The Scientific Basis for the Regulation of Nanoparticles: Challenging Paracelsus and Paré

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I.
INTRODUCTION

In this article I consider the challenges posed by nanotechnology to regulations based on the standard "laws" of toxicology. These "laws", applicable to chemical and physical agents, are: (1) the dose makes the poison; (2) the specificity of effects; and (3) humans are animals. Although these "laws" are somewhat pertinent to nanoparticles, my conclusion is that the properties of nanoparticles can be sufficiently different from other chemical and physical agents so that standard regulatory approaches based upon the three "laws" of toxicology may not be protective of public health or the environment. For the most part I will restrict my comments to the scientific basis for regulation of nanotechnology aimed at protecting human health.[1]

After discussing some of the semantic problems posed by defining a field solely on a physical attribute, I will briefly describe the "laws" of toxicology underlying safety assessment and how nanotechnology provides problems for their routine use for developing regulatory controls—particularly for dose-response assessment. These challenges to protective regulation of nanoparticles are further addressed through the consideration of three other types of agents for which it is known or alleged that the biological response to the dose of the chemical does not fit common dose response characteristics: radionuclides, homeopathic drugs, and agents said to have hormetic properties. Also considered are the challenges posed by nanoparticles to exposure assessment, a central process in regulatory risk assessment and in the public health approach to environmental protection. I conclude that the existing and planned investments in understanding the scientific basis for appropriately regulating nanotechnology are not sufficiently robust to protect the public—or to protect the industry.

This article will not detail the growing literature on the toxicity of nanoparticles. The key point for this article is that there is ample literature to support the contention that, under the appro-

1. The extent of effort to date on exploring the potential effects of nanoparticles on the general environment is relatively abysmal. *See* UN ENVIRONMENT PROGRAMME, 2007 GEO YEARBOOK 61-70 (with contributions by the author and Marilyn Smith).

priate exposure conditions, nanoparticles can cause adverse consequences.[2]

II.
NANOTECHNOLOGY AS A SEMANTIC CHALLENGE TO SCIENCE-BASED REGULATION

The term nanotechnology is useful because it describes a field of endeavor that is linked by novel technical approaches to the generation and use of the special qualities of very fine particles. It is sufficiently distinct from usual incremental advances in research and development to be separable on a company balance sheet, or as a component of a national R&D strategy. Inevitably, any success in one specific nanotechnology will be generalized to all, as will any failures.

Nanotechnology describes a process. This process produces a variety of very different agents with markedly different chemical and biological properties, although at some stage sharing the physical characteristic of size within the nano range. Although knowledge that this small size is involved provides useful guidance to toxicological scientists seeking to provide the basis for regulatory regimes, it is not as helpful as a characterization that is based on use. For example, classification of a compound as a

2. Among the pertinent reviews and prescriptions for further research are ROUNDTABLE ON ENVIRONMENTAL HEALTH SCIENCES, RESEARCH, AND MEDICINE, INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMIES, IMPLICATIONS OF NANOTECHNOLOGY FOR ENVIRONMENTAL HEALTH RESEARCH (Lynn Goldman & Christine Coussens eds., 2005); COMMITTEE FOR REVIEW OF THE FEDERAL STRATEGY TO ADDRESS ENVIRONMENTAL, HEALTH, AND SAFETY RESEARCH NEEDS FOR ENGINEERED NANOSCALE MATERIALS, NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES, REVIEW OF THE FEDERAL STRATEGY FOR NANOTECHNOLOGY-RELATED ENVIRONMENTAL, HEALTH, AND SAFETY RESEARCH (2009) [hereinafter COMMITTEE]; Gunnar Damgård Nielsen et al., In vivo *Biology and Toxicology of Fullerenes and Their Derivatives*, 103 BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY 197 (2008); John M. Balbus et al., *Meeting Report: Hazard Assessment for Nanoparticles—Report from an Interdisciplinary Workshop*, 115 ENVTL. HEALTH PERSP. 1654 (2007); J. Michael Davis, *How to Assess the Risks of Nanotechnology: Learning from Past Experience*, 7 J. NANOSCIENCE NANOTECHNOLOGY 402 (2007); Kiryn Haslinger, *Conference Summary: The National Academies Keck Futures Initiative Stimulates Advances in Nanoscience Through Interdisciplinary Research*, *in* THE NATIONAL ACADEMIES KECK FUTURES INITIATIVE DESIGNING NANOSTRUCTURES AT THE INTERFACE BETWEEN BIOMEDICAL AND PHYSICAL SYSTEMS: CONFERENCE FOCUS GROUP SUMMARIES 1-6 (2005); Andrew D. Maynard et al., *Safe Handling of Nanotechnology*, 444 NATURE 267 (2006); Tian Xia et al., *Potential Health Impact of Nanoparticles*, 30 ANN. REV. PUB. HEALTH 137 (2009); Paul A. Schulte et al., *Issues in the Development of Epidemiologic Studies of Workers Exposed to Engineered Nanoparticles*, 51 J. OCCUP. ENVTL. MED. 323 (2009).

solvent, or as a pesticide, provides far more information about the likelihood for human and environmental exposure and toxicity.[3]

In essence, the term nanotechnology represents a bottleneck based solely on size. But once an agent is through this bottleneck, its effects can go in many different directions—though potential effects can be grouped together based on predicted mechanisms of action, as well as exposure routes and organ specific effects.[4] Semantic generalization across very diverse agents with a wide range of properties, both harmful and helpful, is common.[5] A major threat to all in the nanotechnology field is the possibility that adverse consequences demonstrated to occur from one nanoproduct will apply to all nanotechnology products in the minds of regulators and the public. This effect may detrimentally affect all subsequent regulation.[6] This appears to have occurred with GMO products, particularly foodstuffs that have received the generic label of "Frankenfoods."[7]

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3. I do not argue that knowledge of use is sufficient to understand all exposure or toxicity scenarios. For example, the neurotoxicity of the solvent benzene can be predicted based upon knowledge of chemical structure and of the similar neurotoxicity of alkyl benzenes, such as toluene and ethyl benzene. But among all these related compounds it is only benzene that produces hematological toxicity. However, knowledge of properties is more helpful in assessing the potential for toxicity than is knowledge of processes.

4. Briefly, the respiratory tract, skin and perhaps the brain are considered to be major organ targets for nanoagents; mechanisms of action of concern include enhanced uptake into cells, the bypassing of cellular defense mechanisms, and the production of oxidative stress. As nanoparticles are unlikely to survive in the digestive track without agglomeration or other processes that would remove their special characteristics, the major exposure pathways of concern are inhalation and intradermal.

5. Cass Sunstein refers to an availability heuristic "which can make some risks stand out as particularly salient, regardless of their actual magnitude." Cass R. Sunstein, *Precautions Against What? The Availability Heuristic and Cross-cultural Risk Perception,* 57 ALA. L. REV. 75 (2005). An example of overcoming such a heuristic through semantic ingenuity is the successful launch of "magnetic resonance imaging (MRI)." MRI was developed over decades in the scientific community under the title "nuclear magnetic resonance." The brilliant stroke of removing the word "nuclear" has much to do with public acceptability of the technique.

6. Concern about the use of nanotechnology has recently led Consumers Reports to test sunscreens for nanoparticles. Its article about which sunscreens have or do not have nanoparticles includes a cautionary statement that Consumer Reports does not know whether such products are harmful. The article does, however, urge labeling of nanoproducts. *See No-Nano Sunscreens?*, CONSUMER REPORTS, Dec. 2008, at 13.

7. It is perhaps pertinent to the future path for nanotechnology to observe how the pendulum has swung in regards to GMO. At first, opponents of genetic engineering were generalizing to all GMO products any potential problems or observed

III.
THE TOXICOLOGICAL BASIS FOR THE REGULATION OF CHEMICAL AND PHYSICAL AGENTS[8]

Central to the interest in nanotechnology is that the properties of nanoparticles are often unique or at least far more effective than the same chemical molecules that are not nanostructures. This uniqueness also indicates the challenge to routine safety assessment of nanocompounds and nanoproducts.

It is helpful to explore why nanocompounds are similar to or different from other agents subject to regulation by considering the properties of nanocompounds through the lens provided by the three "laws" of toxicology. Of note is that nanoparticles can have two separate attributes in relation to the same chemical in its larger size: (1) nanoparticles are more effective in performing what would be done by the same chemical if not formulated in a nanosize; and (2) they can have completely different properties than would be observed when in a larger size. The first attribute challenges the first "law" of toxicology, the dose makes the poison. The second attribute relates to the second "law" of toxicology, the specificity of effects.

A. *Paracelsus: The Dose Makes the Poison*

Paracelsus, a fifteenth century scientist and physician, is credited with the formulation that all chemicals are toxic, it is only a question of dose. For nanoparticles, the dose is as or more likely to be related to surface area or surface properties, such as

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mishaps with any single GMO. Now that the potential benefits of GMO are more accepted, environmentalists have focused on the individuality of genetically engineered crops as a reason for specific oversight while industry has taken the position that nothing more is needed. See, for example, Gregory Jaffe of the Center for Science in the Public Interest, who argues that federal oversight of genetically engineered crops based upon adapting existing laws has not resulted in adequate oversight. He states: "While many developers and biotech proponents generalize benefits globally for GE crops, in reality benefits must be analyzed based on the crop, the introduced trait and the specific location and farming condition." Gregory Jaffe, *The Next Generation*, 26 ENVTL. F. 38, 39 (2009). Michael Wach, Managing Director of Science and Regulatory Affairs for Food and Agriculture at the Biotechnology Industry Organization, responds to Jaffe with the industry view against further regulatory oversight. *See* Michael Wach, *Feeding, Fueling, Healing*, 26 ENVTL. F. 41 (2009).

8. For further discussion of the science of toxicology in the legal literature, see Bernard D. Goldstein, *Toxic Torts: The Devil is in the Dose*, 16 J.L. & POL'Y 551 (2008); REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (3d ed. forthcoming); Joseph V. Rodricks, *Evaluating Disease Causation in Humans Exposed to Toxic Substances*, 14 J.L. & POL'Y 39 (2006).

charge, than it is to weight. For any given solid chemical's weight, the finer the particle size, the greater the surface area. This can lead to paradoxical dose response curves based on the weight of the chemical if particle size is not considered. A small amount of chemical formulated in nanoparticles can be more toxic, or more effective in its use, than a larger amount of the same chemical formulated in larger chemical particles.[9] For many specific nanoparticles, the physical phenomena related to a larger surface area are responsible for its intrinsic properties and effects. In essence, nanotechnology can provide an exception to the "dose makes the poison."

B. *Paré's "Law": The Specificity of Effects*[10]

The second law of toxicology, that chemicals have specific effects, is analogous to the legal concept of general causation: can a chemical or physical agent produce a specific effect?

Modern approaches to determining specificity often depend upon focusing on the total weight of evidence, such as the expert panel processes used by the International Agency for Research on Cancer (IARC) or the U.S. National Toxicology Program (NTP) in assessing whether a chemical is a carcinogen. If nanosizing leads to novel properties that cannot be discerned with standard toxicological testing, then Paré's law is significantly challenged.

C. *Humans are Animals*

Central to the science of toxicology is an understanding of the relevance to humans of testing in laboratory animals. The respiratory tract is at particular risk of adverse effects through inhalation of nanoparticles, and there have been numerous studies demonstrating the toxicity of specific nanoparticles to the air-

9. Nanoparticles thus seem to fit well under a central theme of environmental protection, that of pollution prevention through use of less material.

10. B.D. Goldstein & M.A. Gallo, *Paré's Law: The Second Law of Toxicology*, 60 TOXICOLOGICAL SCI. 194 (2001). Ambrose Paré is considered the father of experimental surgery based upon his very practical approach to battlefield injuries which overthrew longstanding but incorrect theories. He told the King of France that an alleged universal antidote to all poisons, purchased by the king at a great price, could not conceivably work because each poison had a specific means of causing death. The king was forced to agree with Paré after the antidote was put to the test by administering it to a poisoned prisoner.

ways and lung.[11] While important information about the potential respiratory toxicity of nanoparticles can be obtained from *in vitro* studies, inhalation studies in laboratory animals are particularly important as the properties of the respiratory tract may alter the physical characteristics of nanoparticles during inhalation. For example, the 100% humidity of the respiratory tract may cause agglomeration of certain types of nanoparticles, a physical process akin to particles of table salt becoming too large to fit through the holes of a salt shaker in humid weather.

D. *Mode of Action*

A central focus of the science of toxicology is to identify the underlying processes by which external agents cause adverse effects. Extensive advances in recent years have built upon the expanding knowledge base in the biological sciences. This has facilitated one of the very positive changes in EPA science-based regulatory approaches, namely, the inclusion of information about an agent's mechanism of action or mode of action.[12] The use of such information in decision-making about the weight of evidence concerning a chemical or physical agent has also occurred in deliberations about cancer-causing agents by IARC and by the U.S. National Toxicology Program.[13] There has been much recent interest in making use of the advances in molecular

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11. *See, e.g.*, Ken-Ichiro Inoue et al., *Effects of Pulmonary Exposure to Carbon Nanotubes on Lung and Systemic Inflammation with Coagulatory Disturbance Induced by Lipopolysaccharide in Mice*, 233 EXPERIMENTAL BIOLOGY MED. 1583 (2008); Timothy S. Hiura et al., *Chemicals in Diesel Exhaust Particles Generate Reactive Oxygen Radicals and Induce Apoptosis in Macrophages*, 163 J. IMMUNOLOGY 5582 (1999); V.E. Kagan et al., *Direct and Indirect Effects of Single Walled Carbon Nanotubes on RAW 264.7 Macrophages: Role of Iron*, 165 TOXICOLOGY LETTERS 88 (2006).

12. The mode of action and the mechanism of action are discussed by two EPA scientists, Dellarco and Baetcke:

> "Because complete knowledge of how an agent causes cancer is unlikely to exist (certainly for the near term), the 1996 guidelines put forth the notion of understanding mode of action versus mechanism of action. The former being a less detailed biochemical description of events than is meant by mechanism of action. The mode of action is sufficient evidence to draw a reasonable working conclusion concerning the agent's influence on key processes. The mode of action concept permits information on precursor events to be evaluated and incorporated into the risk assessment process in a realistic way."

Vicki L. Dellarco & Karl Baetcke, *A Risk Assessment Perspective: Application of Mode of Action and Human Relevance Frameworks to the Analysis of Rodent Tumor Data*, 86 TOXICOLOGICAL SCI. 1, 1 (2005).

13. *See* Vincent J. Cogliano et al., *Use of Mechanistic Data in IARC Evaluations*, 49 ENVTL. & MOLECULAR MUTAGENESIS 100 (2008).

biology and information technology to develop better *in vitro* screening methods for predicting toxicological effects.[14] However, nanoparticles pose additional problems to determining mode of action through *in vitro* testing because of uncertainty about the size dimensions of the nanoparticle in the test system as compared to *in vivo*.

E. *Predictability and Surprise*

As a preventive science, toxicology depends upon providing the tools to predict and avoid the adverse effects of a chemical or physical agent. Simply put, an adverse effect caused by a chemical or physical agent represents the failure of toxicology as a preventive science.[15]

As a generalization, two sets of tools are used to avoid surprise.[16] One is based upon an understanding of the relation between chemical structure and the activity of a chemical in producing its effects. The second is based on testing in biological systems.

Significant investment has been made, particularly by the pharmaceutical industry, in computational technology to improve predictability based upon chemical structure. However, there are limitations posed by three separate problems: (1) the presence of unique biological niches that cannot be predicted based solely on understanding of chemical structure; (2) metabolic processes that change a single administered chemical into one or more other chemicals that may be responsible for adverse effects;[17]and (3) the fact that exposure to chemicals in the real

14. COMMITTEE ON TOXICITY TESTING AND ASSESSMENT OF ENVIRONMENTAL AGENTS, NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES, TOXICITY TESTING IN THE 21ST CENTURY: A VISION AND A STRATEGY (2007); COMMITTEE ON IMPROVING RISK ANALYSIS APPROACHES USED BY THE U.S. EPA, NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES, SCIENCE AND DECISIONS: ADVANCING RISK ASSESSMENT (2009).

15. The need to rely on epidemiology as a backup may also occur even if toxicological testing techniques are capable of predicting an adverse effect, for example, if these tests are not utilized, or the resulting regulations are not enforced.

16. A third approach is used for new drugs—that of a preclinical trial in humans. Such testing is not required for consumer products or for nanoparticles generated in the workplace or general environment.

17. Benzene is an example of a chemical that is not itself toxic to the bone marrow but requires metabolism to produce its adverse hematological effects. The reason for the distinction between benzene and alkyl benzenes in hematotoxicity but not neurotoxicity is that the metabolic products of benzene are uniquely hematotoxic, while neurotoxicity primarily depends upon the effects of unmetabolized benzene or alkyl benzenes. *See supra id.*

world does not occur in isolation, but occur in interaction with other external and internal processes.[18]

Davis has perceptively described the issues presented by the use of methyl tert-butyl ether (MTBE) as a gasoline additive without adequate testing as a cautionary tale for nanotechnology.[19] The petrochemical industry has long downplayed the evidence supporting MTBE as a cause of human toxicity. However, it is not debatable that the sudden ramp up of MTBE usage and the only belated demonstration of its adverse properties led to a boom and bust cycle among the industries involved—something that nanotechnology related industries would best avoid[20].

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18. The discovery that grapefruit juice contains a major inducer of metabolic enzymes was based on tracking down why unexpected results occurred as a result of alcohol administration in grapefruit juice instead of without this juice. Recently, the extent to which benzene produces hematotoxicity in exposed workers in China had been associated with the activity of genetically-determined metabolic pathways. Nathaniel Rothman et al., *Benzene Poisoning, a Risk Factor for Hematological Malignancy, is Associated with the NQO1 609C—>T Mutation and Rapid Fractional Excretion of Chlorzoxazone*, 57 CANCER RES. 2839 (1997).

19. J. Michael Davis, *How to Assess the Risks of Nanotechnology: Learning from Past Experience*, 7 J. NANOSCIENCE NANOTECHNOLOGY 402 (2007).

20. MTBE unquestionably causes cancer in laboratory animals, as observed in more than one species, gender, body organ and testing laboratory. F. Belpoggi et al., *Methyl-Tertiary-Butyl Ether (MTBE)—a Gasoline Additive—Causes Testicular and Lymphohaematopoietic Cancers in Rats*, 11 TOXICOLOGY AND INDUSTRIAL HEALTH 119 (1995); Michael G. Bird et al., *Oncogenicity Studies of Inhaled Methyl Tertiary-butyl Ether (MTBE) in CD-1 Mice and F-344 Rats*, 17 J. APPL. TOXICOLOGY S45 (Supp. 1 1997). Unfortunately, these studies were not available before the major investment by industry in response to the requirement for oxygenated gasoline in the 1990 Clean Air Act Amendments. When introduced public concerns about acute symptomatic effects were also voiced, and major contamination of water sources occurred, the latter was most important to EPA's eventual decision to phase out use of MTBE. While increasing MTBE usage in U.S. gasoline was propelling it to be the second largest volume commodity chemical in the world, the U.S. government responded to concerns about its adverse effects primarily by convening one after another review by a wide variety of organizations, both governmental and non-governmental, before finally beginning to phase out its use. *See supra* note 19. See also Bernard D. Goldstein & Serap Erdal, *Methyl tert-Butly Ether as a Gasoline Oxygenate: Lessons for Environmental Public Policy*, 25 ANN. REV. OF ENERGY ENV'T. 765 (2000) for an accounting of the overall issue and of the various review processes). Whether the findings of cancer in laboratory animals predicted human cancer was much debated in the 1990s, with industry reassuring the public that MTBE should not be considered a probable human carcinogen. However, the science supporting MTBE as a cause of human cancer appears very strong because, among other reasons, formaldehyde, which is a major metabolite of MTBE, is now considered a known cause of human leukemia (for industry view of these recent decisions, see Formaldehyde Council Incorporated, *12/8/09: Formaldehyde Council Comments on the IARC and NTP Decisions on Formaldehyde*, http://www.formaldehyde.org/), and leukemia was one of the cancers reported in labora-

The key issue for nanotechnology is whether we can quickly develop the expertise to be able to utilize knowledge about the physicochemical properties of nanomaterials to accurately predict biological effects. The argument that investment in nanotechnology is of value because there will be many currently unpredictable advantages from the new physicochemical properties of nanomaterials is a frightening argument to those of us in public health and environmental protection.

IV.
EXISTING OR PROPOSED REGULATORY APPROACHES IN SITUATIONS POTENTIALLY NOT RECOGNIZABLE BY PARACELSUS OR PARÉ

Having argued that nanomaterials do not readily follow the "laws" of toxicology on which we base regulatory approaches to protect human health, I next consider three other situations in which there appears to be an exception to these "laws." These are ionizing radiation, homeopathic drugs, and the controversial issue of hormesis.

A. *Radiation*

Radiation science and technology has produced a very wide range of beneficial effects. This article is not the place to consider regulation of ionizing radiation in detail. But it is useful to at least briefly consider how nanoparticles, which are also anticipated to produce a wide range of beneficial effects, are similar to radioactive agents, and to explore whether the current regulatory approach to radiation provides insight into the control of nanotechnology.

The concept that a physical aspect of an agent is more important than its chemistry is central to the regulation of ionizing and non-ionizing radiation. The primary concern about radioactive cesium or strontium or iodine is not the dose of the chemical but its radioactivity. However, the chemical properties of these radionuclides do play a major role in their toxicity. For example, strontium is treated by the body much like calcium, causing the highest radiation dose to occur in bone; and iodine is preferentially taken up into the thyroid where it is a component of thy-

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tory animals exposed to MTBE. Belpoggi et al., *supra.* It is standard risk assessment procedure to consider a chemical that is metabolized to a known human carcinogen to itself be considered a known human carcinogen.

roid hormone.[21] The chemical form of the radionuclide is also crucial to understanding human exposure pathways. Concern about radioactive strontium should lead to careful evaluation of milk as an exposure source. Similarly, guidance about the potential toxicity of nanoparticles could come from understanding the underlying chemistry.[22]

One major difference with the control measures being considered for nanotechnology is that national and international approaches to control radiation, which began in the 1920s, have been in place much longer. The widespread use of radioactive compounds and devices led to an understanding of their potential toxicity and to their regulation long before the modern environmental movement and before the establishment of most of the plethora of environmental laws and treaties. Not surprisingly, the first control efforts were developed through organizations of scientists who spent many years on definitional issues. For example, much work has been required to develop equivalency factors that allow predictive comparisons of the major forms of energetic emissions that are gathered together under the heading of radioactivity. This has led to understanding the effect of different types of radiation and radiation exposure, with factors that are often organ-specific.[23]

Such time is not available for nanotechnology for reasons including its rapid pace of development, the fact that the public now has a much greater role in determining whether it will be subjected to risk from new technological developments, and public skepticism of its value. Nor is it likely that the national and international scientific organizations that continue to be of central importance to developing the scientific basis for standards for ionizing radiation, and which themselves are often involved in

21. The heightened susceptibility of the population in the Chernobyl area to thyroid cancer after exposure to radioactive iodine has been related to a relatively low background level of iodine thereby leading to a larger proportion of the radioactive iodine being taken up into the thyroid. Conversely, non-radioactive potassium iodide is stockpiled as prophylaxis should there be significant release of radioactive iodine from a nuclear incident.

22. For example, there is a robust group of cellular defense mechanisms against the release of free iron, a highly toxic agent, yet one necessary for the function of the cell. Kagan et al. have shown that buckyball nanoparticles made with trace amounts of iron can cause harm through bypassing cellular defenses against free iron. Kagan et al., *supra* note 11.

23. For a review of the history of radiation control, see D.C. Kocher, *Perspective on the Historical Development of Radiation Standards,* 61 HEALTH PHYSICS 519 (1991).

making recommendations about these standards, or about ancillary measures such as radiation measurement and protection, could be developed for nanotechnology. However, the value of such organizations as the International Commission on Radiological Protection, the United Nations Scientific Committee on the Effects of Atomic Radiation and other UN organizations is unquestionable. Duplication of these international efforts for nanotechnology should be explored.

One of the major differences between the regulation of ionizing radiation and that of chemicals is a general tendency to be less concerned about low level risk resulting from long-term exposures to ionizing radiation. This may represent the recognition that background radiation levels naturally vary in a range that dwarfs the usual concerns about the risk of synthetic chemicals. Simply moving to a higher latitude, or frequent air travel, heightens background radiation levels. Wide variations in individual exposure also occur based upon the natural levels of radioactive materials in rock or soil, as well as the radioactive content of building materials.[24] An example of the lower stringency of regulatory concern is that EPA has established a proposed drinking water standard for radon of a maximum contaminant limit of 300 pCi/liter and a proposed alternative maximum contaminant level of 4,000 pCi/liter, despite having estimated a one-in-one-million lifetime risk for radon of 1.5 pCi/liter. This is equivalent to establishing a lifetime risk at the alternative maximum contaminant level of 2.7 in one thousand lifetimes, far more relaxed than standards established for known chemical carcinogens.[25] Whether it is the long familiarity with a mature data base about an established risk, or the wide variation in natural background exposure, there is clearly a difference in consideration of acceptable risk among those in the field of radiation as compared to those who have been involved in environmental chemicals.[26]

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24. COMMITTEE ON EVALUATION OF EPA GUIDELINES FOR EXPOSURE TO NATURALLY OCCURRING RADIOACTIVE MATERIALS, EVALUATION OF GUIDELINES FOR EXPOSURES TO TECHNOLOGICALLY ENHANCED NATURALLY OCCURRING RADIOACTIVE MATERIALS (1999).

25. Not surprisingly, this has been controversial, with environmental groups insisting on a more stringent standard. The argument has spilled over into the issue of the appropriate clean-up standards should a nuclear device or "dirty bomb" be set off in the United States.

26. Gonzalez is instructive as to the cultural differences involved in radiation and chemical risk. He has pointed out that the prevalent opinion of most radiation scientists is that "exposure to radiation, however small its level might be, is not necessarily good for health but that its associated risks are extremely small." Abel J.

Regulatory control of long-term exposure to radiation in the workplace or general environment tends to focus on as-low-as-reasonably-achievable (ALARA) standards, rather than on those that are risk-based.[27] For example, if an emission standard is exceeded, the source is usually required to improve to the best that is reasonably achievable below the standard, not just to a level that achieves the emission standard. Regulatory control of chemical exposures does have a variable mix of technology-based approaches, and it can be argued that there has been movement away from risk-based to technology-based standards for control of chemical pollutants, perhaps related to concepts underlying the precautionary principle.[28]

In summary, perhaps the most important lessons from the complex world of radiation control to nanotechnology are, first, that it is important to pay attention to the chemical carrier and to the exposure pathways as well as to the physical properties of the agent. Second, the development of international organizations specifically focused on providing the scientific basis for the regulation of nanotechnology should be explored. And finally, there is a role for technology-based standards focused on approaches that are consistent with ALARA.

B. *Homeopathy: The Control of Low Dose Medication*

Homeopathy has historically been associated with the belief that high levels of dilution are important to producing a healing effect from a homeopathic agent; and the higher the dilution, the greater the effect.[29] In the United States, these agents are regulated by the Food and Drug Administration, giving them a cachet of approval.[30]

Homeopathy as a formal system of medicine was founded in Germany by Samuel Hahnemann in the early nineteenth cen-

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Gonzalez, *The Debate on the Health Effects Attributable to Low Radiation Exposure*, 1 PIERCE L. REV. 39, 40 (2002).

27. Regulation of nuclear sources also focuses on low risk high consequence issues that do not seem as relevant to nanotechnology issues.

28. Bernard D. Goldstein & Russellyn S. Carruth, *Implications of the Precautionary Principle to Environmental Regulation in the United States: Examples from the Control of Hazardous Air Pollutants in the 1990 Clean Air Act Amendments*, 66 L. & CONTEMP. PROBS. 247 (2003).

29. For example, a tenfold dilution is considered 1X while a 100 fold dilution is considered 2X.

30. This regulation came about in large part because an influential U.S. Senator was also a homeopathic physician and inserted language concerning homeopathy in the Food, Drug and Cosmetic Act.

tury, responding in part to the adverse effects of standard medical treatments. Homeopathy focuses on a holistic approach to health that, in its emphasis on exercise and good nutrition, would be very much in keeping with the preventive health prescriptions of today. But it also has quasi-theoretical underpinnings, such as treatment of like with like; using doses that are highly diluted; and an emphasis on shaking the medicine. Prior to the reforms of medical education in response to the Flexner Report nearly a century ago, there were twenty-five homeopathic medical colleges in the United States, and homeopathy was practiced by 20 percent of American physicians.[31] No homeopathic medical schools now survive. Homeopathy is now considered a form of alternative or complementary medicine and appears to be enjoying a revival with other forms of medicine sometimes considered to be unscientific quackery.[32] Homeopathy is much more in use in Europe than in the United States.[33] In the United States, a mere 3 percent of the population is reported to use homeopathy while in six surveyed European countries usage ranged from 15 percent in Sweden to 56 percent in Belgium.

For the purposes of this article, it is particularly of note that under congressional mandate the FDA legally recognizes an independent body that prepares the Homeopathic Pharmacopeia of the United States (HPUS). FDA accepts without further oversight the agents listed in HPUS for use in homeopathic remedies, as long as they are labeled for such use. HPUS is administered by an independent self-sustaining organization of recognized experts in the field of homeopathic medicine who consider additions and deletions to the pharmacopeia, and who specify the appropriate conditions for use.

The special conditions presented by homeopathy of "less is more", conditions that violate Paracelsus's first "law" of toxicology, led Congress to write into the Food and Drug Act the creation of an independent organization of experts in the field who evaluate the efficacy and potential adverse consequences of individual homeopathic remedies. This represents a potential precedent for a similar organizational review of nanotechnology,

31. Jennifer P. Garner, *Scarlet Fever and a Murder,* W. PA. HIST. Spring 2007, at 42, 48.

32. American Cancer Society News Service, *What is Homeopathy?,* Jan. 5, 2000, http:www.cancer.org/docroot/NWS/contentNWS_2_1x_What_is_Homeopathy_.asp.

33. Peter Fisher & Adam Ward, *Medicine in Europe: Complementary Medicine in Europe,* 309 BRIT. MED. J. 107 tbl.1 (1994).

perhaps in an amended Toxic Substances Control Act.[34] Of course, a major distinction is that nanoparticles can have important biological consequences, while the efficacy of homeopathy aside from a placebo effect is open to question.

C. *Hormesis*

Like nanomaterials, hormesis presents another confounder of standard dose-response considerations, and the hormetic dose-response has been advocated as a basis for a different approach to regulation of chemical and physical agents.[35] Hormesis, which is best described as a U-shaped or J-shaped dose response curve, in which smaller amounts produce beneficial effects while larger amounts produce adverse effects, has been posited for a number of common hazardous chemicals and for ionizing radiation. Hormesis can clearly be observed for certain vitamins, e.g., some level of vitamin A is needed to prevent the adverse effects of vitamin A deficiency, while high levels of vitamin A can produce toxicity.[36]

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34. There is much interest in amending the Toxic Substances Control Act, including the introduction of legislation in Congress, and the development of statements concerning the principles that should guide TSCA reform by the head of EPA, the head of the U.S. National Toxicology Program, and environmental organizations. *See* U.S. EPA, *Essential Principles for Reform of Chemical Management Legislation*, http://www.epa.gov/oppt/existingchemicals/pubs/principles.html (last visited Feb. 10, 2009) (EPA); *Oversight Hearing on the Federal Toxic Substances Control Act: Hearing Before the S. Comm. on Environment and Public Works*, 111th Cong. (2009) (statement of Linda Birnbaum, Director, National Institute of Environmental Health Sciences and the National Toxicology Program) (head of the U.S. National Toxicology Program); Richard A. Denison, *Ten Essential Elements in TSCA Reform* 39 ENVTL. L. REP. 10020 (2009) (senior scientist at Environmental Defense Fund, an environmental organization).

35. Lester B. Lave, *Hormesis: Implications for Public Policy Regarding Toxicants*, 22 ANN. REV. PUB. HEALTH 63 (2001); Lester B. Lave, *Hormesis: Policy Implications*, 20 J. APPLIED TOXICOLOGY, 141 (2000); Frank B. Cross, *Paradoxical Perils of the Precautionary Principle,* 53 WASH. & LEE L. REV. 851 (1996); Sunstein, *supra* note 5; Edward J. Calabrese, *Hormesis, a Revolution in Toxicology, Risk Assessment and Medicine,* 5 EMBO REP. S37, S37–S40 (Supp. 1 2004).

36. Note that while hormesis is often thought of in terms of a single reaction, a little of which is good and too much is bad, it is probably more accurate to consider hormesis in light of the multiplicity of response pathways within the body, including detoxification and repair mechanisms, some of which may be elicited at low doses and some at higher doses. There is no *a priori* reason to anticipate that these multiple pathways will necessarily go in opposite directions. For example, evidence suggests that there is low dose saturation of at least one of the metabolic pathways responsible for the carcinogenicity of benzene resulting in a greater potency per unit benzene at lower dose. The inference is that risk assessment extrapolation from the leukemia incidence observed at much higher dose exposures in the workplace may underestimate the risk of benzene in the general environment.

One aspect of the debate about whether hormesis should be considered in the regulation of chemicals or of ionizing radiation concerns the implication of the natural background to regulatory deliberations, a consideration pertinent to nanoparticles. In response to Cross's argument favoring the use of hormetic dose response curves in regulation, Heinzerling and Lechleider have argued that hormesis might be pertinent to physical or chemical agents that humans have evolved with, such as background radiation or vitamin A, but would not apply to synthetic chemicals.[37] Close scrutiny of this distinction suggests it is not helpful. First, many of the most important toxic chemicals subject to regulation are naturally present as well. Decomposition of organic materials—often through combustion—will produce chemicals such as benzene or polycyclic aromatic hydrocarbons. In contradistinction, many of our most common natural foods, each containing literally thousands of chemicals, have been part of the human diet for too short a time to be of evolutionary significance.[38] This argument distinguishing natural products from synthetic products could be applied to nanoparticles, as there are natural sources of such particles from combustion that we have evolved with. Accordingly, it could be argued, since humans have evolved in the presence of nanoparticles, we should have little to worry about.[39]

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37. L. Heinzerling & R.J. Lechleider, *Hormesis and the Law*, 20 HUM. EXPERIMENTAL TOXICOLOGY 154 (2001).

38. Differences in flavor and texture among foods inevitably reflect differences in chemical constituents and cellular structure. Most of our common food plants have been cultivated for less than a few hundred years out of the 2 million years of human existence, and most of these have undergone major recent changes through selective cultivation for desired properties, including the production of natural pesticides—which are also chemicals.

39. It is pertinent that the recent EU REACH legislation focuses almost totally on synthetic chemicals. Another example of "synthetophobia" is the opposite directions of the switches in the burden of proof for hazardous air pollutants as compared to dietary supplements in the U.S. Under the 1990 Clean Air Act Amendments Section 112, the burden of proof for hazardous air pollutants was switched from EPA, which previously had to demonstrate a significant risk, to industry, which now has to prove safety. But the opposite occurred for dietary supplements in 1994 when the burden of proof for toxicity was switched from the manufacturer to the U.S. Food and Drug Administration. This has crippled the ability of FDA to regulate herbal remedies. As we have previously argued, the greater affinity of Europeans toward homeopathy, and related alternative medicine approaches such as naturopathy, along with the greater penetration of the precautionary principle in Europe, is consistent with the idea that the basis for the precautionary principle is a concern about synthetic chemicals and foods, rather than risk aversion. Goldstein & Carruth, *supra* note 28.

V.
REGULATION BASED ON INADEQUATE SCIENCE: THE PRECAUTIONARY PRINCIPLE

The precautionary principle has been a frequent concomitant of discussions about nanotechnology. For example, typing the term "nanotechnology precautionary principle" into the Google search engine on April 6, 2009 resulted in 24,800 hits.[40] Environmental groups often have advocated that nanotechnology should be regulated on the basis of the precautionary principle.[41] As I have previously commented, there is a tautology inherent in invoking the precautionary principle that inevitably leads to the conclusion that the more precautionary a society, the more likely it is to make costly mistakes.[42] This alone justifies significant investment in good science to make decisions based upon knowledge rather than the uncertain conditions that invoke the use of the precautionary principle. Further, as discussed below, the EU's REACH legislation, advocated based on the precautionary principle, is highly dependent upon toxicological and risk science.

40. *See* RUDIGER HAUM ET AL., NANOTECHNOLOGY AND REGULATION WITHIN THE FRAMEWORK OF THE PRECAUTIONARY PRINCIPLE (2004); Peter Montague, *Welcome to NanoWorld: Nanotechnology and the Precautionary Principle Imperative*, 25 MULTINATIONAL MONITOR, No. 9, Sept. 2004, at 16; Chris Phoenix & Mike Treder, *Applying the Precautionary Principle to Nanotechnology*, http://www.crnano.org/precautionary.htm (last visited Feb. 10, 2009).

41. Friends of the Earth points out the many recent international reviews or pronouncements on nanotechnology that do not even mention the word precaution, let alone the precautionary principle. Georgia Miller, *Who's Afraid of the Precautionary Principle?*, http://nano.foe.org.au/node/186 (last visited Sept. 21, 2009). For the first item on their list, that of the United Nations Environmental Programme review, I can affirm that this was intentional. *See supra* note 1. A scientist from a large developing country, the sole representative of his continent, threatened to walk out of the meeting if the precautionary principle or "precaution" was part of the document—apparently due to what is perceived as a misuse of the precautionary principle by the EU to promote trade barriers. Neither EU representative at the meeting advocated strongly for its inclusion, and left the impression that precautionary concerns would impair the competitiveness of the EU on nanotechnology similarly to what has happened with gene technology.

42. Simply put, if there is ample scientific evidence favoring a cause and effect relationship, there is no need to invoke the precautionary principle; and if there are trivial costs to correct a potentially harmful situation for which the science is not ample, the correction would be made.

VI.
THE NEED FOR NEW SCIENCE

A. *Toxicology*

In recent years there has been a marked increase in the demand for standard toxicological testing. The High Production Volume (HPV) initiative, embraced by regulatory authorities in the United States and EU, by international organizations such as OECD, and by both industry and environmental groups, has focused on increasing knowledge about synthetic chemicals that are in major use. REACH has gone further, creating a voracious and perhaps insatiable demand for new toxicology. The estimates for toxicological testing required to achieve the goals of REACH range in the billions of U.S. dollars.[43] Recognition that few of the long existing chemicals in commerce have been thoroughly tested is a significant part of the rationale for additional toxicological testing in both the HPV and REACH programs.[44] This lack of testing is particularly problematic for chemicals that were in commerce at the time of first passage of the U.S. Toxic Substances Control Act (TSCA).[45]

Inherent within the approaches to additional toxicological testing is the unstated but false assumption that current toxicological testing techniques are adequate to protect the public against the adverse effects of chemical and physical agents prior to introduction into the workplace or marketing. They are not. Perhaps because the thrust has been to level the playing field between old and new chemicals, there has been a notable lack of emphasis on developing new toxicological testing modalities to do a better job of predicting the potential for adverse consequences. Whatever the reason, it is foolhardy to impose billions of dollars of expenditure for toxicological testing, with only miniscule investment in

43. The cost implications of REACH for toxicology testing are variously given, but are well over a billion U.S. dollars in all estimates.

44. John S. Applegate, *The Perils of Unreasonable Risk: Information, Regulatory Policy, and Toxic Substances Control*, 91 COLUM. L. REV. 261, 264-66 (1991) (discussing REACH and its potential impact on the availability of toxicological and risk information); Sven Ove Hansson & Christina Ruden, *Priority Setting in the REACH System*, 90 TOXICOLOGICAL SCI. 304 (2005) (describing the toxicological needs for REACH and its reliance on exposure).

45. For discussion of REACH and TSCA, see John S. Applegate, *Synthesizing TSCA and REACH: Practical Principles for Chemical Regulation Reform*, 35 ECOLOGY L. Q. 721 (2008). Note that MTBE, discussed above and *supra* notes 19-20, is an example of the problems caused by using the provisions of TSCA regarding existing chemicals to regulate a chemical that is undergoing major changes in use and in extent and pathways of human exposure.

the scientific understanding required to develop toxicological test procedures that can more adequately protect the public.

This shortsightedness appears to also apply to nanotechnology. While some excellent work has been done on attempting to develop useful predictive approaches based upon assumptions about the properties of nanomaterials, the current failure of Congress to fund required research is of concern.[46] Similarly, the criticism of the National Nanotechnology Initiative (NNI) by a National Research Council panel suggests that while the field of nanotechnology is moving ahead rapidly, investigating its potential adverse consequences is falling further behind.[47]

EPA's Integrated Risk Information System (IRIS) program is currently a standard approach for describing the toxicology and the risk assessments used for regulatory approaches, although it has fallen into some disrepair. IRIS began as a means of providing consistent information to EPA staff involved in evaluating and regulating environmental chemicals. It has developed into a formal approach by the EPA to gather and evaluate information relevant to health risks posed by specific substances, including a thorough toxicological review subject to external comment and peer review. The usual format of the IRIS database is to provide for each agent of concern risk potency information for both noncancer and cancer risks, and for the various routes of uptake into the body (e.g., inhalation, ingestion).[48]

IRIS could be a useful process and location to consider and list the potential health effects of compounds when they are in nano form, particularly now that the IRIS process is to be streamlined and made more transparent.[49] Alternatively, the IRIS process

46. *See, e.g.*, Senlin Lu et al., *Efficacy of Simple Short-Term in Vitro Assays for Predicting the Potential of Metal Oxide Nanoparticles to Cause Pulmonary Inflammation*, 117 ENVTL. HEALTH PERSP. 241 (2009).

47. COMMITTEE, *supra* note 2. Confidence in the NNI is not enhanced by its defensive bureaucratic response to the NRC review. *See* Inside EPA, *National Nanotechnology Initiative Defends Risk Research Strategy*, RISK POLICY REPORT!, Feb. 24, 2009.

48. U.S. EPA, *Integrated Risk Information System (IRIS)*, http://www.epa.gov/iris/ (last visited Feb. 10, 2010).

49. Changes in the IRIS process during the George W. Bush administration were heavily criticized. *See, e.g.*, *Science Under Siege: Scientific Integrity At The Environmental Protection Agency: Hearing Before the H. Comm. on Energy and the H. Subcomm. on Oversight and Investigations*, 110th Cong. (2008) (statement of Jennifer Sass, Senior Scientist, Natural Resources Defense Council). For a description of the IRIS process, as well as a link to EPA Administrator Lisa Jackson's letter of May 21, 2009 describing recent revisions, see U.S. EPA, *IRIS Process (2009 Update)*, http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=190045 (last visited Feb. 1, 2010).

could be used to develop a separate compendium of the risks of nanoparticles. However, as its focus is on human health effects, IRIS might not be optimum for considering the potential for ecotoxicological effects of nanomaterials.

B. *Exposure Assessment*

Understanding the pathways and extent of human and environmental exposure is central to the effective regulation of nanoparticles. Unfortunately, we know too little about potential exposure scenarios.

Persistence in the environment or the human body is an important characteristic of chemical toxicity. Concern about the toxicity of persistent organic chemicals such as DDT, PCBs, dioxins, and chlorofluorocarbons has taught regulators and responsible industry to be wary of developing new chemicals that will not be rapidly degraded by biological, photochemical or geochemical processes. For nanoparticles, there is the hope that they will not persist for any length of time in the environment—but there are very little data to give a firm foundation to this hope. Of concern is that, for many uses, the effectiveness of nanoproducts can be enhanced by protecting against degradation, thereby giving industry an incentive to devise ways to prolong the effective lifetime of a nanoparticle. Also of concern is that we know so little about what will happen if a product applied as a nanoparticle is reused or discarded.[50]

The bottom line is that if nanotechnology were to be treated as a special case, much the same as radionuclides, then much more emphasis is needed on understanding exposure pathways.

For further context, as well as a recent critique of IRIS, see also Jim Solyst, *Eyeballing IRIS,* 26 ENVTL. FORUM 32 (2009).

50. It is conceivable that once applied in a stable configuration, nanoparticles will not be regenerated if subject to reuse or discard. But in the absence of proof that the lifetime of the nanoparticle will be restricted to first use, it is necessary to consider whether the same concerns applicable to asbestos should apply to nanoparticles. For asbestos, the fact that reentrainment of asbestos fibers of the specific physical size associated with uptake into the lung and with respiratory disease can occur during renovation or demolition of structural asbestos has been a major regulatory concern. The expected health consequences of such reentrainment were particularly pertinent to the World Trade Organization decision that has allowed nations to block the importation of asbestos.

VII.
PUBLIC HEALTH AND ENVIRONMENTAL SURVEILLANCE

Surveillance of human health indicators, which is a basic tool of public health, has been little used by the EPA or similar environmental agencies worldwide.[51] Although excellent work has been done on environmental surveillance by many countries, including such elegant approaches as satellite imaging, it has been difficult to bring these into routine use for regulatory oversight. The U.S. Centers for Disease Control has developed a major environment and human health indicator initiative which seeks to apply human health surveillance (e.g., visits to the emergency room for asthma) as a measure of environmental health.

FDA also uses post-marketing surveillance as a means of searching for adverse consequences of a drug or device that has been permitted to be released.[52] Presumably such surveillance would be helpful for nanomaterials used as pharmaceutical agents. Post-marketing surveillance for all nanoproducts might be a useful idea if better scientific-based regulation cannot be established.

VIII.
SUMMARY

Nanotechnology's promise to produce more with less, and to have characteristics that cannot be predicted based upon the actions of the same chemical in its non-nano form, present challenges to regulatory regimes based upon the "laws" of toxicology. Meeting these challenges requires, at a minimum, a robust multi-disciplinary approach to developing scientific understanding of the likelihood of exposure and of effects on humans and the environment.

It is in the nanotechnology industry's best interest to advocate for such science. A noteworthy example of such advocacy is the

51. For the many routine surveillance approaches applicable to human health, see BRFSS—CDC's Behaviorial Risk Factor Surveillance System, http://cdc.gov/BRFSS (last visited Sept. 21, 2009), as well as CDC WONDER, http://wonder.cdc.gov/ (last visited Feb. 10, 2010).

52. Post marketing surveillance is abetted by the existence of Poison Control Centers which can collect data on adverse events, and by pressures on physicians in large academic centers to look for conditions to report in the medical literature. Unfortunately, the propensity of the plaintiff's bar to collude with the manufacturer of a defective product through non-disclosure agreements impedes the otherwise positive value of tort litigation as a form of post-marketing surveillance.

Environmental Defense/DuPont initiative, which deserves full support[53] In my view it is currently the best regulatory and organizational approach to obtain the scientific basis for appropriate regulation of nanotechnology and nanoproducts, in part because it builds in a degree of both flexibility and of insistence in determining the potential for adverse consequences of any individual nanoproduct.

As described above, specialized organizational approaches have evolved for dealing with other agents characterized by not fitting into standard assumptions about the "laws" of toxicology. In my judgment, it is unfortunate that there is little likelihood that an international scientific body devoted to nanotechnology will be established unless there are first instances in which the human or environmental consequences of nanotechnology appear to be disastrous. But should that occur, it would be better to have the planning in place for such an organization now rather to be reactive to a well-publicized harmful outcome that is unwanted by all.

53. ENVIRONMENTAL DEFENSE-DUPONT NANO PARTNERSHIP, NANO RISK FRAMEWORK (2007), http://www.environmentaldefense.org/documents/6496_Nano%20Risk%20Framework.pdf. The rationale for the initiative was described in a joint opinion piece by DuPont Chairman & CEO Chad Holliday and Environmental Defense President Fred Krupp as "[a]n early and open examination of the potential risks of a new product or technology is not just good common sense—it's good business strategy. We need to make sure this assessment takes place now for today's 'next big thing'—nanotechnology. With the right mix of voluntary corporate leadership, coordinated research, and informed regulation, we can reap the benefits of this promising technology while reducing the likelihood of unintended consequences." Chad Holliday and Fred Krupp, *Let's Get Nanotech Right*, WALL ST. J., June 14, 2005, http://online.wsj.com/article/SB111870930078058710.html. The jointly developed framework for risk assessment and risk management of nanoproducts contains a number of innovative approaches. This includes a focus on developing formal profiles describing the properties, hazards and potential exposures for each nanomaterial and each of its potential applications. There is an emphasis on a detailed life cycle analysis that provides more than the usual information on properties related to environmental fate and transformation. All of this is to be done before decisions are made to manufacture and market the nanomaterial, and the decision making has a level of transparency and of involvement of the external community that goes well beyond usual industrial practices.