

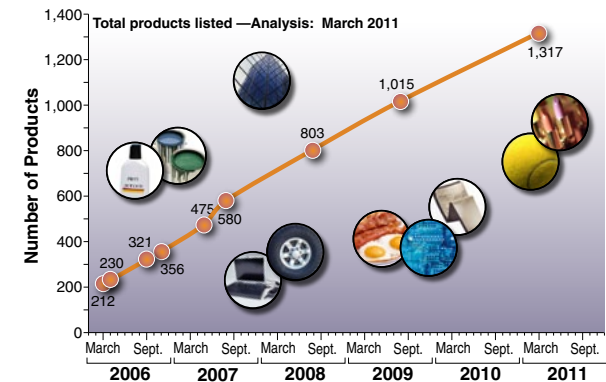


## Beyond Buckyballs—Nanomaterial Product Development Amidst Regulatory Uncertainty

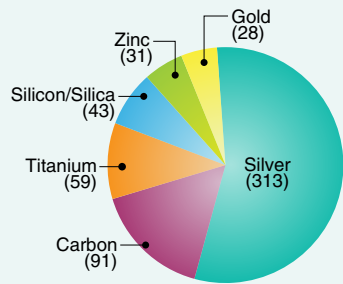
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### Introduction: Growth of Nanotechnology in Products, and Regulatory Developments

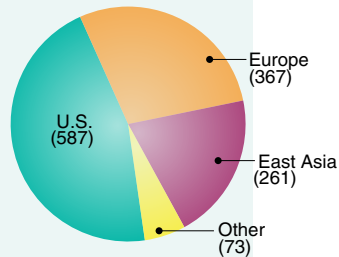
Development of chemically and structurally diverse nanomaterials<sup>1</sup> promises enhanced product applications in medicine, communication, foodstuffs and food packaging, dietary supplements, over-the-counter drugs, and many other consumer products ranging from cosmetics and toothpaste to paints and clothing. The number of consumer products containing nanomaterials has risen steadily over the past 5 years, with the addition of 243 new products per year and more than 1,300 products reported as of March 10, 2011<sup>2</sup> in the Nanotechnology Consumer Products Inventory (Inventory) (Figure 1). This linear rate of increase has not been an exponential explosion, nor has it involved very many types of “bottom up” engineered nanomaterials constructed from the molecular level, although it represents a 521 percent increase in listed products since the inception of the Inventory in March 2006.



**Figure 1.**  
Growth in products containing nanomaterials



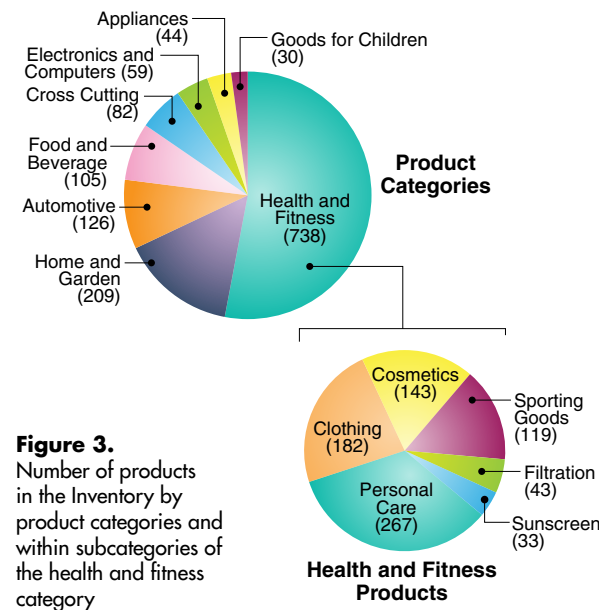
**Figure 2.** Predominant types of nanosubstances in products from the Inventory



**Figure 4.** Number of products containing nanomaterials by country of origin

The largest percentage of products with identified nanomaterials contain nanoscale silver (>55 percent of products), followed by carbon (including carbon nanotubes [CNTs], nanofibers, and fullerenes [also known as buckyballs]), titanium (including titanium dioxide, silica and silicon, zinc (including zinc oxide, and gold (Figure 2). Other nanomaterials (e.g., polymers, clays, quantum dots, organic micelles) are also incorporated in a few products listed in the Inventory and by other sources.<sup>3</sup>

More than half of the total products fall into the health and fitness category, with home and garden, automotive, and food and beverage as the next largest categories with over 100 products each (Figure 3). Within health and fitness, the largest subcategories are personal care, clothing, cosmetics, and sporting goods (Figure 3). The United States is the leader in products containing nanomaterials, followed by Europe and East Asia (Figure 4).



**Figure 3.** Number of products in the Inventory by product categories and within subcategories of the health and fitness category

Determining the health and environmental risks of products associated with nanotechnology has challenged regulatory authorities in the U.S. and abroad, as well as manufacturers of products. Lack of clear regulatory guidance and standards has caused uncertainty and confusion on how to proceed—on the one hand restraining potential innovative research and applications, while on the other allowing less cautious manufacturers to implement applications without the need to assess their safety. Some have questioned whether sufficient exposure and toxicity studies exist, or if such studies could even keep up with the pace at which products are being introduced to the market. For the most part, applications in consumer products to date have involved metal particles of low toxicity (at least to humans), carbonaceous fibers that are encapsulated in other materials (e.g., in sports equipment), or lower toxicity fullerols,<sup>4</sup> rather than fullerenes, in cosmetics. In addition, some substances have always contained nanoscale particles but have not been recognized as such, including clay particles used as fillers, silicon dioxide used as an anti-caking agent in foods, metal pigments, and historical use of colloidal silver in medicine. Fatty acid liposomes used in health and beauty products are another form of conventional substances used in nanoscale micelle form.

Recent regulatory developments indicate a shift from the information-gathering phase on nanomaterials being manufactured, to definition of nanomaterials for labeling and regulation, including requirements to assess product safety and to assess human health and environmental risks. Identifying materials in products that should require safety assessments because of nanoscale functionality is complicated by different particle types and origins, and materials that contain a particle size distribution that may include only a small portion of particles smaller than 100 nm. Nanoparticles also agglomerate readily, resulting in particles that are micron size or larger in finished products, but may still have nanoscale functionality and potentially greater toxicity.

Perhaps given their similarities to mineral fibers with well-known toxicity, regulatory agencies have focused research efforts and reporting requirements on CNTs. Another engineered carbon-based nanomaterial—fullerenes, or buckyballs—has also received such attention. To proactively address potential health risks and provide guidance and protection, agencies need adequate flexibility to appropriately regulate an expanding chemical and physical diversity of nanomaterials beyond carbon-based nanotubes or buckyballs to include novel engineered substances that are yet to come. At the same time, a regulatory definition that is overly inclusive will overwhelm the ability of the authorities to focus on materials with true health and environmental concerns while stifling innovation.

### **Establishing Criteria to Regulate Nanomaterials and Evaluate Risk—What is a Nanomaterial?**

Regulatory authorities are grappling with the definition of nanomaterials that could potentially pose hazards and thus need regulation, resulting in a lack of harmonization even among different agencies within the U.S. Standardization of nanomaterial nomenclature, characterization, and measurement has been a recent focus of research by agencies such as the American Society for Testing Materials, American National Standards Institute (ANSI), and the International Organization for Standardization, due to a wide disparity in characterization among existing nanomaterial studies and general lack of standard reference nanomaterials.<sup>5</sup> These definitions of nanotechnology-related terms are generally broad and are not intended for specific regulatory purposes.

Other than a general acceptance of the primary nanoscale range of interest as 1 nm to 100 nm, regulatory agencies in the U.S., the European Union (EU), Canada, and the Organisation for Economic Cooperation and Development have not established harmonious criteria for identifying nanomaterials.

These differences may result in labeling and regulatory environments that could produce trade barriers and significant differences in data requirements to bring new nanomaterial products to the marketplace. This disparity is illustrated in some recent examples of regulatory announcements, described below.

### **European Commission**

On October 18, 2011, the European Commission (EC) issued a definition of nanomaterial to include, most notably, the following criteria:

- a. *A natural, incidental or manufactured material containing particles in an unbound state or as an aggregate or as an agglomerate and where for 50% or more of the particles in the number size distribution, one or more external dimensions, is in the range 1nm–100nm.*
- b. *In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%.<sup>6</sup>*

This definition is broadly inclusive and appears to cover materials that contain small amounts of naturally occurring nanoparticles. The EC is focused on the amount of nanoparticles in a particular product, regardless of origin, which could be as low as 1 percent by particle number, and far less than 1 percent by weight because of the low mass of the smallest particles. The evaluation of particle size distribution in substances is also contingent on the methods used, and results could vary among laboratories. The EC noted that this definition does not include determination of whether a material is hazardous, poses a risk, or requires some regulatory action; rather, the primary intent is to identify materials for application of special provisions such as risk assessment or labeling.

### Health Canada

On October 6, 2011, Health Canada issued their definition for the purpose of information gathering, to improve the understanding of nanomaterials for risk assessment and risk management purposes. This definition "considers any manufactured substance or product and any component material, ingredient, device, or structure to be nanomaterial if:"

- a) *It is at or within the nanoscale [1 to 100 nanometres] in at least one external dimension, or has internal or surface structure at the nanoscale; or*
- b) *It is smaller or larger than the nanoscale in all dimensions and exhibits one or more nanoscale properties/phenomena.*<sup>7</sup>

Health Canada does not specify the percent of the material with nanoscale dimensions, but does allow for smaller or larger materials to be considered if they exhibit nanoscale properties or phenomena, defined as "...properties which are attributable to size and their effects; these properties are distinguishable from the chemical or physical properties of individual atoms, individual molecules and bulk material."

Health Canada does not consider naturally occurring substances or biological molecules (e.g., nucleic acids/DNA/proteins, micro-organisms, or cell structures) as nanomaterials and already regulates biotechnology products separately.

Health Canada also stresses that they do not assume that all nanomaterials pose increased risks to human health or the environment and that flexibility is necessary in assessing whether specific substances or classes pose a risk of effects.

### U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics

The U.S. Environmental Protection Agency (EPA) Office of Pollution Prevention and Toxics (OPPT) has described nanomaterials under the auspices of the Toxic Substances Control Act (TSCA) to regulate their importation or manufacture in the U.S.:

- *Material having structures with dimensions in the nanoscale (approximately 1–100 nanometers (nm) that may have organizations and properties different than the same chemical substances with structures at a larger scale.*<sup>8</sup>

Beyond this basic definition, a key part of EPA's general approach under TSCA, including for nanomaterials, is to determine whether a chemical differs in molecular identity from an existing chemical in their inventory. EPA OPPT considers organic molecules as chemicals rather than nanomaterials. Similarly, EPA does not consider polymers made up of nanoscale subunits to be nanomaterials under TSCA if they do not exist in the monomer state.

### U.S. Environmental Protection Agency Office of Pesticide Programs

Within the EPA Office of Pesticide Programs (OPP), nanomaterial policy as a part of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) is under development. EPA OPP has noted problems with the subjectivity of some of the commonly used criteria for defining nanomaterials such as "unique or novel properties" or "manufactured or engineered to take advantage of these properties" (76 Fed. Reg. 35387).

EPA OPP has thus proposed:

*Instead OPP will focus on more objective criteria in describing when information about a "nanoscale material" in a pesticide product may be relevant to determining whether*

*the product has an unreasonable adverse environmental effect. Specifically, such information may be relevant in this context when the active or inert ingredient and any component parts thereof is intentionally produced to have at least one dimension that measures between approximately 1 and 100 nanometers, regardless of the aggregation or agglomeration state of the final material. (76 Fed. Reg. 35387)*

EPA's approach under FIFRA appears to start with particle size and assumes that smaller size results in different properties and functionality that may cause adverse environmental effects. EPA OPP, however, has noted that they do not intend to include biological molecules such as DNA or RNA, or substances that exist in nanoscale in their natural state such as clays (76 Fed. Reg. 35387). Registrants will also be allowed to respond to OPP about whether their products contain "nanomaterials" of concern for EPA to consider on a case-by-case basis.

### **U.S. Food and Drug Administration**

In June 2011, the U.S. Food and Drug Administration (FDA) released draft guidance on issues for industry to consider for FDA-regulated products that contain nanomaterials.<sup>10</sup> Specifically, FDA considers "whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer." FDA uses the 1- to 100-nm criterion as a first reference point for evaluation, but could consider larger-sized substances, up to 1  $\mu\text{m}$ , including primary and agglomerated particles.

### **Summary of Definitions**

Regulatory agencies and authorities generally consider 1–100 nm as the primary size range for nanomaterials, although some (e.g., Health Canada and FDA) may include larger particles depending on whether they demonstrate properties that differ from bulk-scale forms, and the EU also includes materials in which only a fraction of particles may be in the nanoscale range (Table 1). The EU also specifically includes natural substances, whereas Health Canada, EPA, and FDA note that natural biological substances are regulated under other programs. With the exception of the EU (includes) and EPA OPPT (doesn't include), other agencies lack clarity on whether naturally occurring inorganic substances such as clays or silicon dioxide would be considered nanomaterials. EPA OPPT's approach does not automatically consider smaller versions of conventional materials to be a significant new use. More liberal interpretations of nanomaterials as any substance that has different properties as a result of its smaller size could result in even powdered sugar qualifying as a nanomaterial because of its more rapid dissolution rate compared to granulated sugar (although solubility is unchanged). The various agencies also acknowledge the limitation of definitions for identifying materials of concern for regulation, and allow specific materials to be considered on a case-by-case basis. Overly broad criteria, however, will result in a large number of materials requiring regulatory scrutiny, including those currently not considered to be nanomaterials. Large numbers of submissions flooding the regulatory agencies could also cause a backlog that would delay approvals and reduce the amount of attention paid to regulating specific hazards.

**Table 1.** Comparison of specific criteria for defining nanomaterials among regulatory agencies

Agency	Engineered Substances	Natural Substances	Specific Criteria Noted			
			Agglomerates and Larger Structures	1–100 nm Range	Outside of 1–100 nm Range	Percentage of Particles
EU/EC	Yes	Yes	Yes	Yes	No	Yes; >1%–50%
Health Canada	Yes	No	Yes	Yes	Yes	No
EPA OPPT	Yes	No	No	Yes	No	No
EPA OPP	Yes	No	Yes	Yes	No	No
FDA	Yes	No	Yes	No	Yes	No

### Insights from Current Regulatory Approaches: Example of TSCA

EPA OPPT's deliberations and actions in developing regulations for nanomaterials under TSCA provide some insight into emerging regulatory approaches. TSCA gives EPA the authority to promulgate rules requiring manufacturers, importers, and processors to test certain chemical substances or mixtures for their effects on human health and the environment. Chemical substances are broadly defined as "any organic and inorganic substance or particular molecular identity" and include "microorganisms as well as traditional chemicals." Foods, food additives, drugs, cosmetics, and devices are expressly excluded from this definition and fall under the purview of FDA.

All new chemicals, including nanomaterials, that are currently not included in the TSCA inventory must undergo a human health and environmental risk assessment by OPPT before being imported into or manufactured in the U.S. A much debated issue over the past several years, particularly for CNTs, is whether nanomaterials should be regulated under TSCA<sup>11</sup> as either 1) a significant new use of an existing chemical on the TSCA inventory, thereby requiring that manufacturers submit a Significant New Use Notification (SNUN), or 2) as a new chemical and thus requiring a Premanufacturing Notification (PMN).

A key lesson learned is to take advantage of the OPPT pre-market meeting process to discuss the available data for the conventional and corresponding nanomaterial and/or to discuss what additional data should be generated to determine a scientifically defensible path forward. Companies bringing new nanomaterials into the marketplace will need to consider whether it is more appropriate to enter the market under the Significant New Use Rule (SNUR) or as a new chemical entity under the PMN process. Overall, it may be a strategic decision that the manufacturer should evaluate thoroughly based on the characteristics of their specific product and the available scientific data on other similar materials, prior to discussions with OPPT to confirm whether their product requires a SNUN or PMN submission. Either regulatory route may require the generation of a battery of mammalian toxicology (e.g., an acute battery, inhalation toxicology, genotoxicity, and reproductive testing) and environmental risk data. Even under the SNUN process, the capability to bridge to an existing data set for a conventional chemical is not always possible since the conventional data may not be relevant for the corresponding nanomaterial due to the differences in chemical and physical properties. Moreover, at this point in time, reference nanomaterials are not generally available. Additionally, the public comment period mandated by the SNUN may exceed the up-to-90-day PMN data process.

EPA's 2008 general approach document<sup>12</sup> provides guidance on criteria to assess whether a nanoscale substance is a "new" chemical for the purposes of the TSCA inventory. In regulating new chemicals under TSCA, EPA generally has not considered units of matter beyond molecules (e.g., physical aggregates) to be reportable to the TSCA inventory:

*... Molecules can themselves be arranged or aggregated into particles or other physical forms of various types, shapes, and sizes with concomitant physical properties. EPA does not consider these particles or physical forms themselves to be different molecules with different molecular identities, but rather to be aggregates of molecules that have the same molecular identity, with no chemical bonding between the molecules. Consequently, EPA has not treated the mere aggregation of molecules into particles or varying physical forms to result in different chemical substances with different molecular identities for the purposes of TSCA (EPA, 2008).*

EPA OPPT has thus favored molecular identity over particle size as the primary regulatory driver of whether a chemical is new or not. EPA OPPT recognizes that the structural and physical chemical properties of the nanomaterial might make a substance chemically and biologically different from its conventional chemical counterpart (i.e., because of number and spatial arrangement of atoms, type and number of chemical bonds). For example, according to EPA's molecular identity criteria, CNTs may or may not have been designated as an allotropic<sup>13</sup> form of carbon. If CNTs are allotropic forms of carbon, these substances would have a different molecular identity from other forms of carbon, such as graphite (carbon arranged in hexagonal sheets) or diamonds (carbon atoms arranged in a tetrahedral lattice).

EPA OPPT has reviewed over 100 new chemical notices for nanomaterials under TSCA, but has released notices for a limited number, including:

- **December 28, 2011:** Citing worker safety and other concerns, EPA proposed SNURs for 17 chemicals, including 8 types of fullerenes, 5 multi-walled CNTs, and a single-walled CNT (76 Fed. Reg. 81447-81462).
- **September 17, 2010:** Final SNURs for two distinct substances identified generically as multi-walled CNTs (PMN P-08-177) and single-walled CNTs (PMN P-08-328), which were the subject of PMNs (75 Fed. Reg. 56880-56889).
- **November 5, 2008:** Siloxane-modified silica nanoparticles and siloxane-modified aluminum nanoparticles described in PMNs are significant new uses based on potential for hazards from respiratory exposure. Ninety-day inhalation toxicity testing in animals was recommended to characterize risk (73 Fed. Reg. 65743-65766).
- **October 31, 2008:** Manufacturers and importers must notify EPA 90 days prior to manufacture or import of new chemical CNTs for commercial purposes (73 Fed. Reg. 64946-64947).

EPA has been developing a set of rules specifically for nanomaterials to protect against unreasonable health or environmental risks: 1) a SNUR under section 5(a)(2) of TSCA to ensure that nanomaterials receive appropriate regulatory evaluation; 2) an information-gathering rule under TSCA section 8(a) to require submission of information on production, use, and health and safety data by manufacturers; and 3) a TSCA Section 4 testing rule for certain nanomaterials already in commerce to aid EPA in assessing potential health and environmental effects.<sup>14</sup> The release of these rules is projected for March 2012.<sup>15</sup>

### **What Can Manufacturers Do?**

Given the current lack of clarity on what will be regulated and how, manufacturers seeking to use nanomaterials in products should monitor developments with the applicable agencies for their specific products. Clues can also be obtained from other national and international agencies as global harmonization progresses. Manufacturers could also obtain information on the specific characteristics of the nanomaterials they use; conduct material science assessments of the nanomaterials within product matrices; assess the potential for exposure and health risks under different use, abuse, and disposal scenarios; and conduct periodic state-of-the science assessments of the types of materials in their products, as well as potentially related materials. In the currently evolving regulatory climate on nanomaterials, manufacturers would be prudent to assess the specific properties and characteristics of their materials and products that could affect health and environmental risks. Potential health risks associated with nano-engineered products, whether actual or not, indicate that manufacturers and researchers should consider product safety early in the process. Such preparation will allow for more efficient and effective responses to potential regulatory requirements as they emerge. In addition, "engineering safety" into products will aid in ensuring that these products eliminate or minimize exposure, thus helping to mitigate public concern that use of smaller particles results in increased health and environmental risks.

### **How Can Exponent Help?**

Exponent is uniquely qualified to assist in the area of nanomaterials. In addition to our project experience in assessing various aspects of nanomaterials in products, Exponent's scientists and engineers have many years of experience in nano-scale product manufacturing settings, including manufacturing yield enhancement, process development, materials degradation, process tooling, clean-room science and micro-contamination, defect reduction, root cause, and corrective action analysis. Our expertise in exposure and risk assessment, materials science, polymer chemistry, food safety, toxicology of novel substances, and industrial hygiene allows us to comprehensively examine the health, regulatory, and environmental exposures and consequences of product design, production, foreseeable use/misuse, wear, and disposal.

Exponent has considerable expertise in other small-scale materials that have been well studied, such as ultra-fine particles, welding fumes, and mineral fibers, which may provide insight into possible health and environmental effects of nanomaterials. The more that is understood about the factors that control material properties, exposure, and toxicity, the better scientific and engineering principles can be applied to reduce potential health and environmental risks. In addition, Exponent scientists are continually involved in nanomaterials-related initiatives, including definition, use, and potential exposures and toxicity of nanomaterials, and have been active participants in regulatory agency hearings (e.g., EPA, FDA), scientific discussions, and standards-setting committees (e.g., ANSI). The combination of high-level engineering, technological expertise, and regulatory experience at Exponent, with strong health sciences, food safety, and environmental practices, provides a complete team to evaluate the diverse issues related to nanomaterials.

Details on our expertise and project experience in nanomaterials are available at: [http://www.exponent.com/NanoParticles/#tab\\_overview](http://www.exponent.com/NanoParticles/#tab_overview)



## References

- 1 Generally defined as substances that measure 1 to 100 nanometers (nm) in any one dimension, where a nanometer is defined as  $1 \times 10^{-9}$  m.
- 2 Project for Emerging Nanotechnologies survey of advertised products containing nanotechnology (<http://www.nanotechproject.org/inventories/consumer/>).
- 3 See, for example, [www.envirosan.com/](http://www.envirosan.com/), [www.voyle.net](http://www.voyle.net), and [www.nanogreencesciences.com/](http://www.nanogreencesciences.com/).
- 4 Fullerenes with functional groups that increase their water solubility and decrease their toxicity.
- 5 The National Institute of Technology and Standards recently announced the first Standard Reference Material (SRM) 2483, "Single-Wall Carbon Nanotubes (Raw Soot)" (see <http://www.nist.gov/srm/> and [https://www-s.nist.gov/srmors/view\\_detail.cfm?srm=2483](https://www-s.nist.gov/srmors/view_detail.cfm?srm=2483)).
- 6 <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF>
- 7 <http://www.hc-sc.gc.ca/sr-sr/pubs/nano/pol-eng.php>
- 8 U.S. EPA. Undated. Concept paper for the nanoscale materials stewardship program under TSCA. Available at: <http://www.epa.gov/oppt/nano/nmsp-conceptpaper.pdf>
- 9 U.S. EPA. 2008. TSCA inventory status of nanoscale substances – general approach. U.S. Environmental Protection Agency. Available at: <http://www.epa.gov/oppt/nano/nmsp-inventorypaper2008.pdf>
- 10 FDA. 2011. Guidance for industry, considering whether an FDA-regulated product involves the application of nanotechnology. Draft Guidance. U.S. Food and Drug Administration. Rockville, MD. Available at: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm>.
- 11 See EPA's New Chemical Program website, <http://www.epa.gov/opptintr/newchems>, and specifics for nanomaterials at <http://www.epa.gov/opptintr/nano>.
- 12 TSCA Inventory Status of Nanoscale Substances – General Approach
- 13 Allotropic forms are different structures of the same element in which the atoms are bonded together in different ways. Allotropic forms of carbon include graphite in pencil lead, diamond, fullerenes, and carbon nanotubes.
- 14 <http://www.epa.gov/opptintr/nano/>
- 15 Lovell, A. 2011. Industry pushes OMB for 'clear definition' of nano in pending EPA rules. Inside EPA's Risk Policy Report 18(49): 1, 9-10.

## About Exponent Health Sciences

Exponent is a leading engineering and scientific consulting firm dedicated to providing solutions to complex problems. Exponent has one of the foremost health sciences consulting practices in the United States. Our scientists, physicians, and regulatory specialists evaluate a full range of environmental and public health issues, including potential health effects associated with environmental agents, chemicals, consumer products, food safety and nutrition, and pharmaceutical products. Our clients rely on us for incisive and objective assessments that address physical, chemical, and biological phenomena in order to arrive at solutions that can be relied upon to make important decisions. In addition, Exponent performs research and analysis in more than 90 science- and engineering-related technical disciplines.

More information about our Health practice, as well as our other capabilities, can be found at [www.exponent.com](http://www.exponent.com).

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