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NANOMATERIAL RISK ASSESSMENT AND RISK MANAGEMENT

Review of Regulatory Frameworks

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Abstract: Managing emerging risks, such as those posed by nanotechnology, is a challenge that requires carefully balancing largely unknown benefits and risks. Here we review current nanomaterial risk management frameworks and related documents, with a focus on identifying and assessing gaps in their coverage. We do so using a *regulatory pyramid,* with self-regulation at the pyramid base and prescriptive legislation at its apex. We find that appropriate regulatory tools, especially at the bottom of the regulatory pyramid, are largely lacking. In addition, we recommend that regulatory agencies employ an adaptive, tiered framework to manage nanotechnology risk. The framework should utilize multiple tools at different levels of the pyramid, with specific tools chosen on a case-by-case basis.

1. Background

Managing emerging risks poses a challenge to regulatory agencies because decisions must be made based on extremely limited information in the face of significant public scrutiny. Regulatory agencies worldwide have successfully implemented health and safety procedures to address environmental and occupational exposure concerns for traditional industrial materials. Newly emerging risks in the realm of nanomaterials may differ from past stressors, but they involve many similar issues, including public pressure, the necessity of making regulatory decisions, and a significant level of uncertainty regarding material properties and impacts throughout

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product life cycles. For many emerging risks, regulatory agencies may need to modify their traditional risk management paradigm, explore innovative hazard identification and risk characterization methods and tools, communicate risks to the public, and integrate risk management with larger societal considerations during the decision-making process.

As with many new technologies, developing a framework for making risk management decisions with regard to nanotechnology is a challenge. Around the world, regulatory agencies, trade organizations, nonprofit organizations, academics, and members of industry are proposing nanomaterial risk management models and frameworks. This chapter reviews current risk management frameworks and related documents for nanotechnology. Many of the regulatory frameworks are designed to address a specific issue, industry, or single class of nanomaterials, and thus may not be directly relevant for every aspect of nanomaterial management. Even though the current knowledge base is limited, this review and evaluation allows identification of gaps in existing frameworks that may be important to managers and other stakeholders.

Thirteen frameworks and related documents were selected for in-depth review. Data were summarized according to criteria associated with each of our four categories, and narratives were developed that describe which documents pertain to which criteria. Preliminary identification of gaps—those criteria that are relatively unaddressed by the reviewed documents—and suggested approaches for formal gap prioritization are given after the review. Taken together, this information could provide the basis for selecting an instrument of choice for regulating nanomaterial risks.

2. Approach

We reviewed documents from a range of countries and purposes. We reviewed comprehensive state-of-the-science regulation framework documents, such as USEPA's "Nanotechnology White Paper" [48], the Royal Society's "Nanoscience and nanotechnologies" report [38], and the International Risk Governance Council's "Nanotechnology Risk Governance" white paper [20]. We also reviewed documents for voluntary programs, such as the Environmental Defense-DuPont "Nano Risk Framework" report [15] and the Voluntary Reporting Scheme for nanomaterial information of the UK's Department for Environment, Food and Rural Affairs [45]. J. Clarence Davies's "Managing the Effects of Nanotechnology" [11] focuses on the regulation of nanomaterials, and the position statement "Ethics and Nanotechnology: A Basis for Action" from the *Québec Commission de l'éthique de la science et de la technologie* [35] gives an ethics-focused view of nanotechnology. A list of documents reviewed and the focus of each is provided below (Table 1).

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Our summary and assimilation of current approaches focused on specific criteria identified as important for a nanomaterial regulation framework. We developed the list of criteria based on Health Canada's framework for nanotechnology products, using its categories as the basis for our review. Our categories are: (1) Science and Research Aspects; (2) Legal and Regulatory Aspects;

TABLE 1. List of Documents Reviewed. Description of Document Focus is often taken Directly from the Document Foreword.

Document	Focus	Citation
USEPA White Paper	Comprehensive framework intended to set forth current scientific knowledge and its gaps related to possible environmental benefits of nanotechnology as well as potential risks from environmental exposure to nanomaterials	[49]
FDA	Report intended to help assess questions regarding the adequacy and application of the FDA's regulatory authority to nanomaterials, and to provide findings and recommendations to the FDA Commissioner	[49]
Woodrow Wilson Center	Paper intended to describe the possibilities for government action to deal with the adverse effects of nanotechnology, and to provide evidence relevant for determining what needs to be done to manage nanotechnology	[11]
ED-DuPont	Comprehensive framework for the responsible development, production, use, and end-of-life disposal of nanomaterials, intended for use by companies and other organizations	[15]
Québec Commission	Comprehensive discussion of the scientific, legal and ethical implications of nanotechnology, intended to help uphold the protection of health and the environment, as well as respect for many values such as dignity, liberty, integrity, justice, transparency, and democracy	[35]
Royal Society	Comprehensive framework intended to summarize current scientific knowledge and applications of nanotechnology, and to identify possible health and safety, environmental, ethical, and societal implications or uncertainties	[38]
DEFRA	Trial Voluntary Reporting Scheme to collect data from organizations in the nanotechnology industry to help the UK develop appropriate controls for risks to the environment and human health from nanomaterials	[44]

(continued)

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TABLE 1. (continued)

Document	Focus	Citation
Responsible NanoCode	Paper intended to highlight key issues that emerged from a business workshop on nanotechnology, including development of a responsible nanotechnology code	[36]
EC SCENIHR	Technical document intended to assess the appropriateness of current risk assessment methodologies for the risk assessment of nanomaterials, and to provide suggestions for improvements to the methodologies	[14]
EC Action Plan	Plan intended to help Europe build on its strengths and advances to ensure that nanotechnology research is carried out with maximum impact and responsibility, and that the resulting knowledge is applied in products that are useful, safe, and profitable	[13]
IRGC Policy Brief	Brief intended to assist policy makers in developing the processes and regulations to enable the development and public acceptance of nanotechnology	[21]
IRGC White Paper 1	Comprehensive framework intended to advance the development of an integrated, holistic, and structured approach for the investigation of risk issues and the governance processes and structures pertaining to them	[19]
IRGC White Paper 2	Comprehensive framework which applies general IRGC risk governance framework to the field of nanotechnology	[20]

(3) Social Engagement and Partnerships; and (4) Leadership and Governance. Within each category, we modified Health Canada's specific criteria to fit our categories. For example, our "Science and Research Aspects" are adapted from the US Nanotechnology Environmental and Health Implications Working Group research needs categories [51], and our Legal and Regulatory Aspects are adapted from Davies [12]. The categories and criteria used in the review are shown below; there are four criteria per category.

- Category 1: Science and Research Aspects
  1. Development of methods for detection/characterization/data collection
  2. Assessment of environmental fate and transport/impacts
  3. Assessment of toxicology/human health impacts
  4. Assessment of health and environmental exposure

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- Category 2: Legal and Regulatory Aspects
  1. Voluntary regulatory and best-practices measures
  2. Information-based regulatory tools (e.g., labeling)
  3. Economics-based regulatory tools (e.g., tax or fee for safety testing)
  4. Liability-based regulatory tools (e.g., penalty for pollution)
- Category 3: Social Engagement and Partnerships
  1. Promotion of education and distribution of information/use of risk communication tools
  2. Use of stakeholder engagement tools
  3. Development of partnerships with academia, industry, public organizations, provinces, and international regulators
  4. Emphasis on ethical conduct
- Category 4: Leadership and Governance
  1. Transparency in nanotechnology-related decisions
  2. Consideration of the benefits of nanotechnology
  3. Adaptive modification of existing or development of new legislation
  4. Consideration of precautionary principle

3. Results

3.1. SCIENCE AND RESEARCH ASPECTS

We have divided the review by category, and within each category we discuss the documents that relate to each criterion. We begin by discussing science and research—a topic covered, of course, by every document reviewed.

3.1.1. Development of Methods for Detection/Characterization/Data Collection

Various frameworks discuss the scientific and research aspects of nanomaterial regulation, including methods for detection and characterization of nanomaterials. In the U.S., the EPA Nanotechnology White Paper [48] comprehensively describes the aspects of nanotechnology relevant to USEPA, as well as the many gaps in current scientific knowledge that will need to be filled before the Agency can reliably regulate nanomaterials. An entire chapter is dedicated to the risk assessment of nanomaterials, and it discusses

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at length the current scientific knowledge of detection and characterization methods (for example, dynamic light scattering to obtain particle size distributions, mass spectrometry to obtain chemical composition, and electron microscopy to obtain images).

The Nanotechnology Report by the US Food and Drug Administration Nanotechnology Task Force [49] focuses on how the FDA will need to change in order to be better prepared to regulate products that contain nanomaterials. The report describes the agency's science needs, such as the development of methods for identifying FDA-regulated products that contain nanomaterials. The report also describes the agency's regulatory needs, including a discussion of the need for more guidance as to when a nanomaterial becomes a dietary ingredient that requires regulation.

Like the USEPA White Paper, the Royal Society report "Nanoscience and nanotechnologies: opportunities and uncertainties" [38] is comprehensive, containing a thorough view of nanotechnology, including knowledge gaps and regulatory issues, and scientific issues such as detection methods. Detection is also discussed in the ED-DuPont framework for nanomaterial management, which includes base sets of data that describe basic characteristics to be taken into account during the risk management process [15].

The European Commission's Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) offers a guidance document [14] that has a technical focus and is an excellent resource for the details of risk assessment. The EC SCENIRH covers measurement methods for nanoparticles, and, like other documents, it cautions that current detection methods need to be improved.

Detection and characterization are, of course, important steps in nanomaterial risk assessment, and these are included in many of the other documents reviewed, including all three IRGC publications [19–21].

3.1.2. Assessment of Environmental Fate and Transport/Impacts

The assessments of environmental fate, transport, and possible environmental impacts are other important steps in risk assessment. The USEPA White Paper's chapter on risk assessment [48] includes a discussion of environmental fate and transport of nanomaterials and their possible ecological effects; in many cases, current knowledge is quite uncertain, and the report describes areas that will require further research. Likewise, the Royal Society report [38] discusses risks to the environment, including environmental fate and transport, and these concerns are included in the ED-DuPont framework's base sets (such as bioaccumulation potential) as well [15].

The EC SCENIHR guidance document also includes consideration of the environment, including ecotoxicology issues [14]. The SCENIHR, among

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others, believes that the appropriateness of existing methodologies for evaluating environmental effects is not clear. It recommends that environmental exposure models be validated, and that additional research be conducted into the fate, transport, and effects of nanomaterials in the environment.

The International Risk Governance Council addresses environmental concerns in its nanotechnology Policy Brief [21]. The IRGC divides the development of nanotechnology into two *frames*: Frame 1 includes *passive* nanostructures (those with a "steady function" that is constant over time) and Frame 2 includes *active* nanostructures (those with an "evolving function" that can change during operation). The IRGC Policy Brief discusses the possible risks of both passive and active nanostructures, ranging from health and environmental risks to ethical and social concerns, and notes that more information will be needed to assess the environmental and human health impacts of nanomaterials.

3.1.3. Assessment of Toxicology/Human Health Impacts

Consideration of the possible toxic effects of nanomaterials on human health was the only one of the 16 review criteria to be discussed in some form by every document reviewed. The USEPA White Paper's chapter on risk assessment [48] includes a lengthy discussion of human health effects, as does the Royal Society report [38]. Assessment of possible toxic effects is also included in the ED-DuPont base sets [15].

The EC SCENIHR thoroughly describes the risk assessment process for nanomaterials, including toxicity assessment, and it believes that current methodologies are generally likely to be able to identify human health hazards of nanoparticles [14]. It describes the relevant physicochemical properties for hazard characterization, the steps of health effects assessment, and toxicology concerns such as absorption, distribution, metabolism, and excretion.

The IRGC Policy Brief on nanotechnology [21] includes a discussion of human health concerns, and health concerns are the primary focus of the general IRGC risk governance framework, described in the IRGC white paper on "Risk Governance: Towards an Integrative Approach" [19]. The general governance framework consists of three main phases: pre-assessment, appraisal, and management. First, the pre-assessment phase includes risk framing, early warning and monitoring, prescreening, and selection of assumptions and conventions for the subsequent risk assessment. Second, the risk appraisal phase includes both risk assessment and "concern assessment." Risk assessment pertains to the scientific aspects of the risk, including hazard identification, exposure estimation, and risk estimation, with a focus on human health. Concern assessment, meanwhile, deals with the social aspects of the risk, such as the public's

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concerns and perceptions of the risk, as well as possible socioeconomic impacts. Finally, the risk management phase includes the actions taken to mitigate the risk. This phase includes six steps: generation of management options, technical evaluation of options, subjective evaluation of options, option selection, implementation, and—lastly—monitoring and review. The decision should take possible benefits and tradeoffs into account, and the framework is cyclical to allow for adaptation of the risk governance process based on new information gained during monitoring and review. It intends to be a holistic framework for the governance of risk, with a focus on human health.

Most documents note that current information on the toxic effects of nanomaterials is greatly lacking, and the FDA in particular notes that it will need further toxicology studies and greater in-house expertise to develop a knowledge base suitable for reviewing nanomaterials [49]. Because of this uncertainty, the *Québec Commission de l'Éthique de la Science et de la Technologie* recommends thorough toxicology studies be undertaken of the long-term use of any product that will be released to the public [35].

3.1.4. Assessment of Health and Environmental Exposure

Assessment of exposure to possibly hazardous materials is, of course, another important step in health risk assessment. The USEPA White Paper's chapter on risk assessment includes discussion of human exposures [48], as does the Royal Society report [38]. Exposure assessment is also included in the ED-DuPont framework [15].

The EC SCENIHR covers steps for exposure assessment and exposure control measures [14]. The document cautions that mass concentration may not be the best metric for measurement of exposure, since numbers of (solid) nanoparticles, given differing surface area-to-volume ratios, may also be important.

Exposure assessment is part of IRGC general risk governance approach [19], and is also in the IRGC's white paper on "Nanotechnology Risk Governance" [20], which applies the IRGC risk governance framework to nanotechnology. This white paper includes nanotechnology-related ideas and concepts from the IRGC Nanotechnology Policy Brief [21], differentiating between Frame 1 (passive) and Frame 2 (active) nanostructures; like the risk governance framework, it adopts an adaptive structure that includes pre-assessment, risk assessment, concern assessment, risk management, risk communication, and stakeholder participation. The paper identifies scientific needs for risk assessment such as better tools for measuring exposure and—like the Policy Brief—notes that more attention to exposure monitoring is needed.

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3.2. LEGAL AND REGULATORY ASPECTS

3.2.1. Voluntary Regulatory and Best-Practices Measures

Many of the documents reviewed recommend that industry voluntarily adopt best-practices measures. The Environmental Defense-DuPont Nano Risk Framework mentioned in the scientific sections above [15] is a good example of this: the document describes a voluntary, adaptive framework for the risk management of nanomaterials within a company. The framework includes an initial step in which risk managers describe the material to be managed and its application. The managers then consider the properties, possible health and environmental hazards, and possible exposures to the material. When assessing risks, the framework takes a lifecycle approach in which all phases of the material's production, use, and disposal are considered. The managers then consider different risk management options, make a decision, and take an action. The action's performance is monitored, adapted if necessary, and the process then iterates. The framework is intended to provide best-practices guidance for companies and other organizations.

A voluntary code of best-practices conduct for businesses in the nanotechnology industry is called for by the Responsible NanoCode workshop report, which describes a November 2006 meeting between the Royal Society, Insight Investment, and the Nanotechnology Industries Association [36]. The workshop report discusses uncertainties faced by businesses in the technical, social, and commercial arenas. The report stresses that the risks and uncertainties are all interconnected, and the workshop participants agreed that they need a new approach to responding to these risks. The next steps recommended after the workshop include the development and implementation of a voluntary code of responsible conduct for the nanotechnology industry.

In another voluntary effort, the United Kingdom Department for Environment, Food and Rural Affairs enacted a Voluntary Reporting Scheme for engineered nanoscale materials in September 2006 [44]. The program requests submission of data related to the material and its production and use (including composition, manufacturing process, size and shape, intended use, exposure pathways, and benefits), its health- and environment-related properties (including physicochemical properties, toxicology, ecotoxicology, environmental fate), as well as measurement techniques and current risk management practices. DEFRA is not asking companies to generate new data for submission; it is simply asking that companies which generate data during the course of their normal business submit the data to the agency so that it may gain a better knowledge base for the regulation of nanomaterials. The program is a two-year trial, and it has received nine submissions (seven from industry and two from academia) as of December 2007 [45].

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Davies [11], in the Woodrow Wilson Center document "Managing the Effects of Nanotechnology," focuses on the regulation of nanomaterials. One of the options he considers is voluntary self-regulation; he believes voluntary measures must include incentives for companies to participate, and he notes that companies that do not volunteer might be those most in need of regulation. Davies concludes that nanotechnology risk management will likely require new laws, and he imagines a product-focused, rather than environment-focused, law in which the manufacturer must provide reliable evidence to support the proposition that its nanomaterial-containing product is safe.

Many of the other documents reviewed also discuss voluntary programs, including the USEPA White Paper [48], which describes a voluntary nanomaterial stewardship program undertaken by USEPA's Office of Pollution Prevention and Toxics (OPPT). The OPPT held several public meetings to discuss the program. Other documents such as the Québec Commission report [35] advocate the development of a best-practices guide.

3.2.2. Information-Based Regulatory Tools

The Québec Commission [35] believes that labeling is important for enabling freedom of choice, but it also believes that labeling will not be useful for nanomaterials until they are better understood. Labeling is an option that Davies considers [11], but he does not believe that labeling specific products would necessarily change consumer behavior.

Other documents also discuss labeling, including the Royal Society report [38], which recommends that products' ingredients lists should declare the presence of any added nanomaterials. The IRGC also considers labeling to be a useful tool for communicating possible risk to consumers.

3.2.3. Economics-Based Regulatory Tools

Davies [11] includes economics-based regulatory tools as part of his four possible incentives for promoting uses of nanomaterials that benefit the environment or improve public health. He suggests: (1) research funding to facilitate the identification of helpful and harmful applications of nanomaterials; (2) tax breaks and tax penalties to promote government-defined environmentally beneficial behaviors while penalizing pollution; (3) acquisition programs in which federal and local governments, as significant and large consumers, are required to purchase or underwrite products deemed environmentally beneficial; and (4) regulatory advantages that accelerate the review and approval process for environmentally beneficial new products.

Regulation is also discussed by the Royal Society [38], which includes a case study of the regulation of nanomaterial-containing cosmetics, and the

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FDA [49], which discusses its pre-market review process. These documents do not go into depth on specific types of regulatory tools.

3.2.4. Liability-Based Regulatory Tools

The documents in our review cover liability-based regulatory tools only to the extent that they discuss existing regulations. USEPA [48] has regulations in place (e.g., under the Toxic Substances Control Act, Superfund, and the Clean Water Act) to control toxic substances and contaminated sites and to manage the effects of hazardous substances. All other developed nations have similar laws and regulations. Nanomaterials that meet the criteria of these acts would be subject to the regulations imposed on these substances. Similarly, the Royal Society holds that regulations currently in place are broad enough to have authority over harmful nanomaterials [38].

Davies [11], in contrast, recommends that nanomaterials be treated as if all are entirely new substances that fall under the regulation of the Toxic Substances Control Act (TSCA). Davies warns that existing legal measures do not necessarily apply to nanomaterials, which by virtue of their size may be exempt from regulation (because they would not reach 10,000 kg of production per year) or may display properties that are inconsistent with similar but larger materials. Also, Davies points out the seeming contradiction that the default position of TSCA is to not regulate substances with unknown health and environmental effects unless there is "unreasonable risk," yet these are the substances whose risk is not known.

3.3. SOCIAL ENGAGEMENT AND PARTNERSHIPS

3.3.1. Promotion of Education and Distribution of Information/Use of Risk Communication Tools

Many documents discussing the regulation of nanomaterials consider public information and risk communication to be vital parts of the process. The IRGC general risk governance approach recommends the use of risk communication tools at each step of its framework [19]. This is intended to enable citizens to become involved in the process, the decision, and its implications. The IRGC Policy Brief on nanotechnology also advocates public education [21], and the IRGC nanotechnology governance framework emphasizes risk communication and recommends that the public be provided with information [20]. In addition to discussing health and environmental concerns in its risk assessment framework, it also considers educational gap risks, such as when technical knowledge is not shared with regulatory agencies, civil

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society, and the public, leading to skewed perceptions of health and environmental risks.

The IRGC nanotechnology governance gives specific examples of risk communication tools and information to be communicated. Information to be communicated could relate to the benefits and harmful effects of nanotechnology, updates on scientific research, information on the methods used to test nanotechnology products and assess potential health or ecological impacts, and debate on the ethical acceptability of certain nanotechnology applications. Risk communication tools include product labeling; press releases and consumer hot lines; risk communication training courses and exercises for scientists; and integrated risk communication programs for scientists, regulators, industrial developers, representatives of NGOs, the media, and other interested parties.

Other documents also recommend the use of risk communication tools. Davies [11] holds that the public needs to be included for nonmaterial management to be successful. The Royal Society report discusses stakeholder and public dialogue, including the importance of working with the public with regard to nanotechnology-related issues and promoting a wider public dialogue about the field [38]. The FDA recommends communication with the public about the presence of nanomaterials in FDA-regulated products [49], and the ED-DuPont framework [15] and several other documents also state that public involvement is important.

3.3.2. Use of Stakeholder Engagement Tools

Like risk communication tools, stakeholder engagement tools are advocated by many frameworks. The IRGC general risk governance approach recommends the use of stakeholder engagement tools at each step [19]. This is intended to learn about citizens' opinions; the document contains a discussion of risk perception and the factors that affect it, including availability bias, anchoring effect, and uncertainty. The IRGC Policy Brief and IRGC nanotechnology governance framework also advocate government interaction with stakeholders and opinion research to improve both risk management and public acceptance of genuinely benign technologies [20, 21].

Other documents, such as the USEPA White Paper, recommend stakeholder engagement as well, and call for public meetings and interactions with stakeholders [48]. The Royal Society report includes research into public knowledge of nanotechnology in Britain, workshop findings, and the incorporation of public values into decisions [38]. Davies [11] maintains that the public needs to be listened to, and he wants greater public participation in the regulatory process. Responsible NanoCode workshop participants also

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believe that they should develop a forum for discussion of responsible work in the nanotechnology sector [36].

Many social recommendations are also made in the European Commission report "Nanosciences and nanotechnologies: An action plan for Europe 2005–2009," which gives an outline of the actions and infrastructure required for European Union (EU) countries to succeed in the nanotechnology industry [13]. It lists actions that the Commission will take and that it calls on the EU member states to perform. For example, the report recommends that the EU invest more money in the nanotechnology industry, construct new research infrastructure, and increase funding for the training of scientists in nanotechnology. Notably, it recommends that governments provide multilingual information about nanotechnology to the public and pursue a dialogue with stakeholders about nanotechnology. It calls for an increase of nanotechnology awareness at universities and in industry, and for programs that encourage university students to pursue nanotechnology research. It also calls for the international exchange of best-practice guidelines, the development of common standards for nanotechnology, and the development or adaptation of existing regulations for nanomaterials.

3.3.3. Development of Partnerships with Academia, Industry, Public Organizations, Provinces, and International Regulators

Many documents recommend collaboration. The Eurpean Community (EC) Action Plan, for example, calls for the development of partnerships and collaborative efforts across the EU [13]. The report recommends that the EU states increase collaborative research and coordinate research programs, support networking and integration of resources, promote networking of people, promote international collaboration, and increase industrial involvement in collaborative efforts.

The USEPA White Paper recommends that USEPA collaborate with other countries, and that its own researchers collaborate more actively among themselves [48], while the FDA recommends that it pursue collaborative relationships with other federal agencies and other stakeholders [49]. The IRGC policy brief and general governance approach recommends collaboration with and among stakeholders, and the IRGC nanotechnology governance framework identifies better collaboration between institutions and better coordination among stakeholders as institutional and social needs [19–21]. Davies [11] also encourages greater institutional coordination in the nanomaterial regulation process.

Several other documents echo the message of collaboration. The Québec Commission [35] recommends wide collaboration in nanotechnology regulation, and the Royal Society recommends that scientists

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collaborate, as well as regulators [38]. Responsible NanoCode workship participants decided that their code of conduct should be developed in cooperation with a wide range of stakeholders [36]. DEFRA's solicitation of voluntary information, meanwhile, is essentially a collaboration with willing stakeholders [44].

3.3.4. Emphasis on Ethical Conduct

Ethics also play an important role in nanotechnology regulation, as elaborated by the *Québec Commission de l'Éthique de la Science et de la Technologie* [35]. It begins its position statement "Ethics and Nanotechnology: A Basis for Action" by discussing the state of nanotechnology science, possible risks, and regulatory tools, but its main focus is ethical issues. For example, the Commission believes that companies must protect human dignity by not treating workers simply as means of production, but rather as people whose exposure to harmful materials must be minimized, especially when possible effects are not known. When nanomaterials are used in biomedical applications, the Commission believes that researchers must consider ethical issues such as confidentiality of personal information and respect for free and informed consent. When nanotechnology is used in surveillance, biometric controls, or substance detection in the name of security, the Commission warns that they must not be used in a way that impinges upon civil liberties. The Commission also discusses other ethical issues, such as the purpose and secrecy of military applications, the legitimacy and transparency of the government decision-making process, the fair worldwide distribution of nanotechnology benefits and risks, and whether nanotechnology can fundamentally alter human identity (through performance enhancement) or human relationship with nature (by modifying the environment).

The Royal Society report includes a focus on the social and ethical implications of nanotechnology alongside its discussion of science issues [38]. For example, the Royal Society notes that nanomaterials in devices capable of collecting personal information must not be used to compromise people's civil liberties. The report also considers the possibility that nanotechnology may primarily benefit the well-to-do social classes, and that this might exacerbate the problems of class division. The Royal Society takes these issues seriously, and it recommends that all scientists working in the field consider the social and ethical consequences of nanotechnology as part of their training.

The IRGC policy brief also expresses concerns about whether the advantages of nanotechnology will favor one country over another, or whether certain countries will lower safety requirements in order to gain a

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competitive technological advantage [21]. Other ethical concerns include whether human identity will be compromised by nanotechnology, as well as what might happen if hybrid "nanobio" devices escape human control. In the IRGC general risk governance approach, the ethical acceptability of the process and its outcome is also emphasized [19]. Ethical acceptability is emphasized in the IRGC nanotechnology governance document as well; it also considers political and security risks, such as uneven distributions of risks and benefits in the international community [20]. The EC Action Plan includes consideration of broader social impacts and recommends an ethical analysis of nanomedicine and a study of nanotechnology's likely impact on society [13]. For its voluntary reporting scheme, DEFRA specifically discourages the generation of new information that would require animal testing [44].

3.4. LEADERSHIP AND GOVERNANCE

3.4.1. Transparency in Nanotechnology-Related Decisions

Many guidance documents recommend transparency in the regulatory process [35, 38, 48, 49]. The ED-DuPont framework recommends that decisions are documented to increase the transparency of the process [15]. Because of collaborative and inclusive nature of the IRGC general risk governance approach, each step of the process is intended to be transparent to the public, and transparency is emphasized [19]. Transparency is emphasized in the IRGC nanotechnology governance document as well [20].

3.4.2. Consideration of the Benefits of Nanotechnology

While assessing the possible risks of nanomaterials, many frameworks appropriately weigh the risks against a given nanomaterial's possible benefits. The USEPA White Paper has a separate chapter to consider the environmental benefits of nanotechnology, including zero-valent iron for the remediation of chlorinated hydrocarbons in groundwater, nanosensors for the detection of pollutants, and nanotechnologies that support—or could support—sustainability [48], however defined.

The Royal Society report also considers the beneficial applications of nanotechnology, as do ED-DuPont, the IRGC, and other organizations [15, 21, 38]. The Québec Commission discusses possible applications and benefits of nanotechnology in relation to their ethical employment, and the EC Action Plan is predicated on building infrastructure to take advantage of nanotechnology's benefits [13].

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3.4.3. Adaptive Modifications of Existing or Development of New Legislation

Two of the framework documents discussed contain important adaptive elements. The ED-DuPont framework, for example, is essentially an adaptive management procedure [15]. Its iterative framework allows for the incorporation of new information into the management process, so that the regulation evolves to incorporate best practices and recently acquired scientific knowledge. The IRGC general risk governance approach is also iterative, enabling adaptive learning to take place [19]. The IRGC nanotechnology governance approach, meanwhile, recognizes that existing legislation might need to be adapted [20].

Davies [11] maintains that if existing laws are to be applied to nanotechnology, they will need to be strengthened or adapted for their new purpose, because each suffers from certain shortcomings. For example, the Toxic Substances Control Act has broad coverage, but it would be complicated to apply because it covers substances "of a particular molecular identity," and Davies notes that the physicochemical properties of a nanomaterial may change with its size or form, even if its molecular identity does not change. The possible need to modify laws to accommodate nanotechnology regulation is also mentioned by the USEPA White Paper, the Royal Society, and others [38, 48].

3.4.4. Consideration of Precautionary Principle

Many of the documents reviewed discuss the precautionary principle. The Québec Commission holds that use of the precautionary principle is essential to nanotechnology regulation in the face of uncertainty, claiming that use of this principle will ensure that no harm is caused [35]. Given the significant uncertainty in the field of nanotechnology risk assessment, the Royal Society takes a similar stance, saying that environmental releases of nanoparticles should be avoided until more is known about their effects [38]. The ED-DuPont framework says it espouses values "similar" to the precautionary principle, but does not espouse it directly because it is defined different ways in different places [15]. The IRGC general risk governance takes a "precautionary" approach in high-uncertainty situations [19].

The IRGC nanotechnology governance framework, in contrast, opposes use of the precautionary principle [20]. The document holds that the precautionary principle would lead to a moratorium on technology development, causing industry to move out of the country. For Davies [11] as well, the precautionary principle is equated with a ban, and he says that this is not helpful for a field in which continued development is expected to be beneficial.

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3.5. FRAMEWORKS SUMMARY

Overall, out of the four categories discussed, the greatest attention is paid to the scientific and research aspects of nanomaterial regulation. The knowledge needed to conduct risk assessment—and the research needed to create new knowledge—is discussed to some extent in virtually all of the documents reviewed. Every document expresses concerns about nanomaterials' possible adverse effects on human health, and the more comprehensive documents reviewed define a framework for the assessment of such risks, despite significant uncertainties in necessary information.

Less attention is paid to regulatory tools. The ED-DuPont Nano Risk Framework is a good example of a framework for voluntary best practices [15], and a few sources discuss regulation tools such as labeling or tax breaks, but many agencies have not begun to write in terms of using new tools to regulate nanomaterials. USEPA and Royal Society, for example, both discuss existing regulations that are expected to be sufficient to cover nanomaterials, perhaps with slight modification [38, 48].

The social engagement/partnerships and leadership/governance categories share the trait of being often recommended in general terms. Agencies are aware that it is important to communicate risk and engage stakeholders, so they recommend doing these things; they know that it is important to be transparent and to be adaptive, so they recommend these qualities as well, although often without clear directions for how to achieve transparency or adaptiveness. More concrete examples are given for social engagement tools than for governance tools, and the lack of specific tools makes leadership/governance another knowledge gap for nanomaterial regulation.

Table 2 summarizes the areas discussed by each document.

4. Regulatory Gaps and Possible Solutions

Our review indicates that many nanomaterial management frameworks primarily focus on scientific and research aspects and, to a somewhat lesser degree, on social engagement and partnerships. Legal and regulatory aspects, as well as governance, have received comparably little discussion. The following section provides an overview of issues and approaches discussed in the peer-reviewed literature that could help in bridging these gaps. Specifically, we introduce the regulatory pyramid approach originally proposed by Ayres and Braithwaite [2] and adopted for nanomaterial regulations by Bowman and Hodge [6] and Marchant et al. [29] as a guiding framework for nanotechnology regulation. We then discuss risk assessment and the precautionary principle, as well as voluntary programs, self-regulation, and other tools.

TABLE 2. Elements of Nanomaterial Regulation Frameworks Discussed in each Document (criteria are numbered 1 to 4 under each Category; for each Document and Criterion, ■ = Document Discussed the Criterion, ▪= Document Mentioned the Criterion, and (Blank) = Document did not Address the Criterion).

	Science and research aspects				Legal and regulatory aspects				Social engagement and partnerships				Leadership and governance			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
USEPA White Paper	■	■	■	■	■	▪	▪	▪	■	▪	■	▪	▪	■	▪	
FDA	■		■			■	■		■	▪	▪		▪			
Woodrow Wilson Center	▪	▪	■	▪	■	■	■	▪	■	■	■			▪	■	▪
ED-DuPont	■	■	■	■	■	▪			▪	▪			■	▪	■	▪
Québec Commission	▪	■	■	■	■	■			■	▪	■	■	■	■	▪	■
Royal Society	■	■	■	■	▪	■	■	▪	■	■	▪	■	▪	■	▪	▪
DEFRA	▪	▪	▪	▪	■				▪	▪	▪					
Responsible NanoCode			▪		■				▪	▪	▪					
EC SCENIHR	■	■	■	■												
EC Action Plan	▪	▪	▪	▪		▪			■	■	■	■		▪	▪	
IRGC Policy Brief	▪	■	■	■	■	▪			■	■	■	■	▪	■	▪	▪
IRGC White Paper 1	▪	▪	■	■	▪	▪	▪	▪	■	■	■	■	■	■	■	■
IRGC White Paper 2	▪	■	■	■	▪	▪	▪	▪	■	■	■	■	■	■	■	■

Subcriteria for the table are as follows:

- **Science and research aspects**
  1. Development of methods for detection/characterization/data collection
  2. Assessment of environmental fate and transport/impacts
  3. Assessment of toxicology/human health impacts
  4. Assessment of health and environmental exposure
- **Legal and regulatory aspects**
  1. Voluntary regulatory and best-practices measures
  2. Information-based regulatory tools (e.g., labeling)
  3. Economics-based regulatory tools (e.g., tax or fee for safety testing)
  4. Liability-based regulatory tools (e.g., penalty for pollution)
- **Social engagement and partnerships**
  1. Promotion of education and distribution of information/use of risk communication tools
  2. Use of stakeholder engagement tools
  3. Partnerships with academia, industry, public organizations, provinces, and international regulators
  4. Emphasis on ethical conduct
- **Leadership and g**overnance
  1. Transparency in nanotechnology-related decisions
  2. Consideration of the benefits of nanotechnology
  3. Adaptive modification of existing or development of new legislation
  4. Consideration of precautionary principle

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This section concludes with a discussion of a framework and supporting methods and tools applicable to governance of nanotechnology.

4.1. REGULATORY PYRAMID APPROACH

Our review identified multiple regulatory policy instruments (e.g., voluntary programs, labeling, tax incentives). A regulatory pyramid approach and responsive regulations [2] provide a good framework for classifying these regulatory policy instruments and associated tools (Figure 1). The underlying idea of responsive regulation is that the degree of regulatory intervention and supervision is based on a dynamic assessment of market conditions and regulated community performance, rather than a one-size-fits-all prescription. Self-regulation and best practices are characteristic of the base of the pyramid, representing the bulk of matters that can be handled informally without oversight by regulatory agencies. The regulatory approach becomes more prescriptive and punitive at the top of the pyramid. The regulatory response depends on the effectiveness of individual firms' self-regulation activities, as well as on how successfully they have responded to hazards and risks.

Bowman and Hodge [6] adjusted the regulatory pyramid approach for nanomaterial regulations. Here the pyramid has been replaced by a hexagon that

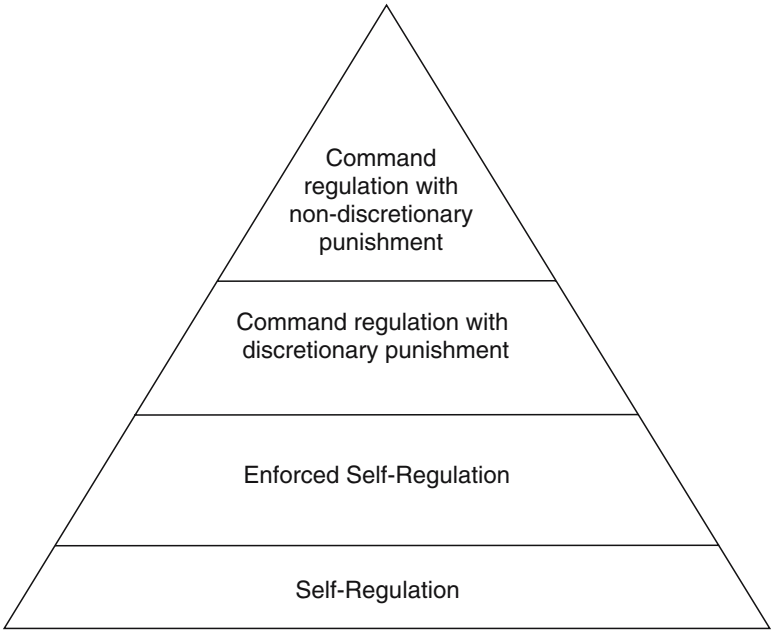

Figure 1. Regulatory Pyramid [2].

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includes six regulatory *frontiers*: product safety, privacy and civil liberties, occupational health and safety (OH&S), intellectual property (IP), international law, and environmental law. In each of these areas, a range of regulatory mechanisms and tools is available to regulators, from *hard law* at the top, through licensing, codes of practice, guidelines, and other *soft law* options at the base.

Marchant et al. [29], however, maintain that the approaches of both Ayers and Braithwaite [2] and Bowman and Hodge [6] are static, while the field of nanotechnology requires dynamic and adaptive views. Thus, incremental nanotechnology regulation is proposed in their paper and depicted in their own pyramid (Figure 2). Marchant et al. [29] argue that nanotechnology regulatory activities should start with information gathering and self-regulation should and move towards hard law/legislation once more information is collected. This framework is supposed to provide an adaptive approach for addressing changes in the regulatory environment and an increasing knowledge base in the regulated community.

4.2. REGULATORY TOOLS OPERATING FROM THE APEX OF THE PYRAMID

Risk assessment and the precautionary principle have been used by regulatory agencies worldwide in various settings. This section provides an overview of the difficulties in applying these tools to nanomaterial risk management.

4.2.1. Traditional Risk Assessment Framework

Risk assessment has been practiced by USEPA and other agencies as a tool to evaluate risks associated with chemicals in the environment. Risk assessment approaches and procedures have been formulated by the US National Academy of Sciences [50] and subsequently tailored to specific applications by USEPA [46, 47] and other agencies in the US and worldwide. Risk management was initially separated from risk assessment; risk assessment was perceived as a scientific activity while risk management was dealt with in a policy framework. A risk assessment is generally constructed to have four components: hazard identification, toxicity assessment, exposure assessment, and risk characterization. Most of the documents we reviewed attempted to adjust the traditional scientific risk assessment framework to the regulation of nanomaterials.

4.2.2. Difficulties in Applying Traditional Risk Assessment Framework

Recent articles, as well as the frameworks reviewed in this study, generally use several different characteristics in their assessment of nanomaterial risk. These characteristics include chemical composition, size/shape, surface chemistry and reactivity, solubility/environmental mobility, and agglomeration

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[3–5, 8, 18, 22, 30, 32, 34, 43]. In fact, there are many subcategories and other characteristics that may well prove critical to both the benefits and the risks of any given nanotechnology.

Thus, even though the risk assessment paradigm successfully used by the scientific community since the early 1980s may be generally applicable, its application to nanotechnology requires a significant information base. As described, nanomaterial exposure and toxicity assessment are complicated by the need to take several variables into account, and they require incorporating an uncertainty in basic knowledge that at present seems much larger than the uncertainty for macromaterials. Even given estimates of exposure and toxicity, risk characterizations must be developed separately for each nanomaterial, or even similar nanomaterials with different functionalization or at different environmental lifecycle stages. Because of the required effort, detailed risk characterizations may not always be possible. In some cases, knowledge of a similar compound or class of compounds may be available, but methods for incorporating information on broad toxicity and exposure classes into the traditional risk assessment regulatory framework have not been discussed in the literature.

For the most part, it is still too early to know what specific endpoints constitute evidence of harm with regard to nanoparticles. Effects of various kinds have been reported from in vivo and in vitro studies [39, 40] (and many others), and concern that use of products containing nanomaterials may lead to chronic health risks has been expressed (Peters et al. [52] and others). Fundamentally, we still do not know enough about the toxic potentials of most nanoparticles to apply traditional risk assessment techniques.

Regulatory agencies, as well as the popular and scientific media, are thus shifting their focus from the initial euphoria about the potential of the technology to concern about possible deleterious effects resulting from nanomaterial manufacture and use. Uncertainty regarding the health impacts associated with nanotechnologies and their potentially uncontrolled market growth has resulted in calls from environmental and political bodies to limit the use of nanomaterials, increase the stringency of governmental regulations, and—in extreme cases—to ban the use of nanomaterials completely. As noted in our review, the *Québec Commission de l'éthique de la science et de la technologie* believes that the precautionary principle is an essential method for ensuring that no harm is caused in situations where nanotechnology risk information is uncertain [35], and other documents make similar recommendations [38]. However, the precautionary principle is not always seen as a helpful approach [20]. As also noted in our review, Davies [11] does not believe that the technology slowdown resulting from a regulatory implementation of the precautionary principle would be helpful for nanotechnology, since development

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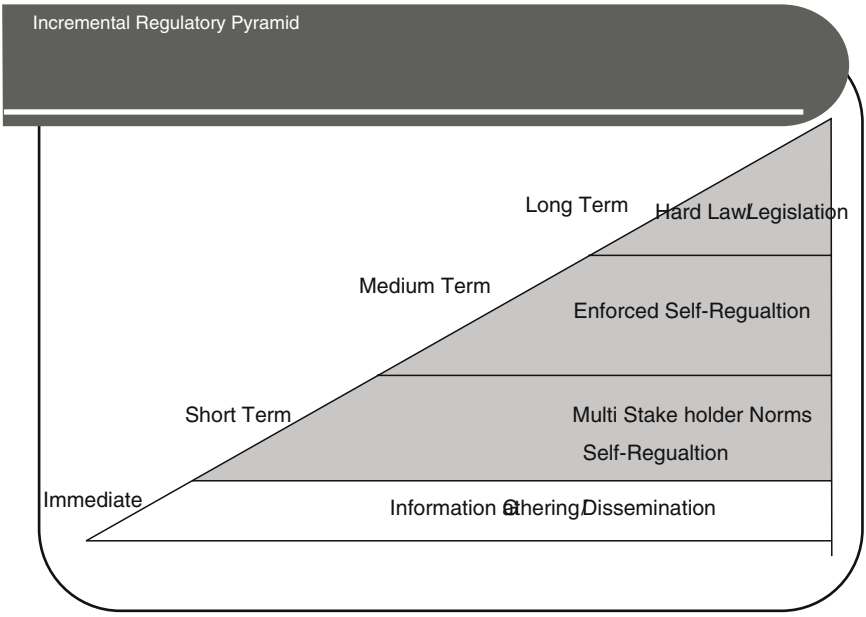

Figure 2. Incremental Regulatory Pyramid [29].

of the field should be beneficial. A responsible risk-based approach for regulation of the developing field would thus be ideal.

In fact, recent risk assessment literature and applications show that risk assessment is evolving toward integration with risk management and decision support. Risk assessment is becoming a participatory process where multiple stakeholders and their views on risks are explicitly or implicitly incorporated in the assessment. The IRGC general risk governance framework explicitly calls for inclusion of the societal context and categorization of risk-related knowledge to deal with data uncertainty [19]. In a sense, this trend indicates movement from the top of the regulatory pyramid toward its base. Such a move requires new methods and tools that are discussed in the next section.

4.3. REGULATORY TOOLS OPERATING FROM THE BASE OF THE PYRAMID

As noted above, the base of the regulatory pyramid is self-regulation. In industry, one example is the Environmental Defense-DuPont Responsible Nano Code framework. Davies [12] believes that the Responsible Care program of the American Chemistry Council (ACC) may also be a useful

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example for the nanotechnology industry. Reponsible Care requires member companies to measure and publicly report performance, as well as obtain independent third-party verification that their operations are up to standards, however defined [1]. Voluntary programs have also been initiated by government, such as the DEFRA Voluntary Reporting Scheme [44], and USEPA's voluntary nanomaterial stewardship program [48].

Davies [12] notes that voluntary codes often suffer from lack of participation, as well as lack of transparency and specificity. Indeed, public opinion surveys reveal skepticism about self-regulatory programs alone [33]; failures of self-regulation could damage public acceptance of nanotechnology. Effective self-regulation with the threat of external pressure has been found to be more effective [17]. Selecting the appropriate regulatory tools for this external preassure may be crucial. Ayers and Braithwaite recommend engagement of public interest groups in this process [2], and Marchant et al. [29] expand the recommendation to include multiple stakeholder groups.

Information-based tools may play a role in applying external pressure. As Davies [12] discusses, two examples of programs that use this strategy in the U.S. are the Toxics Release Inventory (TRI) and California Proposition 65. Under the TRI, companies that release more than de minimis amounts of potentially hazardous chemicals must inform USEPA, which then publicly releases the information. In California, Proposition 65 established a state-maintained list of chemicals known to cause cancer, birth defects, or reproductive harm [9]. A product's label must declare if it contains any of the chemicals on the list (again, above de minimis amounts). Davies notes that the enforcement of these regulations is not always straightforward. Nonetheless, the tools are conceptually simple, and they inform the public of a company's or chemical's behavior, applying pressure on companies to seek safer substitutes, as appropriate.

External pressure could also be applied in the form of economic incentives. Davies [11] suggests tools such as tax breaks and tax penalties to promote adherence of companies to their industry code of conduct while penalizing those that fall behind. Another economic tool is acceleration of the review and approval process for environmentally beneficial new products. These actions would provide real incentive for companies in the nanotechnology industry to follow a code of conduct and act in an environmentally responsible manner. Davies [12] is less enthusiastic about liability tools, since these require the enforcement of tort law and are applied only after some demonstrable environmental or health harm has been committed.

Any method selected for applying external pressure to self-regulation should include information gathering tools. Information requests could help build databases of nanomaterial properties, as well as allowing the communication of risks associated with nanomaterials.

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5. Risk-Informed Decision Framework for Nanotechnology Governance

The emergence of nanotechnology products has occurred much faster than the generation of corresponding environmental health and safety (EHS) data [27]. Moreover, the ability of regulatory agencies to use the EHS data also lags (Figure 3) due to the lack of data and limited resources. Given that the shelf life of new nanotechnology products is about two years or less, approaches to regulate these materials should be adjusted to the evolving nature of the field.

Our review indicates that there are many existing tools for assessing toxicities and risks; however, their application to new materials may be difficult. Traditional risk assessment boils down to comparison of exposures associated with specific hazards to regulatory benchmarks corresponding to safe exposure levels expressed in units of concentration, dose, or risk. Although agencies have tried to apply the traditional risk assessment paradigm to emerging materials, its application to nanomaterials requires dealing with a very large uncertainty in basic knowledge, while tools that are currently used for uncertainty analysis may not be easily applied to emerging threats. Integrating the heterogeneous and uncertain information in nanomaterial risk management therefore demands a systematic and understandable framework to organize the scarce technical information and expert judgment.

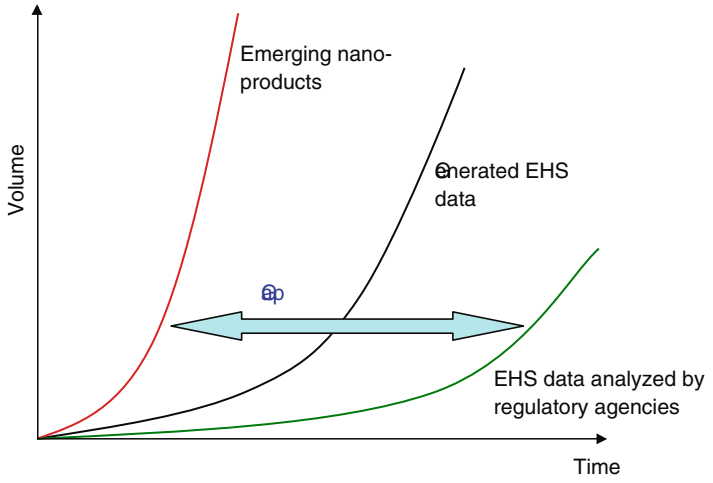

Figure 3. Schematic Representation of Emergence of Nanotechnology Products in Comparison to Generated EHS Data (based on breakout group meeting, Canadian Workshop, Edmonton 2008). This Diagram is Purely Qualitative and is Meant to Illustrate the Relative Amount of time between the Emergence of Nanoproducts, the Generation of EHS Data, and the Analysis of those EHS Data by Regulatory Agencies.

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Multicriteria decision analysis (MCDA) methods provide a sound approach for decision making and management in the face of heterogeneous information, uncertainty, and risk [16, 23, 25, 41]. MCDA is recognized as legitimate and useful by organizations such as the IRGC [19], and it has been applied to multiple environmental management programs [24]. It has been recommended as one of the most promising risk governance tools [37], and an example application to nanomaterials has been reported [26, 42]. The advantages of using MCDA techniques over other less structured decision-making methods are numerous: MCDA provides a clear and transparent methodology for making decisions and also provides a formal way for combining information from disparate sources. These qualities make decisions made through MCDA more thorough and defensible than decisions made through less structured methods. The US Army Corps of Engineers is currently working on integrating risk assessment and MCDA in a joint framework (risk-informed decision framework, or RIDF) and is applying it to highly contentious restoration planning in areas affected by Hurricane Katrina [7].

Nanomaterial regulatory frameworks could be built on existing approaches with the added rigorous and transparent method for integrating technical information and expert judgment offered by MCDA. Scientific aspects of risk management are well covered by existing frameworks, and gaps in current knowledge are spelled out by many groups, including the US National Nanotechnology Initiative [38]. However, actual methods for ranking alternative management options and selecting a best option are lacking.

An MCDA approach for ranking alternative risk management tools and making efficient decisions on other issues would allow joint consideration of the benefits and risks along with associated uncertainties relevant to the decision. A generalized MCDA process follows two basic themes: (i) generating alternative options, success criteria, and value judgments and (ii) ranking the alternatives by applying value weights. The first part of the process generates and defines choices, performance levels, and preferences. The latter section methodically prunes nonfeasible alternatives by first applying screening mechanisms (e.g., harmful environmental or health effects, excessive cost) and then ranking in detail the remaining management alternatives by MCDA techniques that use the various criteria levels generated by fate and transport models, risk assessment, experimental data, or expert judgment.

Decision analysis tools can help to generate and map technical data as well as individual judgments into organized structures that can be linked with other technical tools from risk analysis, modeling, monitoring, and cost estimation. Decision analysis software can also provide useful graphical techniques and visualization methods to express the gathered information in understandable formats. When changes occur in the requirements or the decision process, decision analysis tools can respond efficiently to reprocess and iterate with the new

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inputs. This integration of decision tools and scientific and engineering tools allows users to have a unique and valuable role in the decision process without attempting to apply either type of tool beyond its intended scope.

The result of MCDA application is a comprehensive, structured process for selecting the optimal alternative in any given situation, drawing from stakeholder preferences and value judgments as well as scientific modeling and risk analysis. This structured process would be of great benefit to decision making in risk management, where there is currently no structured approach for making justifiable and transparent decisions with explicit tradeoffs between social and technical factors. Regulatory agencies could employ MCDA in many different situations, such as selecting the best regulatory tool to use in certain situations, prioritizing gaps in knowledge, or selecting the optimal allocation of funding.

6. Conclusions

We have reviewed current nanomaterial risk management frameworks and related documents, with a focus on identifying and assessing gaps in their coverage. We found that regulatory tools, especially from the base of the regulatory pyramid, are an important gap in the knowledge necessary for nanomaterial regulation. Current tools recommended in the literature that help fill this gap are self-regulation and enforced self-regulation; information-based tools or economics-based tools can be used to exert pressure for enforcement. These tools would help to regulate the nanotechnology industry from the bottom up, in addition to the top-down approach offered by traditional risk assessment.

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