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MECHANISMS FOR ADDRESSING EXPOSURE TO NANOTECHNOLOGIES

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Nanotechnology is an emerging science that takes advantage of the novel properties of matter at the nanometer scale, and it carries with it promises of advances across a broad spectrum of applications, including electronics, pharmaceuticals, and industrial products. However, products utilizing nanotechnology may also present unique problems to human and environmental health, precisely because they do not behave in the body or environment in the manner expected from conventional materials. As the field of nanotechnology expands and becomes widely integrated across many applications, human exposure to nanomaterials will become more likely. The human health effects of such exposure remains largely unknown, though studies have linked nanoparticle exposure with a variety of impacts, ranging from inflammation to carcinogenicity. With the safety of nanomaterials still in question, this paper examines methods for preventing unwanted exposure through regulation, the likely biological responses that will follow exposure, and the safety considerations that must inform the initial stages of engineering new nanomaterials. The uncertainty of the risks posed by nanotechnology requires that some action be taken in the short-term to safeguard human health, while more information is developed regarding the adverse health effects that nanomaterials may display.

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I. INTRODUCTION

A. *Definitions and Applications of Nanotechnology*

While there is no standard definition for nanotechnology, the word is most commonly used to identify technologies whose particles measure between ten and 300 nanometers (one nanometer is 1/1,000,000,000 of a meter) in at least one dimension. The field of nanotechnology relies on the novel properties of particles at the nanometer scale (“nanoparticles”). Compared to conventional particles, nanoparticles have a greater surface-area to volume ratio. As the surface of a particle is the area of greatest reactivity, this increased ratio generally makes nanoparticles more reactive than an equal amount of conventional materials. In addition to this increased reactivity, many substances exhibit novel properties at the nano level that are not seen at the conventional scale.¹

While it is already being utilized in a number of consumer products, nanotechnology as an industry is still largely in an infant state. However, the field is expected to undergo rapid expansion in the coming years.² Beyond consumer products, nanotechnology is being investigated for its potential in the realm of medicine. “Nanomedicine” is defined as the application of nanotechnology to medicine, based on three overlapping and progressively more powerful molecular technologies; nanostructured materials and devices, the benefits of molecular

¹ Karen Florini et al., *Nanotechnology: Getting It Right the First Time*, 3 NANOTECH. L. & BUS. 39, 41 (2006).

² There are already more than 800 commercial products containing nanoparticles, that number is expected to increase dramatically in the coming years. Bryce J. Marquis et al., *Analytical Methods to Assess Nanoparticle Toxicity*, 134 ANALYST 425, 425 (2009).

medicine via genomics, and molecular machine systems (“nanorobots”).³ This paper focuses only on the first category of nanostructured materials and devices, as they present the only area likely to reach humans in the near future, and thus is the area of immediate concern.⁴

Nanotechnology may also enable the slow release of directed cytotoxicity (toxicity toward cells) in the body, enabling a kind of targeted chemotherapy that will help eliminate the need for recurring injections that increase patient toxicity and the incidence of complications.⁵

B. The Problem with Nanotechnology

As the use of nanotechnology becomes more widespread, humans will become exposed to more nanoparticles—both accidentally and deliberately—in the course of daily life. However, the potential risks posed by nanomaterials to both humans and the environment are not well understood.⁶ The same properties that make nanotechnology useful for such a wide array of applications (specifically, the traits of novelty and reactivity) also make health and environmental impacts both potentially dangerous and particularly hard to predict.⁷ Engineered nanoparticles have many traits that raise concerns regarding human and environmental health and safety: novelty in form and function, unique chemistry and physics, complex interactions with biological and environmental milieu, biopersistence (both organismal and within the food chain), ready dispersibility, tissue penetration, and irreversible biochemical and material

³ KEWAL K. JAIN, THE HANDBOOK OF NANOMEDICINE 1-2 (2008).

⁴ Jain notes that there are approximately 150 cancer-targeting drugs in development that are based on nanotechnology. *Id.* at 195.

⁵ Robert Lam & Dean Ho, *The Coalescence of Nanotechnology with Systems Biology for Optimized Drug Delivery*, 5 NANOTECH. L. & BUS. 125, 128 (2008).

⁶ Gregory Mandel, *Nanotechnology Governance*, 59 ALA. L. REV. 1323, 1343 (2008); JAIN, *supra* note 3, at 344.

⁷ Kerriann Greenhalgh & Edward Turos, *In Vivo Studies of Polyacrylate Nanoparticle Emulsions for Topical and Systemic Applications*, 5 NANOMEDICINE: NANOTECH., BIOLOGY, & MED. 46, 47 (2009); JAIN, *supra* note 3, at 331 (noting that nanoparticles have the unique ability to cross barriers in the body that traditional particles cannot); Mandel, *supra* note 6, at 1340-41 (noting that toxicity generally increases as particle size decreases and the particle’s surface-area to mass ratio increases, and that macro-scale toxicity information can’t simply be extrapolated to engineered nanoparticles).

activities.⁸ Carbon nanotubes (cylindrical fullerenes with a diameter of a few nanometers and variable length) have exhibited variable toxicity under some circumstances (including inflammation, epithelioid granulomas, fibrosis, and lesions in the lungs), silver nanoparticles may interfere with DNA replication and impair mitochondrial function, and titanium dioxide nanoparticles have displayed clastogenicity, genotoxicity, oxidative DNA damage, and inflammation *in vivo*.⁹ Following inhalation, nanoparticles may penetrate into different tissue compartments of the lungs and eventually reach the bloodstream. Once in the bloodstream they can circulate throughout the body and potentially be deposited in organs such as the liver, spleen, kidneys, heart, or brain.¹⁰

The field is not indifferent to this potential for adverse health effects, and indeed many studies of so-called “nanotoxicity” have been undertaken. However, the evaluation of new nanoparticles for cytotoxic or systemic toxicity has not kept up with the rapid development of the industry,¹¹ and problems remain in reconciling the often-conflicting safety data.¹² Testing results also vary greatly across nanomaterial applications, and so the results of any particular nanotoxicity investigation cannot be applied with any confidence to other nanoparticles.

Currently there are no harmonized standards or established methods for testing nanotechnology

⁸ David W. Grainger, *Nanotoxicity Assessment: All Small Talk?*, 61 *ADVANCED DRUG DELIVERY REVIEWS* 419, 419 (2009).

⁹ Kevin Rollins, *Nanobiotechnology Regulation: A Proposal for Self-Regulation with Limited Oversight*, 6 *NANOTECH. L. & BUS.* 221, 224-25 (2009); Chiu-wing Lam et al., *A Review of Carbon Nanotube Toxicity and Assessment of Potential Occupational and Environmental Health Risks*, 36 *CRITICAL REVIEWS IN TOXICOLOGY* 189, 213 (2006); Benedicte Trouiller et al., *Titanium Dioxide Nanoparticles Induce DNA Damage and Genetic Instability In Vivo in Mice*, 69 *CANCER RES.* 8784, 8788 (2009).

¹⁰ JAIN, *supra* note 3, at 334.

¹¹ Greenhalgh & Turos, *supra* note 7, at 47; A.A. Shvedova et al., *Mechanisms of Pulmonary Toxicity and Medical Applications of Carbon Nanotubes: Two Faces of Janus?*, 121 *PHARMACOLOGY & THERAPEUTICS* 192, 193 (2009).

¹² Giuseppe Bardi et al., *Pluronic-Coated Carbon Nanotubes Do Not Induce Degeneration of Cortical Neurons In Vivo and In Vitro*, 5 *NANOMEDICINE: NANOTECHN. BIOLOGY & MED.* 96, 96 (2009); Marquis et al., *supra* note 2, at 436.

products for potential dangers.¹³ Further, no one has yet created a realistic test for determining the effects of inhaled nanoparticles, and such a test could end up being prohibitively expensive both to design and carry-out.¹⁴ Such nanoparticle testing needs to be done over a range of sizes and charges in order to assist in the tailoring of nanodevices for biological use.¹⁵ Testing for chronic effects also presents difficulties, and little long-term chronic exposure data regarding nanomaterials is available.¹⁶ Chronic toxicity will be important as nanoparticles that enter organisms and are not excreted or degraded may accumulate in cells and tissues in the body, giving rise to long-term health risks that may not be presented by acute exposures.¹⁷ Additionally, we generally lack an understanding of the connections between acute-exposure, cell-based testing models *in vitro* and any *in vivo* responses.¹⁸

This difficulty in assessing the safety of nanotechnology through laboratory testing is compounded by the fact that our understanding of nanoparticle routes of exposure and *in vivo* behavior are limited,¹⁹ as is our knowledge of the mechanisms for the adverse effects (such as inflammation, immunoreaction, and carcinogenicity) that can result from exposure.²⁰ The degree of uncertainty regarding the metabolism and distribution of nanomaterials in the body, and the fact that the effects of exposure can be influenced by multiple, particle-specific factors, prevents

¹³ Rollins, *supra* note 9, at 224.

¹⁴ JAIN, *supra* note 3, at 336 (noting that such a test may cost more than \$1,000,000); Lam et al., *supra* note 9, at 199, 213 (discussing the prohibitive cost and technical difficulty of inhalation toxicity experimentation that has caused the scientific community to instead utilize intratracheal instillation for the purposes of testing, which is of limited accuracy in predicting health impacts in the upper respiratory tract or for establishing exposure limits).

¹⁵ Lajos Balogh et al., *Significant Effect of Size on the In Vivo Biodistribution of Gold Composite Nanodevices in Mouse Tumor Models*, 3 NANOMEDICINE: NANOTECH. BIOLOGY & MED. 281, 295 (2007).

¹⁶ Clinton F. Jones & David W. Grainger, *In Vitro Assessments of Nanomaterial Toxicity*, 61 ADVANCED DRUG DELIVERY REVIEWS 438, 439 (2009).

¹⁷ Kristina Riehemann et al., *Nanomedicine—Challenge and Perspectives* 48 ANGEWANDTE CHEMIE (INT’L EDITION) 872, 891 (2009).

¹⁸ Jones & Grainger, *supra* note 16, at 439.

¹⁹ JAIN, *supra* note 3, at 331.

²⁰ Riehemann et al., *supra* note 17, at 891.

nanomaterials from fitting the traditional risk assessment model.²¹ The end result is an emerging technology with a strong potential for adverse health impacts that is surrounded by uncertainty as to the magnitude, frequency, and ultimate likelihood of those impacts.

C. Article Scope and Overview

It is against the background of this uncertainty that this paper examines what can be done to limit exposure to potentially hazardous nanoparticles, as well as what can be done to limit any hazardous effects they might have once they are in the body. This paper begins by examining adequacy of the existing regulatory state to address the problems that will likely be posed by nanotechnology as the field develops, and outlines some regulatory proposals for augmenting to replacing this regulatory scheme. Because exposure cannot (and, in medical contexts, should not) be completely prevented, this paper goes on to evaluate the current options for addressing human exposure to nanoparticles. Finally, recommendations are presented on how to best move forward without sacrificing safety for innovation, or innovation for safety.

II. REGULATORY OPTIONS

As the maxim goes, an ounce of prevention is worth a pound of cure. Accordingly, it will generally be the case that the most efficient way to avoid any harmful effects caused by exposure to nanoparticles (while still enjoying the benefits of nanotechnology) will be to avoid, or at least minimize, exposure. As the proliferation of nanotechnology continues, the need to prevent unnecessary and potentially dangerous exposure to nanoparticles through front-end regulation becomes more pressing. Currently, there is no federal law or agency geared specifically to the regulation of nanotechnology as an industry, rather the current scheme would likely apply only

²¹ Igor Linkov et al., *Nanotoxicology and Nanomedicine: Making the Hard Decisions*, 4 NANOMEDICINE: NANOTECH., BIOLOGY & MED. 167, 168 (2008).

to particular products that may incorporate nanotechnology. Because nanotechnology will present unique challenges, the existing regulatory scheme may be inadequate to safeguard human and environmental health.²² In order to protect human health and the environment, it may be necessary to amend the current regulatory scheme, or replace it altogether with new legislation meant to address nanotechnology as an industry.

Regulatory choices carry considerable consequences. In addition to potential adverse impacts on human health and the environment, ineffective regulation may undermine public confidence in nanotechnology (making it difficult for manufacturers to recruit patients for nanomedical clinical trials), and may cause unnecessary delays in bringing beneficial products to market.²³ This section begins with an examination of how nanotechnology may be regulated under existing laws, and then proceeds to examine the merits of other proposals for regulating nanotechnology.

A. *Current Schemes*

Under the current regulatory scheme, some nanotechnology products may be regulated by the FDA and the EPA primarily through the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Toxic Substances Control Act (TOSCA) respectively. Under the 2001 National Nanotechnology Initiative, the FDA is the principle regulator of nanobiotechnology. So far, the FDA has created the NanoTechnology Interest Group comprised of members from the FDA centers (such as the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research, among others) and meets quarterly to ensure there is effective communication between the centers that regulate nanotechnology. In addition, the FDA has

²² Rollins, *supra* note 9, at 224.

²³ John Miller, Note, *Beyond Biotechnology: FDA Regulation of Nanomedicine*, 4 COLUM. SCI. & TECH. L. REV. 1, 39-41 (2003).

established the Nanotechnology Task Force, which is charged with identifying and addressing existing policy gaps and determining regulatory approaches that will foster both innovation and safety.²⁴

i. Toxic Substances Control Act (TOSCA)

Through TOSCA the EPA can regulate chemicals that are manufactured in excess of 10,000 kilograms per year.²⁵ TOSCA requires a manufacturer to submit a premanufacture notice (PMN) to the EPA before beginning the manufacture of a chemical. While manufacturers must submit any toxicity testing done on a chemical to the EPA with the PMN, they are not required to actually perform any such testing before submission.²⁶ If the EPA can demonstrate that a chemical may (or does) pose an unreasonable risk to human or environmental health, they can, among other things, compel a company to perform additional safety testing. However, significant barriers exist that may prevent the effective regulation of nanotechnology through TOSCA, at least without significant modification. The most significant of these obstacles are the distinction made by TOSCA between existing and new chemicals, and the difficulty faced by the EPA in demonstrating the presence of health risks significant enough to compel additional testing.

For the purposes of regulation, TOSCA distinguishes between “new” and “existing” chemicals. “Existing” chemicals are defined as those that were being manufactured prior to the passing of TOSCA in 1976 (as well as those which have since been approved for manufacture), while “new” chemicals are those that were not on the market prior to the implementation of TOSCA that must be submitted for regulatory approval. Whether a particular substance is

²⁴ Rollins, *supra* note 9, at 227-28.

²⁵ Mandel, *supra* note 6, at 1351.

²⁶ U.S. ENVTL. PROT. AGENCY, OVERVIEW: OFFICE OF POLLUTION PREVENTION AND TOXICS PROGRAMS 8 (DRAFT VERSION 2.0 2003), available at <http://www.chemicalspolicy.org/downloads/TSCA10112-24-03.pdf>.

characterized as new or existing has significant impacts on how it is regulated under TOSCA. Existing chemicals are presumed to be safe and ready for manufacture, and the EPA's burden in overcoming this presumption is high enough to have effectively prevented the EPA from regulating any existing chemicals since the inception of TOSCA.²⁷ While it may seem that nanoproducts, by virtue of their novel properties and recent development, should be considered new substances, the opposite is actually more likely as the determination of new or existing is made solely on the basis of chemical identity. Most nanoproducts are likely to be composed of substances (e.g. carbon, silver, and titanium dioxide) that are chemically identical to existing products, and thus are likely to be characterized as existing chemicals for the purposes of TOSCA, despite significant differences in other properties. Not surprisingly, under this definition the EPA has generally concluded that nanomaterials will not be considered "new" chemicals.²⁸

In order to regulate nanomaterials under TOSCA, the EPA will have to demonstrate by "substantial evidence" that a chemical may pose (to require testing for new chemicals) or does pose (for existing chemicals) an unreasonable risk to human health or the environment.²⁹ This standard has historically been very difficult for the EPA to meet, as evidenced by how rarely the EPA has regulated an existing chemical through TOSCA.³⁰ Meeting this standard is particularly

²⁷ Since 1976, only five existing chemicals have been the subject of regulatory action under TOSCA. U.S. GOV'T ACCOUNTABILITY OFF., CHEMICAL REGULATION: COMPARISON OF U.S. AND RECENTLY ENACTED EUROPEAN UNION APPROACHES TO PROTECT AGAINST THE RISKS OF TOXIC CHEMICALS 18 (2007), *available at* <http://www.gao.gov/new.items/d07825.pdf>. While more action has been taken with respect to new chemicals, many manufacturers will simply withdraw a PMN rather than undergo expensive safety testing. Those that do not withdraw usually arrive at voluntary agreements with the EPA. U.S. GEN. ACCOUNTING OFF., TOXIC SUBSTANCES CONTROL ACT: LEGISLATIVE CHANGES COULD MAKE THE ACT MORE EFFECTIVE 15, 56 (1994), *available at* <http://archive.gao.gov/t2pbat2/152799.pdf>.

²⁸ Mandel, *supra* note 6, at 1350 (also noting that the EPA has not yet decided if the use or production of a chemical at the nanoscale will constitute a "significant new use" for purposes of TOSCA, which could be another avenue of regulatory action).

²⁹ U.S. GOV'T ACCOUNTABILITY OFF., *supra* note 27 at 18, 21.

³⁰ Mandel, *supra* note 6, at 1351.

difficult, as the agency is required to demonstrate harm by substantial evidence when the uncertain nature of a chemical's potential for harm may be precisely what is compelling the agency's action.³¹ This standard also creates disincentives for nanomaterial manufacturers to perform thorough toxicity testing, as any additional information provided beyond the minimum required only has the potential to restrict production.³²

It is also possible that some nanomaterials will not meet the minimum manufacturing level required for regulation under TOSCA. As noted above, nanoparticles are generally more reactive than their conventional counterparts, and thus a smaller mass is needed to effectuate a particular response. As such, the volume of production may be lower than for conventional chemical products, while the potential for harm will not. Accordingly, care should be taken to ensure that the production of potentially harmful nanomaterials will not be overlooked simply because of the minimum mass requirement of TOSCA.

Thus, while TOSCA's definition of "chemical" is broad enough to encompass a broad array of nanomaterials, the effectiveness of regulating nanomaterials under TOSCA is the subject of much doubt and uncertainty.

ii. Federal Food, Drug, and Cosmetic Act (FFDCA)

The FDA (through the FFDCA) regulates products rather than specific industries. Much like TOSCA, the FDA regulatory scheme seems able to capture certain nanotechnology products (particularly medical and some consumer applications of nanomaterials), but there are substantial obstacles and concerns about the FDA's ability for *effective* regulation. For example, while

³¹ John S. Applegate, *The Perils of Unreasonable Risk: Information, Regulatory Policy, and Toxic Substances Control*, 91 COLUM. L. REV. 261, 309 (1991).

³² Robert B. Haemer, *Reform of the Toxic Substances Control Act: Achieving Balance in the Regulation of Toxic Substances*, 6 ENVTL. LAW. 99, 123 (1999); Wendy E. Wagner, *Commons Ignorance: The Failure of Environmental Law to Produce Needed Information on Health and the Environment*, 53 DUKE L.J. 1619, 1633-34 (2004); Richard Dennison, *Ten Essential Elements in TSCA Reform*, 39 ENVTL. L. REP. 10020, 10021 (2009).

cosmetics and dietary supplements fall under the FDA's regulatory purview, right now they are essentially unregulated. Generally there is no pre-market approval required for food or cosmetic products: instead it is up to the producer or manufacturer to ensure safety, with the FDA only getting involved if a product has an adverse impact on health.³³ The incorporation of nanotechnology in these areas is likely to substantially increase in the future, which would then require significant expansion of FDA regulations to effectively guard against the potential harm posed by these nanotechnology-incorporating products.³⁴

Perhaps the greatest benefit of nanotechnology is its application to the field of medicine in the areas of drug-delivery, pharmaceuticals, and diagnostics. These areas are currently subject to FDA regulation and require safety testing prior to receiving market approval by the FDA.³⁵ However, as under TOSCA, the FDA makes exceptions regarding safety testing in certain situations when an applicant can demonstrate that the product seeking approval is the same as one which has already been approved. Here there is the same potential for under-regulation as was seen in the TOSCA distinction between new and existing chemicals. Questions arise as to whether a nanoparticle that is chemically identical to a conventional product will still require a New Drug Application.³⁶ Many nanomaterials are likely to be composed of materials for which safety has already been demonstrated at the macro-scale.³⁷ But while nanoparticle products may be

³³ Mandel, *supra* note 6, at 1357-58 (adding that there is also no labeling requirement for food or cosmetic products that contain nanoparticles).

³⁴ Jessica K. Fender, Note, *The FDA and Nano: Big Problems with Tiny Technology*, 83 CHI.-KENT L. REV. 1063, 1074 (2008); J. CLARENCE DAVIES, NANOTECHNOLOGY OVERSIGHT: AN AGENDA FOR THE NEXT ADMINISTRATION 11 (Woodrow Wilson Int'l Center for Scholars, Project on Emerging Nanotechnologies, Washington D.C. 2008), available at <http://www.nanotechproject.org/process/assets/files/6709/pen13.pdf>.

³⁵ Jordan Paradise et al., *Exploring Emerging Nanobiotechnology Drugs and Medical Devices*, 63 FOOD & DRUG L.J. 407, 408 (2008).

³⁶ Mandel, *supra* note 6, at 1358-59.

³⁷ For example, many existing nanodevice products (such as anti-microbial nanocoatings, dental bond agents, diagnostic test kits and immunoassays) are cleared by the FDA as being substantially equivalent to a predicate device, and thus only require pre-market notification. Paradise et al., *supra* note 35, at 414-15.

chemically identical to their macro-scale counterparts, they may exhibit novel properties that raise new health concerns.

Additionally, nanotechnology-based products will likely blur the lines of the traditional classification scheme employed by the FDA.³⁸ While many nanoproducts will likely fall into the catch-all “combination product” classification,³⁹ determining a nanoproduct’s primary mode of action will still be difficult,⁴⁰ and may allow for a certain amount of “steering” or “positioning” on behalf of manufacturers to get their product classified in such a way as to minimize their burden to demonstrate safety.⁴¹

The extent to which the FDA will be able to effectively regulate nanoproducts is thus uncertain. There are also questions about the FDA’s ability to acquire and maintain the expertise needed to effectively approve of and monitor sophisticated nanotechnological research. This is particular true in the field of nanomedicine, which is a unique branch of medical technology in which there are currently few experts.⁴²

iii. Other Current Regulatory Options

While TOSCA and FFDCRA represent the primary possibilities for the regulation of nanotechnology, there are other statutes in place that may play a role in regulating nanotechnology or certain nanotechnology products.

The Resource Conservation and Recovery Act (RCRA) may regulate some nanotechnology products, but would likely need revisions to play a substantive role in effectively

³⁸ Miller, *supra* note 23, at 60.

³⁹ Nakissa Sadrieh & Parvaneh Espandiari, *Nanotechnology and the FDA: What are the Scientific and Regulatory Considerations for Products Containing Nanomaterials?*, 3 NANOTECH. L. & BUS. 339, 343 (2006).

⁴⁰ Gabriel A. Silva, *Nanotechnology Approaches to Crossing the Blood-Brain Barrier and Drug Delivery to the CNS*, 9 BMC Neuroscience (Suppl 3):S4 (2008) (noting that the biologically active component being delivered is just one element of a nanoengineered complex, other components will be designed to shield the active drug from producing systemic side effects or being prematurely metabolized, to cross the blood-brain barrier, and to target specific cells after it has gained access to the central nervous system).

⁴¹ Mandel, *supra* note 6, at 1360-61.

⁴² Miller, *supra* note 23, at 75-79.

regulating the potential risks of nanotechnology. Specifically, the definition or agency interpretation of “hazardous waste” would need to be expanded to guarantee that it would capture the broad array of nanotechnology product applications. However, even if RCRA were to apply to nanotechnology products, doubts remain as to how effective regulation would be under RCRA. As it stands now, RCRA approaches risk as proportional to mass, and thus, much like TOSCA, it has the potential to under-regulate given the increased reactivity of nanoparticles.⁴³ There are also concerns that some nanotechnology consumer products and nanomaterial wastes would be exempt from the RCRA requirements, creating the need for supplemental regulation or further revision to RCRA.⁴⁴

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) may also be used to regulate nanotechnology. CERCLA is able to deal with contamination that the regulatory system has failed to prevent on the front-end. It gives the EPA broad authority to address the release of pollutants, and provides for far-reaching liability.⁴⁵ As with RCRA, uncertainty exists as to whether or not nanoproducts will be considered “hazardous” under the statute.⁴⁶ Even if CERCLA can be used to regulate nanotechnology, the fact that the EPA will bear significant costs in implementation makes it a poor choice as a primary (rather than supplemental) regulatory mechanism.⁴⁷

⁴³ LINDA K. BREGGIN & JOHN A. PENDERGRASS, WHERE DOES THE NANO GO? END-OF-LIFE REGULATION OF NANOTECHNOLOGIES 22 (Woodrow Wilson Int’l Center for Scholars, Project on Emerging Nanotechnologies, Washington D.C. 2007), *available at* http://www.nanotechproject.org/process/assets/files/2699/208_nanoend_of_life_pen10.pdf; DAVID REJESKI, FEYNMAN, VOLTAIRE AND BECKETT ON NANOTECHNOLOGY, PRESENTATION TO THE NANOPOLICY CONFERENCE, NATIONAL PRESS CLUB (Woodrow Wilson Int’l Center for Scholars, Project on Emerging Nanotechnologies, Washington D.C. 2007), *available at* http://www.nanotechproject.org/process/assets/files/5946/120307_rejesi_nationalpressclub.pdf.

⁴⁴ BREGGIN & PENDERGRASS, *supra* note 43, at 19-21.

⁴⁵ *Id.* at 30-32.

⁴⁶ *Id.* at 28.

⁴⁷ *Id.* at 51.

Finally, the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) may be appropriate for regulating certain nanotechnology products. To make full use of FIFRA, any new use of a nanoparticle should be treated as a “new” chemical.⁴⁸ Even if this is done, FIFRA is likely not a realistic option as the primary mechanism for nanotechnology, as it has fairly specific areas of applicability. However, unlike the other current regulatory schemes, FIFRA will be readily applicable to some nanoparticle products without significant revision. For example, there has been indication that the EPA will use FIFRA to regulate the use of anti-microbial silver nanoparticles,⁴⁹ though they have made it clear that this is a product-specific choice and not part of a regulatory response to nanotechnology as an industry.⁵⁰

B. Potential Schemes

While the uncertainty surrounding nanotechnology makes crafting an efficient and successful regulatory scheme difficult, it is this uncertainty that may make new regulation necessary. New or additional regulations can take many forms, though all proposals attempt to balance, to some extent, the needs of safety with technological development. The result of this balancing will often depend on the importance placed on those respective goals. Those who place greater importance on safeguarding safety in the face of uncertainty will likely favor more stringent regulation that generally presumes nanotechnology products are inherently unsafe until proven otherwise. On the other hand, those who stress the need to safeguard the development of the nanotechnology industry, or believe nanotechnology to be inherently safe, will likely propose less stringent regulation, or a scheme that places the onus on government agencies to

⁴⁸ Reut Snir, *Regulating Risks of Nanotechnologies for Water Treatment*, 38 ENVTL. L. REP. 10233, 10245 (2008).

⁴⁹ Jordan Paradise et al., *Developing Oversight Frameworks for Nanobiotechnology*, 9 MINN. J.L. SCI. & TECH. 399, 403 (2008).

⁵⁰ Mandel, *supra* note 6, at 1354.

demonstrate harm or danger before they can take action to limit production or manufacture of a product.⁵¹

i. New Agency or Department

One solution to the problems posed by nanotechnology is to establish a new department or agency to specifically oversee all regulation of the nanotechnology industry as a whole. This new department could be exclusively geared toward nanotechnology or could encompass emerging and novel technologies more broadly.⁵² Concentrating oversight within a single agency may be the best way to address the unique problems presented in the development and production of nanomaterials. Creating an agency broad enough to capture similar emerging industries would help to avoid over-regulation or other regulatory inefficiencies. Any such agency would be responsible for promulgating regulatory standards and mechanisms, directing research (particularly toxicity testing), and providing centralized data collection and analysis. A single agency speaking with one voice regarding the nanotechnology industry as a whole would provide clarity to both consumers and manufacturers regarding the regulatory requirements that nanoproducts must meet. A single department could also ease the negotiation and implementation of any international standards or regulatory approaches, both of which will likely be important issues regarding long-term industry oversight.⁵³

⁵¹ In other words, the differences in regulatory proposals can be explained by differing views of the precautionary principle, and how and to what extent that should guide nanotechnology-specific regulation.

⁵² Lindsay V. Dennis, *Nanotechnology: Unique Science Requires Unique Solutions*, 25 TEMP. J. SCI. TECH. & ENVTL. L. 87, 111-12 (2006).

⁵³ Additionally the department would be able to push industry toward standardizing nanoparticle composition within individual classes of nanoproducts, which would help alleviate the regulatory burden of responding to several permutations of the same nanoparticle all meant for the same application. While such standardization would be desirable from the side of regulators, to the extent that it may impact the ability of the industry to take advantage of proprietary design or engineering consideration or limit competition in the market for nanoproducts, such efforts may be opposed by industry members. There is also uncertainty regarding the extent to which such standardization of composition is currently practicable. As discussed below, at this point manufacturers have difficulty achieving consistency both across different manufacturing attempts and even within a single 'batch' of certain nanoparticles.

As manufacturing ability increases and mass-production becomes more practicable, the need for standards will become more pressing. At a minimum, such efforts would likely contain standards for manufacturing processes and testing procedures,⁵⁴ but standardization of composition within nanoparticle categories may be inevitable.

Unfortunately, creating a new agency or department would also present several practical difficulties. The two most immediate problems would probably be those of funding and staffing. Such a department could be funded with money taken from the EPA and FDA, which will no longer have to regulate nanotechnology products, but this could put significant stress on these already underfunded agencies, impacting their regulatory action in regard to other technologies and products. If the nanotechnology industry does undergo the predicted rapid expansion as it is applied across more and more disciplines, the budget necessary to conduct oversight over the industry as a whole would also likely increase. Given the current economic recession, Congress may be reluctant to approve the funding necessary for a new regulatory agency without making some offsetting cutbacks.

Even if funding is approved and a new agency established, there would likely be difficulties in attracting a staff with the requisite nanotechnology experience and expertise necessary for effective oversight. As nanotechnology is still a fairly burgeoning industry, there are simply not many people who have any expertise with nanotechnology, much less specific applications such as nanomedicine. As discussed below, this problem is not unique to the establishment of a new agency, but rather will be a difficulty under any scheme meant to provide meaningful governmental oversight over the agency. However, in the context of creating a new

⁵⁴ Marquis et al., *supra* note 2, at 436.

agency, this may mean drawing staff away from the FDA and EPA, and consideration should be paid as to what effect this may have on the ability of those agencies to effectively regulate.⁵⁵

ii. Insurance and Liability Schemes

Another possible solution is to create nano-specific regulation following the guideline of regulations like the Price-Anderson Act, which is used to address nuclear accidents.⁵⁶ Under the Price-Anderson Act, industry members are forced to obtain the maximum level of insurance available in the private sector and contribute to a secondary insurance fund which is pooled across the industry. The government agrees to pay for any losses or damages greater than those that can be covered by this insurance system. While the degree to which the Price-Anderson Act actually adequately addresses the potential for harm posed by the nuclear industry is questionable given that the large magnitude of nuclear accidents means that industry damage pools are quickly exhausted, such a scheme might still be suitable for nanotechnology regulation. Right now there is no reason to assume that the harms posed by the nanotechnology industry are of the magnitude and severity of nuclear accidents, which means that this scheme may still force the industry to bear most if not all of the damages from such events.⁵⁷ Ideally, such a scheme would protect the industry from the deterring effect of potentially unlimited liability, and thus allow the industry to grow (an especially important aspect for emerging technologies like nanotechnology).

⁵⁵ For example, if a member of the FDA's staff who had expertise regarding pharmaceutical products and nanotechnology transferred from the FDA to the new agency, the FDA would lose that pharmaceutical expertise.

⁵⁶ Maksim Rakhlin, *Regulating Nanotechnology: A Private-Public Insurance Solution*, 2008 DUKE L. & TECH. REV. 2, 34-36 (2008).

⁵⁷ The efficacy of such a scheme is thus something of an empirical question regarding the risk surrounding nanotechnology, and currently not enough is known to fully answer this question. As it may still be an option for regulation that is worth consideration (even if it is to learn from the perceived mistakes of how we regulate the nuclear industry), this brief discussion has been included.

The problem with such a scheme stems from uncertainty. Generally speaking, as uncertainty increases, so will the cost of insurance. As discussed in this paper, the uncertainty regarding the potential for harm stemming from nanotechnology is high. This high cost of insurance may force small start-up companies out of the picture, or, if uncertainty is high enough, insurance may be entirely unavailable, which would completely foreclose implementation of such a scheme.⁵⁸ There is also the concern presented by any insurance-based scheme; that the fact that industry actors are partially indemnified from liability may cause them to take fewer safety precautions.⁵⁹ Additionally, insurers would have the ability to condition continued coverage on a manufacturer's compliance with safety standards decided by the insurer.⁶⁰

iii. State and Local Measures

The slow pace of federal regulatory action potentially opens the field for state and local regulatory measures (at least until federal regulation is promulgated). While such action may result in a regulatory patchwork across the country that is of questionable efficiency and wisdom, such lower-level action can at least play the role of regulatory place-holder or stop-gap. Some tech-heavy states (e.g. California, Massachusetts, and New York) are in position to regulate nanotechnology development. California has already taken some initiative on the issue. Early in 2009, the California Department of Toxic Substances Control exercised its authority under

⁵⁸ Albert C. Lin, *The Unifying Role of Harm in Environmental Law*, 2006 WIS. L. REV. 897, 975.

⁵⁹ This concern is referred to as "moral hazard theory," which generally refers to the idea that when an actor is indemnified either through the presence of insurance or the preclusion of legal liability, that actor will have less incentive to behave cautiously, thus increasing the likelihood that some harm will occur.

⁶⁰ JENNIFER KUZMA, THE NANOTECHNOLOGY-BIOLOGY INTERFACE: EXPLORING MODELS FOR OVERSIGHT 28 (Hubert Humphrey Inst. of Pub. Aff., U. Minn. 2005), available at http://www.hhh.umn.edu/img/assets/9685/nanotech_jan06.pdf (quoting Alan Ziegler). Ziegler proposes a similar scheme that combines insurance and liability to remedy harms and compensate victims. To Ziegler, the concept of fairness requires that the burden be placed on those who have the ability to pay (here, through liability) and can spread the risk through insurance. He posits that liability will incentivize manufacturers to reduce the potential for harm caused by their products. The presence of insurance can limit the extent to which an unmitigated liability scheme could stifle innovation.

Health and Safety Code Chapter 699, sections 57018-57020, to require manufacturers and importers of carbon nanotubes to submit information regarding testing methods and environmental fate. The Department has also indicated a desire to make a similar request to manufacturers and importers of “reactive nanometal oxides.”⁶¹ Other possible measures for states to enact include, among other things, requiring disclosure of health and environmental hazards (similar to what California has done regarding nanotubes), establishing regional standards through intra-state collaboration, and designing oversight programs.⁶²

iv. No Governmental Regulation and/or Industry Self-regulation

This idea to some extent embodies the core of the harm principle—that we should not regulate until the presence of a health or environmental harm justifies such regulatory action. While industry self-regulation may seem like a free pass for manufacturers, the industry is not without incentives to develop safe products. As a whole, manufacturers of nanotechnology will need to garner public trust and will want to avoid potential product liability for adverse impacts caused by their products. In its nascent stage, the loss of consumer confidence could effectively cripple the industry as a whole—without consumer confidence the potential market for nanoproducts would dry up, and without a potential market, nanotechnology research funding would likely decline.⁶³

However, the nanotechnology industry can only be relied upon to voluntarily assume the level of safety that is most economically beneficial for itself, and this is not necessarily the optimal level of safety for society as a whole. Additionally, there is no effective enforcement

⁶¹ California Department of Toxic Substances, <http://www.dtsc.ca.gov/TechnologyDevelopment/Nanotechnology/index.cfm>.

⁶² SUELLEN KEINER, ROOM AT THE BOTTOM? POTENTIAL STATE AND LOCAL STRATEGIES FOR MANAGING THE RISKS AND BENEFITS OF NANOTECHNOLOGY 34 (Woodrow Wilson Int’l Center for Scholars, Project on Emerging Nanotechnologies 2008), available at http://www.nanotechproject.org/process/assets/files/6112/pen11_keiner.pdf.

⁶³ Glenn Harlan Reynolds, *Nanotechnology and Regulatory Policy: Three Futures*, 17 HARV. J.L. & TECH. 179, 208-09 (2003).

mechanism for industry self-regulation. This creates a temptation for a particular manufacturer to take advantage of the public good will established for the industry as a whole at the expense of other manufacturers.⁶⁴ There is thus no guarantee that all manufacturers will comply with these standards.⁶⁵ Without a mandatory, enforceable, labeling scheme, manufacturers could trade on nanotechnology's good will by erroneously calling their products nanoproducts, or escape any ill-will by repackaging products that do contain nanomaterials as conventional products. Furthermore, the voluntary nature of these measures means that standards can be variable over time, which could create public confusion and prevent effective public reliance on industry self-regulation. These serious shortcomings prevent industry self-regulation from being the sole regulatory mechanism for overseeing nanotechnology. However, voluntary industry measures remain an attractive piece of the regulatory puzzle.⁶⁶

v. Moratorium on Nanotechnology

Simply stated, it is possible that potential health and environmental risks of nanotechnology may be of such magnitude that it is simply imprudent to proceed with its development. Under this view, the uncertainty surrounding both the magnitude and frequency of adverse impacts of nanotechnology creates an unacceptable potential for danger.⁶⁷ A moratorium need not be permanent (though some may prefer it to be), but may be lifted when the uncertainty surrounding the attendant risks of wide-spread commercialization and manufacture of nanotechnology products has decreased to the point where we can predict, with reasonable

⁶⁴ This, of course, assumes that employing safety measures would result in a decrease in profits for a manufacturer. While this is not an unreasonable assumption, it is not necessarily going to be true in every situation.

⁶⁵ David Forrest, *Regulating Nanotechnology Development*, (1989), available at <http://www.foresight.org/nano/Forrest1989.html>.

⁶⁶ Linda K. Breggin & Leslie Carothers, *Governing Uncertainty: The Nanotechnology Environmental, Health, and Safety Challenge*, 31 COLUM. J. ENVTL. L. 285, 321-22 (2006); Florini et al., *supra* note 1, at 52-3; LeRoy C. Paddock, *Green Governance: Building the Competencies Necessary for Effective Environmental Management*, 38 ENVTL. L. REP. NEWS & ANALYSIS 10609, 10631-32 (2008).

⁶⁷ Brent Blackwelder, Response, *Comment on A Framework Convention for Nanotechnology?*, 38 ENVTL. L. REP. NEWS & ANALYSIS 10520 (2008).

accuracy, the potential dangers to human and environmental health that may be embodied by nanotechnology products. It is possible that at its most extreme (the implementation of self-replicating, independently powered nanomachines either within or outside of the human body), nanotechnology may never be reduced to an acceptable level, and thus should never be pursued.

Such a severe response to all forms of nanotechnology, however, is largely regarded as unwise at this point in time. Aside from the potential nanotechnology manufacturing industry, a number of independent research labs (not to mention the government itself)⁶⁸ are heavily invested in nanotechnology, and would face considerable economic losses if a moratorium were imposed. Aside from this perceived waste in funding dollars is the loss of potential technological, engineering, and medical benefits to be derived from nanotechnology.⁶⁹ As discussed above, research suggests that nanotechnology has the potential to significantly impact areas of therapeutic and diagnostic medicine, to the benefit of our quality of life. To this end, our society as a whole (and those afflicted with diseases to which nanotechnology promises a cure or more efficient or effective treatment in particular) stands to receive substantial benefits as nanotechnology develops. Putting aside these potential gains for an indefinite amount of time as a purely precautionary measure may require more forbearance than any government or agency (either individually or as a collective) can realistically be expected to exercise. While a moratorium may be the only way to completely protect ourselves from any and all of the potential dangers of nanotechnology, the benefits may simply be too promising to pass up.

III. REMEDIAL BIOMECHANICAL AND BIOCHEMICAL OPTIONS

⁶⁸ Davies, *supra* note 34, at 2.

⁶⁹ Emmanuelle Schuler, *Potential Risks and Remedies*, in BIOMEDICAL NANOTECHNOLOGY 177, 178-80 (Neelina H. Malsch, ed., 2005).

Front-end regulation can only do so much work. Even a robust, nanotechnology-focused regulatory scheme will not be able to completely prevent exposure to nanoparticles or completely remove the potential danger surrounding any such exposure. Moreover, many applications of nanotechnology, particularly in the realm of nanomedicine, will entail deliberately exposing the human body to nanoproducts of some variety.

The effects of nanoparticles on the human body depend, in part, on the route of exposure (such as the gastro-intestinal tract, skin, or lungs). Additionally, interactions with cells, body fluids, and proteins will all impact both the ability of nanoparticles to distribute throughout the body and the biological effects they exhibit.⁷⁰ This section examines the options that currently exist for dealing with nanoparticles once they have entered the body. First, the response of the body's biological systems are examined, followed by an examination of the options for intervention following deliberate and accidental exposure.

A. *Biological Response to Nanoparticle Exposure*

Nanoparticles in the body would encounter a number of defenses that may be able to eliminate, sequester, or dissolve them.⁷¹ However, faith in biological systems to adequately respond to engineered nanoparticles is troublesome given that many nanoparticles have demonstrated an unconventional ability to cross body system boundaries and display undesirable novel, sometimes unpredictable, properties.⁷² A large portion of nanoparticles either accidentally or deliberately introduced into the body will end up in the liver, and accumulation in the spleen, intestine, bone marrow, lymph nodes, and brain has also been shown to be possible.⁷³

⁷⁰ JAIN, *supra* note 3, at 331.

⁷¹ *Id.* at 332.

⁷² Fender, *supra* note 34, at 1068; Deming Liu, *Nanotechnology in China: Regulations and Patents*, 5 NANOTECH. L. & BUS. 465, 469 (2008); Rollins, *supra* note 9, at 225.

⁷³ M. C. Garnett & P. Kallinteri, *Nanomedicines and Nanotoxicology: Some Physiological Principles*, 56 OCCUPATIONAL MED. 307, 310-11 (2006).

Non-degradable, bioaccumulating nanoparticles are likely to have a number of effects in the body. If they are taken up by macrophages, they would likely trigger free radical release which would result in cell damage and inflammation. If they accumulate in the lysosomal compartment they can cause toxicity.⁷⁴ As with most materials, nanoparticles will likely be immediately coated by proteins upon contact with biological matrices, which is referred to as a “protein corona.” The presence of certain components of this corona (called opsonins) on the particle surface creates a molecular signature which is recognized by immune cells and determines the route of particle internalization (which will affect the eventual fate of the nanoparticle in the body).⁷⁵ Thus, protein binding is one of the most important factors influencing biodistribution, and evidence suggests that the extent of protein binding is a function of particle surface area.⁷⁶ Therefore, nanoparticles should exhibit more protein binding (relative to mass) than a particle of larger size. However, we currently lack an understanding of how other biodistribution factors (such as size, aggregation, chemical composition, surface structure, solubility, and particle geometry⁷⁷) influence plasma protein binding to nanoparticles, or how the amount of protein binding influence biological responses.⁷⁸ These parameters can modify cellular uptake, protein binding, translocation, and the possibility of causing tissue injury.⁷⁹ Further complicating the issue is the fact that the composition of the protein corona on a nanoparticle at any given time will depend on the concentrations and kinetic properties of the

⁷⁴ *Id.* at 310.

⁷⁵ Parag Aggarwal et al., *Nanoparticle Interaction with Plasma Proteins as it Relates to Particle Biodistribution, Biocompatibility and Therapeutic Efficacy*, 61 *ADVANCED DRUG DELIVERY REVIEWS* 428, 429 (2009).

⁷⁶ *Id.*

⁷⁷ JAIN, *supra* note 3, at 331; Nuria Sanvicens & M. Pilar Marco, *Multifunctional Nanoparticles—Properties and Prospects for their use in Human Medicine*, 26 *TRENDS IN BIOTECHNOLOGY* 425, 429 (2008); Balogh et al., *supra* note 15, at 282.

⁷⁸ Aggarwal et al., *supra* note 76, at 429.

⁷⁹ JAIN, *supra* note 3, at 331.

proteins found in plasma.⁸⁰ This means that the biodistribution of identical nanoparticles may vary not only from person to person, but even within a single person over time.

B. Deliberate Exposures

The most common routes of deliberate exposure will be in the context of nanomedical products (either as therapeutic agents, drug-delivery devices, or diagnostic agents). Because these products are specifically designed and engineered for application in the human body, consideration can be paid as to how the nanomaterials will react with biological systems. These front-end considerations are largely concerned with biocompatibility and biodegradability, which address the problems of toxicity and fate respectively. Medical nanomaterials are designed with goals of creating a product that will not display cytotoxicity (or will display a directed or specific cytotoxicity, for example, to cancer cells)⁸¹ and will not remain in the body longer than necessary—either because they degrade into other, non-toxic products, or because they are expelled from the body.⁸²

i. Nanoparticle Surface Modifications

These concerns do not exist only in the abstract, studies have shown the ability to alter or direct the behavior of nanoparticles through front-end design considerations. Single-walled carbon nanotubes (SWCNTs) present an illustrative example of the influence that can be exerted by choices in the design phase. Newly manufactured or “pure” SWCNTs have shown considerable cytotoxicity concerns. Some studies have suggested that they can enter the bloodstream through the lungs, and can have asbestos-like effects *in vivo*.⁸³ However, when the SWCNTs have been “functionalized” (the binding of different atoms or molecules to the surfaces

⁸⁰ Aggarwal et al., *supra* note 76, at 431.

⁸¹ JAIN, *supra* note 3, at 331.

⁸² Wim H. De Jong & Paul J.A. Borm, *Drug Delivery and Nanoparticles: Applications and Hazards*, 3 INT’L J. NANOMEDICINE 133, 134 (2008).

⁸³ Rollins, *supra* note 9, at 224.

of the SWCNTs by either adsorption, electrostatic interaction, or covalent bonding), they exhibit a drastically different behavior—rather than exhibiting any harmful or toxic side-effects, evidence suggests they become water soluble and are rapidly filtered and passed through the body’s normal waste systems.⁸⁴ Being able to control biodistribution through this kind of surface functionalization will be instrumental in safely utilizing nanoparticles for applications in the human body.⁸⁵ However, it is worth noting that severe limitations persist regarding the production of structurally and chemically identical batches of carbon nanotubes,⁸⁶ which means uniform functionalization, and thus in-body behavior, cannot be guaranteed at this point.

Studies on quantum dots (semiconductors made of nanocrystals) have shown similar results. Quantum dots made from cadmium selenide (CdSe) exhibit toxicity in the body from the release of free cadmium ions (Cd²⁺). However, these quantum dots can be rendered nontoxic in the body by functionalizing quantum dots by giving them a second coating, or “nanoshell,” composed of a dielectric core made of silica and surrounded by a thin metal shell (usually made of gold).⁸⁷ The thickness of the nanoshell can influence the extent of nanoparticle translocation.⁸⁸ Such coatings may also be used to prevent the body from eliminating a nanoparticle through normal biological systems, and thus allow the particle to be biologically active.⁸⁹ For example, polymer polyethylene glycol coatings have been shown to minimize

⁸⁴ JAIN, *supra* note 3, at 333-34; Lara Lacerda et al., *Carbon Nanotubes as Nanomedicines: From Toxicology to Pharmacology*, 58 ADVANCED DRUG DELIVERY REVIEWS 1460, 1463 (2006).

⁸⁵ Shvedova et al., *supra* note 11, at 199.

⁸⁶ Lacerda et al., *supra* note 85, at 1463.

⁸⁷ Selvarajan Sandhiya et al., *Emerging Trends of Nanomedicine*, 23 FUNDAMENTAL & CLINICAL PHARMACOLOGY 263, 264-65 (2009); JAIN, *supra* note 3, at 332..

⁸⁸ Garnett & Kallinteri, *supra* note 74, at 310.

⁸⁹ Ron Hardman, *A Toxicological Review of Quantum Dots: Toxicity Depends on Physiochemical and Environmental Factors*, 114 ENVTL. HEALTH PERSP. 165, 166 (2006).

unwanted recognition by the body's systems, thus increasing the circulation and half-life of a nanoparticle.⁹⁰

A number of different effects can, theoretically, be obtained by functionalizing the surfaces of nanoparticles in the design and engineering phase. These design choices can be directed to influence the aggregation and longevity of nanoparticles in the body. Choices in functionalization can also determine how a nanoparticle interacts with the body's immune system—particularly whether and how a particle is absorbed by the body's macrophages.⁹¹

ii. Other Design Considerations

However, surface characteristics are not the only characteristics that will determine physiological responses in the body. Some evidence suggests that length of carbon nanotubes can influence the immune response of the body, regardless of whether or not they have been functionalized. Other particle characteristics such as particle stability, solubility, aggregation behavior, and chemical composition can all influence the pharmacological and toxicity profile of nanotubes.⁹² Accordingly, any nanoparticle with potential *in vivo* applications will need to undergo substantial testing to determine what immune response they are likely to illicit, what characteristics drive this response, and to what extent these characteristics can be reliably and consistently altered to influence the immune response in a positive way.

Beyond the considerations surrounding individual nanoparticle applications, the potential impacts surrounding multiple exposures must also be taken into account. As exposure to nanoparticles increases, the possibility for interactions between different nanoparticles becomes

⁹⁰ Sanvicens & Marco, *supra* note 78, at 429.

⁹¹ Valerian E. Kagan, Hulya Bayir & Anna A. Shvedova, *Nanomedicine and Nanotoxicology: Two Sides of the Same Coin*, 1 NANOMEDICINE: NANOTECHNOLOGY, BIOLOGY, & MED. 313, 315 (2005); Catarina Gonçalves et al., *Dextrin Nanoparticles: Studies on the Interaction with Murine Macrophages and Blood Clearance*, 75 COLLOIDS AND SURFACES B: BIOINTERFACES 483, 487-88 (2010).

⁹² Lacerda et al., *supra* note 85, at 1466-67.

more likely within the body. To the extent that these interactions are foreseeable, they can be avoided in the realm of deliberate exposure through the keeping of routine medical records (as drug interactions are monitored now).⁹³ However, as discussed below, this will not be true regarding accidental exposure, as exposures will be hard to both predict and control.

C. *Accidental Exposures*

The risk of accidental exposure will increase with the predicted increase in the manufacturing of consumer and industrial products containing nanoparticles and nanomaterials.⁹⁴ As large-scale manufacturing of nanomaterials becomes routine, risks regarding handling and worker exposure to nanoparticles will arise.⁹⁵ A number of factors make accidental exposure more problematic than deliberate exposure. Because these nanoparticles are not specifically designed for human consumption, the front-end considerations of biodegradability and biocompatibility are less likely to come into play (or will likely be made secondary concerns).⁹⁶ Additionally, the environmental impacts of their manufacture and disposal are generally not taken into consideration during the engineering process.⁹⁷ The toxicity of these non-medical nanoparticles will largely be determined by their material composition and surface characteristics (which will likely play an important role in determining where in the body they accumulate).⁹⁸

There is also greater uncertainty inherent in accidental exposure, which may increase the potential for adverse health impacts. Consumer and industrial applications will likely be far more common than nanomedical applications, which will create more chances for initial and continued exposure to nanoparticles. Additionally, this exposure will not occur in the carefully

⁹³ Though it is by no means certain that the majority of these interactions will be foreseeable, as there is a dearth of toxicological studies focusing on *in vivo* nanoparticle interactions.

⁹⁴ Sandhiya et al., *supra* note 88, at 268; Jones & Grainger, *supra* note 16, at 439.

⁹⁵ Lacerda et al., *supra* note 85, at 1463.

⁹⁶ Garnett & Kallinteri, *supra* note 74, at 310.

⁹⁷ Linkov et al., *supra* note 21, at 167.

⁹⁸ Garnett & Kallinteri, *supra* note 74, at 310.

supervised and regulated manner of deliberate nanomedical applications. Instead, dose and duration will likely be widely variable, making effects hard to accurately foresee based on conventional toxicity test data. Moreover, the nanomaterials to which people are exposed will also be largely variable, as nanotechnology has potential applications across many different fields of products. The likelihood of multiple exposures will increase, raising concerns regarding the potential for the harmful interaction of different nanoparticles in the body.

Prophylactic and remedial measures to remove nanoparticles from the body have not been developed. Such measures will be difficult to develop due to the lack of understanding of *in vivo* particle behavior and the wide variety of possible exposure routes and nanoparticle identities. Any such measures would likely be particle-specific, and thus would be fairly costly to develop in response to all potential exposure pathways. There has been some reliance that biological systems will be able to deal with any non-native particles in the body. The expectation has been that the biodistribution of nanoparticles would be very limited and uncoated particles would be rapidly taken up and eliminated by the spleen and liver.⁹⁹ However, evidence now suggests that nanoparticles can accumulate selectively in specific areas of the body.¹⁰⁰

IV. CONCLUSIONS AND RECOMMENDATIONS

While it is indeed important to foster the development of nanotechnology, to do so at the expense of all safety concerns seems to be as unnecessary as it is foolhardy. The traditional reactionary approach to regulation may be appropriate when uncertainty is relatively small and there are reasonable reassurances that regulatory mechanisms will be able to respond quickly enough to address any hazard that may develop in sufficient time to prevent the continuation of

⁹⁹ *Id.* at 309.

¹⁰⁰ *Id.* at 310.

harm. Nanotechnology, however, carries with it significant uncertainty and potential for harm. Toxicity testing has shown that, in certain circumstances, nanoparticles can have serious impacts on health. As discussed above, the safety and toxicity of nanoparticles will rely on a number of factors, the interactions of which are not fully understood. There is also very little information on chronic toxicity of nanomaterials, so even if a given nanoparticle does not have observable acute toxicity, the product still may not be safe in the long-term. Chronic toxicity will depend on a number of factors—not only those that govern acute toxicity, but also their persistence and accumulation in the body, and how they interact with other nanoparticles.¹⁰¹ These complex interactions are hard to effectively test and harder to accurately predict. A reactionary approach to regulation is poorly suited to address such long-term, chronic harm, because by the time the effects of chronic exposure are noticed and connected to a particular nanomaterial, the regulatory scheme will not be able to prevent such harms from developing in other sections of the population that have already endured such chronic exposure.

A. *The Need for Regulatory Change*

In the face of the novel properties of nanoparticles, the potential for wide-spread accidental and deliberate nanoparticle exposure by a large segment of the population, and uncertainty regarding the toxic potential and physiological *in vivo* responses of nanoparticles, concerns about the potential adverse health effects of nanoparticles are justified. In order to respond to these concerns, a new regulatory scheme must be adopted, or the existing regulatory scheme must be revised or augmented in order to better safeguard against the potential harms of nanotechnology. Nanotechnology-specific front-end regulation will not only help to protect against potential unwanted side-effects of new nanotechnology-based products, but will help

¹⁰¹ Jones & Grainger, *supra* note 16, at 439-40.

inspire public confidence in nanotechnology, which will help drive the field forward by establishing some measure of market security.¹⁰²

However appealing it may seem to wipe the regulatory slate clean and enact an entirely new scheme particularly geared toward nanotechnology, such an approach is not without serious consequences. Creating a new legislative approach would involve a costly, resource-draining, lengthy, and highly uncertain process without any real guarantee of more effective or efficient regulatory action.¹⁰³ Our ability to confidently draft and implement a novel, well-functioning regulatory scheme is limited by the degree of uncertainty regarding health and environmental effects and the effectiveness of safety precautions.¹⁰⁴ Put bluntly; good science makes good law. Unfortunately, our scientific understanding regarding nanotechnology safety doesn't seem to yet be at the point where we can create an effective regulatory scheme. Thus, creating and implementing a new regulatory scheme could impose serious costs without generating any real benefit in safety. Moreover, there is a very real chance that we could incur these costs and develop a new regulatory system now, only to find that it is inadequate. If such a failure occurs, or significant public health concerns surface regardless of the new regulation, it could seriously undermine public confidence in both the government and the nanotechnology industry.

B. Recommendations for Future Regulation

Notwithstanding the difficulties of implementing a new regulatory scheme, the health concerns implemented by nanotechnology are too serious to go unaddressed while we wait for the science on safety to catch up to the technology itself. Accordingly, we should take some action in the short-term to respond to some health and safety concerns, while more testing is

¹⁰² Mandel, *supra* note 6, at 1364.

¹⁰³ *Id.* at 1363.

¹⁰⁴ *Id.* at 1371-72.

done that can guide a future regulatory effort. In the short-term, the best approach will likely be smaller amendments to the existing regulatory scheme geared toward filling regulatory gaps (e.g. mass limits and classification issues, as discussed in the sections above regarding the EPA and FDA). Revisions made to the existing regulatory scheme should, at a minimum, include clear definitions of what constitutes nanotechnology, treatment of nanotechnology products as “new” substances for regulatory purposes, and a labeling requirement for nanotechnology products.¹⁰⁵ Any such labeling requirement should not only require products containing nanomaterials to clearly disclose as much to consumers, but should also prevent products that do not contain nanomaterials from insinuating otherwise in order to trade on any public good will established by the nanotechnology industry.

Additionally, the government should increase agency coordination in the regulatory approach to nanotechnology (similar to the intra-agency groups developed by the FDA).¹⁰⁶ This will increase regulatory efficiency by helping to guarantee regulatory gaps are being filled and that redundant regulation is being avoided. The EPA and FDA should also work together to establish an interagency database that will help standardize the collection format for nanotechnology data.¹⁰⁷ Agencies must acquire personnel with expertise in nanotechnology, to ensure that this scientific knowledge is being internalized by regulators.¹⁰⁸ The government should work to develop incentives for the nanotechnology industry to act in a socially

¹⁰⁵ George A. Kimbrell, *Nanomaterial Consumer Products and FDA Regulation: Regulatory Challenges and Necessary Amendments*, 3 NANOTECH. L. & BUS. 329, 336-37 (2006).

¹⁰⁶ Mandel, *supra* note 6, at 1369; J. CLARENCE DAVIES, EPA AND NANOTECHNOLOGY: OVERSIGHT FOR THE 21ST CENTURY 59-60 (Woodrow Wilson Int’l Center for Scholars, Project on Emerging Technologies, Washington D.C. 2007), available at http://www.nanotechproject.org/process/assets/files/2698/197_nanoepa_pen9.pdf.

¹⁰⁷ Rollins, *supra* note 9, at 229-30.

¹⁰⁸ Miller, *supra* note 23, at 64-67.

responsible manner as it develops further, and should encourage voluntary industry leadership programs.¹⁰⁹

C. *Nanoparticle Design Recommendations*

In addition to front-end regulation, design considerations will be important in ameliorating the adverse effects of exposure. The considerations of biodegradability and biocompatibility are already taken into consideration in regard to nanoparticles being engineered for deliberate human exposure. However, the factors contributing to biodegradability and biocompatibility in particular, and physiological fate in general, are varied, and the interactions between these factors are not yet completely understood. As it stands right now, it is unclear whether these same design considerations will influence the development of all nanoproducts, including those not intended for introduction into the body. Most of the exposure to nanomaterials will likely be accidental rather than deliberate. The nature of accidental exposure, the wide variety of possible manufactured nanoparticles, and the difficulties of developing methods for nanoparticle extraction or post-exposure degradation make front-end design choices even more important for products for which human consumption may not be intended.

Accordingly, it is important that the same considerations that go into designing, engineering, and manufacturing nanomedical products also go into nanomaterials in consumer and industrial products. Additionally, the need for continuing toxicity and physiological behavior testing is clear, particularly in regard to interactions between different nanoparticles that may occur in the body, and the interplay of the factors that influence biodegradability and biocompatibility. More information is needed regarding the ability for nanoparticles to translocate among biological systems, as well as any tendencies for aggregation, persistence, and

¹⁰⁹ Paddock, *supra* note 67, at 10636; DAVIES, *supra* note 107, at 60.

accumulation, as these factors will play heavily in determinations of chronic toxicity, which is not yet well understood.

As it is unlikely that front-end design considerations will be able to completely ameliorate the potential dangers of all nanotechnology products, work should be done to develop remedial measures that can counteract nanoparticle exposure either by removing nanoparticles from the body completely, or by degrading nanoparticles into biocompatible pieces. To this end, conventional treatment methods such as chelation should be examined for their efficacy of remedying exposure to appropriate classes of nanoparticles. While the use of chelation to remove nanoparticles has not been addressed, nanoparticles themselves have been examined as potential delivery mechanisms for an iron-removing chelation agent as a potential treatment for Alzheimer's.¹¹⁰ Additionally, investigations should be made as to novel methods for removal, particularly by taking advantage of the magnetic properties of some materials at the nano-scale, which has been examined as a means of removing particular materials from aqueous solution.¹¹¹ Research should also be done to determine the practicality of utilizing the charge of some ionic nanoparticles to remove them from biological systems. However, the extent to which these characteristics can be utilized to remove nanoparticles from the body has yet to be seen.

While nanotechnology has the potential to improve the performance of countless consumer products and offer powerful health benefits, it is important that society not lose sight of safety considerations. Much is still unknown about nanotechnology, and we cannot ignore or minimize the risks of nanotechnology for the sake of pushing innovation forward. The need for

¹¹⁰ Gang Liu, et al., *Metal Chelators Coupled with Nanoparticles as Potential Therapeutic Agents for Alzheimer's Disease*, 1 J. NANONEUROSCIENCE 42 (2009).

¹¹¹ Xiaoli Zhao et al., *Removal of Fluoride from Aqueous Media by Fe₃O₄@Al(OH)₃ Magnetic Nanoparticles*, 173 J. HAZARDOUS MATERIALS 102 (2010); Peng Yuan et al., *Removal of Hexavalent Chromium [Cr(VI)] from Aqueous Solutions by the Diatomite-Supported/Unsupported Magnetite Nanoparticles*, 173 J. HAZARDOUS MATERIALS 614 (2010).

at least some measure of precaution is all the more apparent considering the lack of remedial measures currently available to address any potentially hazardous nanoparticle exposure. Front-end design and regulatory caution will be necessary to protect human and environmental health until the nature of the dangers posed by nanotechnology become more certain or alternative measures are developed to address toxicity without hampering scientific development. It is only by addressing the uncertainty regarding nanoparticle toxicity and by carefully balancing caution with innovation that will we be able to make safe use of nanotechnology in the immediate future.