of a new nanoparticle drug delivery mechanism designed to treat cancer. While it might carry significant risks, those risks might be an improvement over the existing treatments. Where this is the case, taking a precautionary stance may actually increase overall risk. If society fails to adopt a technology that offers either of the risk-reducing possibilities then it may lose the opportunity for a net reduction in risk.

The difficulty lies in predicting both the risks and the risk-reducing benefits associated with new technologies. There may be substantial uncertainty in qualitatively assessing projected health and/or environmental benefits that may accrue from specific risk-reduction benefits of new technologies. Generally, the uncertainties associated with the risks and benefits of new products and technologies are greater than those of the existing technologies they are intended to replace. Risk characterization can suggest where the greatest uncertainties lie, and how the risk balance might change if parameter estimates or assumptions change. These results can give risk managers a richer source of information from which to make a decision. However, this presumes that the risk management model is not based solely on the inherent risks of the new technology with some threshold for risk or uncertainty that must be crossed before approval. In general, food and color additives are only approved based on characterization of safety, while their functionality and the products they replace are not lawfully allowed to be considered. Drug approval, on the other hand, considers both risks and benefits.

New technologies like nanotechnology face an additional wrinkle. Even if the benefits of the new technology, including the potential to reduce risks (e.g., the irradiation of foods to reduce food poisoning), appear to outweigh the risks of that technology, there may be a failure to introduce the technology if the perception of its riskiness has been skewed in the public consciousness or other social questions about its adoption (e.g., misplaced concerns about the food irradiation) remain unanswered. Even where introduction of a new technology is successful, significant societal resources may be spent on researching relatively insignificant risks.

However, just as there are examples of failures to introduce new potentially beneficial technologies and too many wasted resources in pursuit of insignificant risks, there have been numerous examples of where the rush to introduce new technologies has ultimately proved harmful and where there have been insufficient investments in science. As JoAnne Shatkin has noted: "Perfluorinated organic compounds, lead, PCBs and asbestos are examples of substances that have an environmental legacy that proved costly."[3] So in the end, perhaps we should follow the advice of Aaron Wildavsky who said: "The trick is to discover not how to avoid risk, for this is impossible, but how

to use risk to get more of the good and less of the bad. The search for safety is a balancing act . . . there is no choice that results in no harm."[4]

A final issue for risk characterization is to describe the unit of analysis for which the risk is being assessed. Is it the risk of a marketed product, the risk of certain components of the product, the process used to produce the product, risks to the environment, or some combination of all of the above? In general, since we are interested in risks and benefits over a product's lifecycle, we will want to know the combination of consumer, labor, and environmental risks of a product from manufacture through use and disposal. In the case of nanotechnology, which is still significantly in the experimental stage, the lifecycle includes the research and development environments.

How risks will be characterized depends on the framework for analysis, for example, risk/benefit, a precautionary threshold, or some other standard; a related question of whether the decision is *ex ante* approval or *ex post* regulation; the degree of concern about consumer market acceptance and the unit of analysis.

3. STAKEHOLDER INVOLVEMENT IN RISK CHARACTERIZATION AND RISK MANAGEMENT

The importance of involving key stakeholders as a central component of the risk analytic process has been underscored in several prominent risk assessment/management models and reports, notably the 1997 Presidential/Congressional Commission on Risk Assessment and Risk Management.[5] This approach of effectively engaging key stakeholders (e.g., consumers, academics, nanotechnology industry, governmental regulators, workers, nongovernmental organizations) into the entire risk analytic process will be particularly important in assessing and managing novel risks, like those from nanotechnology.

Because many different types of stakeholders will be interested in the characterization of nanotechnology risk, and because they have different needs for different kinds of information, it is important that the risks, benefits, and uncertainties be characterized as broadly as possible. In general, the different kinds of information should be a natural outgrowth of an interactive risk analytic process that has involved stakeholders at every stage. Consumers, in particular, do not think about risks in the same way that risk scientists do. Risk communication research has uncovered a much richer way that consumers think about risks and includes issues such as familiarity, dread, personal ability to control risks, possibility of a catastrophe, and potential benefits. If stakeholders are involved throughout the process, these issues should emerge.

4. PUTTING THE NANO IN NANO RISK CHARACTERIZATION

Nanomaterials exploit some novel feature or property that is enabled or enhanced within the 1–100 nm range. This distinguishes engineered nanomaterials from those incidentally produced as a byproduct of some other process of human or natural origin, such as the nanoparticulate component of diesel exhaust (also known as ultrafine particulate matter), sea spray, or volcanic eruption. Another distinguishing feature of engineered nanoparticles is the control that materials scientists and engineers can exhibit over the precise features of the materials. This control may extend to the size, shape, surface chemistry, coating, and composition, alteration of any of which may result in a functionally different material with unique properties. Thus, as the polymer chemist can change the functional moieties or branching ratio of a polymer chain to make different types of plastic from the same feedstock, so the nanoscientist has a whole toolkit with which to alter the features of a nanomaterial to confer the precise property desired. Slight changes in the features of the nanomaterial can result in changes to its electrical conductivity, color, chemical reactivity, magnetism, mechanical strength, or biocompatibility.

Size is one feature of a nanoparticle that can influence its properties and behavior. Indeed, a distinguishing feature of nanomaterials compared with larger particles is the size-dependency of some of the physicochemical properties. A semiconducting nanoparticle, known as a quantum dot, provides a simple and visually appealing example of this unique-to-nano feature: a whole rainbow of glowing particles of CdSe can be created just by changing the particle's size from 2 nm (blue) to 8 nm (red). This is illustrated in Fig. 1. A larger-than-nano particle does not exhibit such size-dependent behavior. Size has another important implication for a nanomaterial's properties. Dividing a solid into lots of nanoparticles also exposes much of the particle's surface to its surroundings and can greatly impact its chemical reactivity. This high-surface-area-to-volume ratio may be

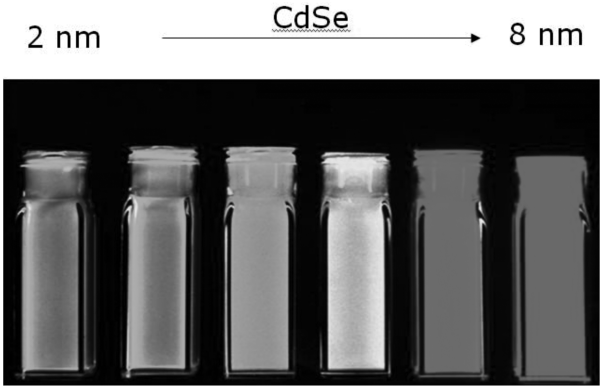

Fig. 1. Fluorescence image of CdSe quantum dots as a function of size. Courtesy: Bawendi, MIT.

a part of what makes a nanomaterial more versatile than its larger counterpart of the same composition.

The novelty, diversity, and alterability of nanomaterials' physicochemical properties may have important implications for assessing their interactions with living systems, which may in turn complicate risk characterization. There are a host of issues that derive from the unique features of nanomaterials, including the large surface area, the diversity of structural forms that can be created from the same material, and the lack of validation of standard techniques for assessing hazard. A separate set of issues derives from the novelty of the enterprise itself, including the quality control of nanomaterial manufacturing techniques and the lack of standards for even such fundamentals as terminology and nomenclature.

There is currently a critical lack of data regarding potential hazards, dose-response relationships, and exposure levels for most currently available nanomaterials. Without a substantial increase in research in this area, as well as a regulatory structure that requires development of such data, this fundamental problem can be expected to grow with the dramatic increase in nanomaterials projected over the next decade and beyond. A basic question that must be asked at the outset is to what extent risk information about the conventional, larger-scale material or the smaller, molecular species can serve as a starting point for risk characterization of the nanomaterial. This issue raises uncertainties similar to the classic problem in risk assessment for chemicals with respect to the extrapolation of dose-response relationships from the large doses administered to animals to the much smaller actual doses received by humans. In some cases, a nanomaterial is a smaller version of the conventional material and exhibits few significant differences in biological or chemical activity. However, extrapolating unknown nanomaterial behavior from known behavior of the larger (or smaller) analog may be reliant on faulty assumptions. One place this can be seen immediately is in the use of mass or volume as the basis for a risk assessment, which does not take into account the immense surface area presented by the nanomaterial. Relying on the content of the nanoparticle to predict its behavior may also prove unwise since a composition-based risk assessment does not account for structural effects, such as the impact of a coating or surface functionalization, which can radically alter biological behavior. Even the standard toolbox employed by the risk assessor must be reexamined. Recently, it was shown that several different types of carbon-containing nanoparticles interact with the dye molecules used in standard toxicity assays, resulting in false positives or false negatives depending on the test.[6] Furthermore, as nanomaterials evolve beyond the passive phase into more adaptive and complex systems there may be no larger-scale analog to serve as a benchmark.

As with many chemical processes, quality control becomes a factor when laboratory synthesis techniques are scaled up to industrial levels. What was a nice, homogeneous, monodisperse sample in the beaker turns into a mixture of products when made on a large scale in the factory. These mixtures may be sold "as is" if impurity or dispersity do not compromise the quality of the final product. However, mixtures are difficult to do science-based risk analysis on, and even when this is possible, batch-to-batch variability increases the uncertainty of any assessment of a particular product or process.[7] Therefore, until nanomaterial processing technologies improve, this will remain a point of difficulty for risk characterization.

The dynamic nature of nanomaterials throughout the product lifecycle has yet to be well studied and will be a critical component of any risk characterization process. Nanoparticles should not be thought of as static entities but must be characterized in the context in which they are used. When a nanoparticle enters a biological medium, for example, its surface attracts a variety of biomolecules that attach and detach from the surface in an unpredictable and dynamic manner. The precise nature of that dynamic coating can have large implications for the particle's interaction with a living system. This has been observed, for example, in the quantum dots

where an intentionally engineered coating influenced the particle's ability to penetrate a cell membrane.[8] The nanoparticle may also go through several stages along the value chain from primary particle through formulation or coating to incorporation into the final product. At each stage its behavior may vary, which can impact how risk assessment is performed and the risk characterization is interpreted.

Risk characterization of nanotechnology may be easier if there is development and adoption of stringent standards across its diverse areas, including terminology, metrology, and characterization. Efforts are underway within several national and international standard-developing organizations, including ASTM International, the British Standards Institute, and the International Organization for Standardization (ISO), but widespread adoption of standards that will improve risk characterization is likely years away. One possible interim approach to characterizing the potential risks of nanomaterials is to categorize them according to exposure potential. Thus, materials that may be highly toxic but with minimal exposure potential may be of less concern in terms of health or environmental risks when compared with materials that may be less toxic but with a higher potential level of exposure. However, even this approach requires some fundamental understanding of the potential hazards associated with nanomaterials, though not necessarily requiring dose-response data.

5. SAFETY ASSESSMENT VERSUS RISK ASSESSMENT

Much of what is practiced today in the risk analysis field for environmental health hazards can be termed "safety assessment." A safety assessment identifies a standard or value, such as a risk level or dose level that represents a threshold of no or insignificant concern. Examples would be the U.S. Environmental Protection Agency's (EPA) chronic reference dose (RfD), the U.S. Agency for Toxic Substances and Disease Registry's minimum risk levels (MRLs), the U.S. Food and Drug Administration's acceptable daily intakes (ADIs), the EPA's drinking water standards (MCLs or maximum contaminant-level goals), and the U.S. Occupational Safety and Health Administration's permissible exposure limits (PELs).[9] All of these decision models follow a general model, starting with a studied dose that is either a "No Adverse Effect Level" (NOAEL) or the lowest level at which there have been effects (LOAEL) and reduce that level using safety factors to come up with a permissible ("safe") level. There is no prediction of the actual risks from exposure to the compound. For nanotechnology, this type of analysis would be useful as a screening tool to determine whether there are any safety thresholds that are crossed and are of potential concern. If a threshold is crossed, then a risk assessment that estimates risks at various exposure levels would be necessary. Risk assessments, as opposed to safety assessments, are clearly necessary when there are two kinds of benefits that will be considered, a nanoproduct replacing an existing risky product or a nanoproduct that offers risk-reducing potential. Both safety assessment and risk assessment should play a role in the governance of nanotechnologies. Safety assessments can provide screens to assess where concern may be dropped or a more thorough risk assessment approach should be pursued that may lead to new requirements for production or sale.

6. EVOLUTIONARY VERSUS REVOLUTIONARY POTENTIAL BENEFITS OF NANOTECHNOLOGY

Just as there is a tremendous amount of uncertainty in estimating risks for new technologies, we should expect that there is uncertainty in predicting benefits. Nanotechnology is predicted to have both evolutionary and revolutionary effects on our economy. Because it represents a fundamentally different way of doing things, rather than simply a single new technology, the impact can be both small and large. We are still at the beginning of exploring evolutionary uses of nanotechnology to improve existing products and processes, ranging from applications such as smaller transistors in computers to germ-resistant coatings on kitchen appliances, and therapies that can selectively target diseased cells.

Models currently do not exist that adequately predict the rate of development for these kinds of technologies, that is, those that have the potential to both improve existing technologies (evolutionary) as well as develop entirely new technologies (revolutionary), based on different risk management approaches and the evolution of risk communication strategies. This deficit severely hampers risk managers in making decisions that involve considering alternative approaches for controlling risks for such new technologies. Development of such models and data and improving the ability to forecast technology development under different risk management

paradigms will be important in conjunction with efforts to reduce uncertainty about risks.

The enormous benefits that nanotechnology could potentially have for our society begin to brush the edges of its revolutionary potential as not all the applications of nanotechnology will be simple improvements on old products. Areas with the greatest potential for revolutionary changes from nanotechnology are medicine, computer science, and environmental science. Furthermore, nanotechnology is not simply one technology, but has applications to existing technologies and the ability to create new fields *de novo*. Current market predictions are only capturing an increase in nanoapplications to existing technologies. Substantial though that will be, it fails to take into account the field's revolutionary possibilities. However, any optimism about the potential benefits of nanotechnology must be tempered by the realization that some of these benefits are likely to be long term and may have associated risks.

The Presidential/Congressional Commission on Risk Assessment and Risk Management advised that specific risk characterizations should be compared with other similar health risks.[10] It is important that only like risks are compared, for example, the risks associated with nanotechnology cannot be compared to the risks of being struck by lightning. These comparisons may also include comparing the risks from prescribed policies for nanotechnology to other risks that would arise under different policy options.

The same concept of "like comparability" will also need to be considered in evaluating the potential risks and benefits associated with specific nanomaterials or technologies. A broader societal context will need to inform the assessment of nanotechnology-related potential risks balanced against the potential benefits from new nanotechnologies, both in terms of new applications or by replacing more hazardous materials or technologies. The need to integrate the viewpoints and values from the public and key stakeholders has been a fundamental component of numerous recommendations for the application of risk characterizations in risk management decision making.[10] For example, societal views regarding the benefits of potential medical treatment applications of nanoparticles might outweigh concerns regarding any potential risks associated with this type of nanomaterial application. However, societal judgments regarding the risk-benefit tradeoffs associated with the use of nanomaterials in consumer products may be less favorable if evidence of potential hazard and exposure emerges.

7. UNCERTAINTY AND VARIABILITY IN NANOTECHNOLOGY RISK ASSESSMENTS

Communicating what is known and what is not known about every stage within risk analysis is vital so as not to give decisionmakers a false sense of security. Uncertainty, which is the lack of knowledge of the scientific "truth," is a property of all steps in risk analysis and is potentially reducible with more information (but can never be eliminated). In this sense, uncertainty is a property of the analyst, what the particular analyst knows and does not know. Variability, which is the variation in data across space, time, and populations, is a property of nature and it cannot be reduced through more research. A discussion of risk variability for populations provides risk managers with information to determine how to protect small, highly exposed, or highly vulnerable subpopulations.

There are broad uncertainties that characterize nanotechnologies in the sense that there are many parameters for which we will have very little information. As noted above and in the accompanying articles, significant uncertainties exist regarding the parameters (i.e., input data) that will be required to assess the risks associated with nanomaterials. However, in addition to acknowledging the parameter uncertainties, the risk analyst must communicate the uncertainties associated with the models used to generate risk estimates. The classic model for carcinogens and pathogens is one that characterizes risk by a level of health response, (e.g., cancer, death) to a given dose. But, as discussed earlier, that model may not work for nanotechnologies. The physical characteristics of the compound, including size, shape, surface coating, surface area, and porosity, all may be as important, or more important, than dose. Complicating that fact is the realization that some of these characteristics may be affected by the quality of the manufacturing process such that there are, for example, problems of purity that will give rise to variability in these parameters.

One approach to reducing the uncertainties associated with risk management decisions is to invest in more science to fill the data gaps for key uncertainties that might change a final decision as to regulation or market dispersion. Documenting how the substantial uncertainties associated with nanotechnology risk assessment components are integrated in the risk characterization phase will be particularly important and presents substantial challenges for the risk assessor, and ultimately for the risk

manager regarding interpretation of risk characterization results.

Numerous approaches to considering uncertainty and variability in the risk assessment process have been developed over the years, with the tendency toward quantifying both components.[11] In some cases, risk analysts are quantifying the total extent of uncertainty surrounding summary risk statistics and in others demonstrating what investments in more information might be able to do to reduce the uncertainties. A key point of quantifying uncertainty is so that a picture of false precision is not presented to the risk manager and to show how, if within the bands of uncertainty certain conditions prevail, the risk estimates change. For safety assessments, the analyst controls for uncertainty and variability by choosing values that ensure that there is a fairly high certainty that, under the studied conditions, there would be no actual harm. Risk managers typically have a more limited range of options when these types of assessments are done.[12]

The onus on risk analysts to explain how uncertainty and variability have been addressed in their risk assessments is one that is likely to be particularly difficult for nanotechnology risk assessments given the current state of scientific knowledge. One source of variability not often discussed is the variability in knowledge and abilities of risk managers to process this information and make intelligent decisions. If consumers are to be their own risk managers, this difficulty is further compounded. This variability should be an important factor for risk characterization, particularly when the primary audience is a risk manager.

8. CONCLUSION

As nanotechnology advances, people in various roles, such as consumers deciding to buy or not buy products, manufacturers deciding what to bring to market, and governments making decisions on controls, will all make decisions that will determine the acceptability of these products. Currently, we do not have a good risk characterization model that informs us about both risks and benefits that will serve both risk management and risk perceptions issues for nanotechnology. Such a model would present the uncertainties on both sides of the equation in an equivalent fashion and would help us to set research priorities to reduce those uncertainties. The elements of this model would include, for example, a cost-effective screening process that will allow us to identify and target our resources toward the risks that are of greatest concern. This article has begun the process of establishing such a model and identifying some key uncertainties. Development of several comprehensive nanotechnology risk assessment case studies utilizing a multidisciplinary group of experts would provide insights into advancing the science of nanotechnology risk assessment. It will be imperative that these case studies be transparent in terms of data selection, quantitative methods, and levels of uncertainty associated with the risk assessment components.

How we choose to regulate these products, prior approval based on a precautionary principle or post-market approval, will both be determined by and will determine the risk characterization. Undoubtedly, ultimately, there will be a need for a dynamic decision system that constantly updates information, characterization, and decisions. Besides the choice of risk characterization models, we have raised other key questions including how to draw inferences, if any, for the risks associated with the bulk materials when produced at nanosize and how to think about variability in processing that may lead to variable risks from batch to batch or plant to plant. Finally, we need to better understand how to predict and assess the uncertainties associated with the future innovation and invention associated with nanoproducts.

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