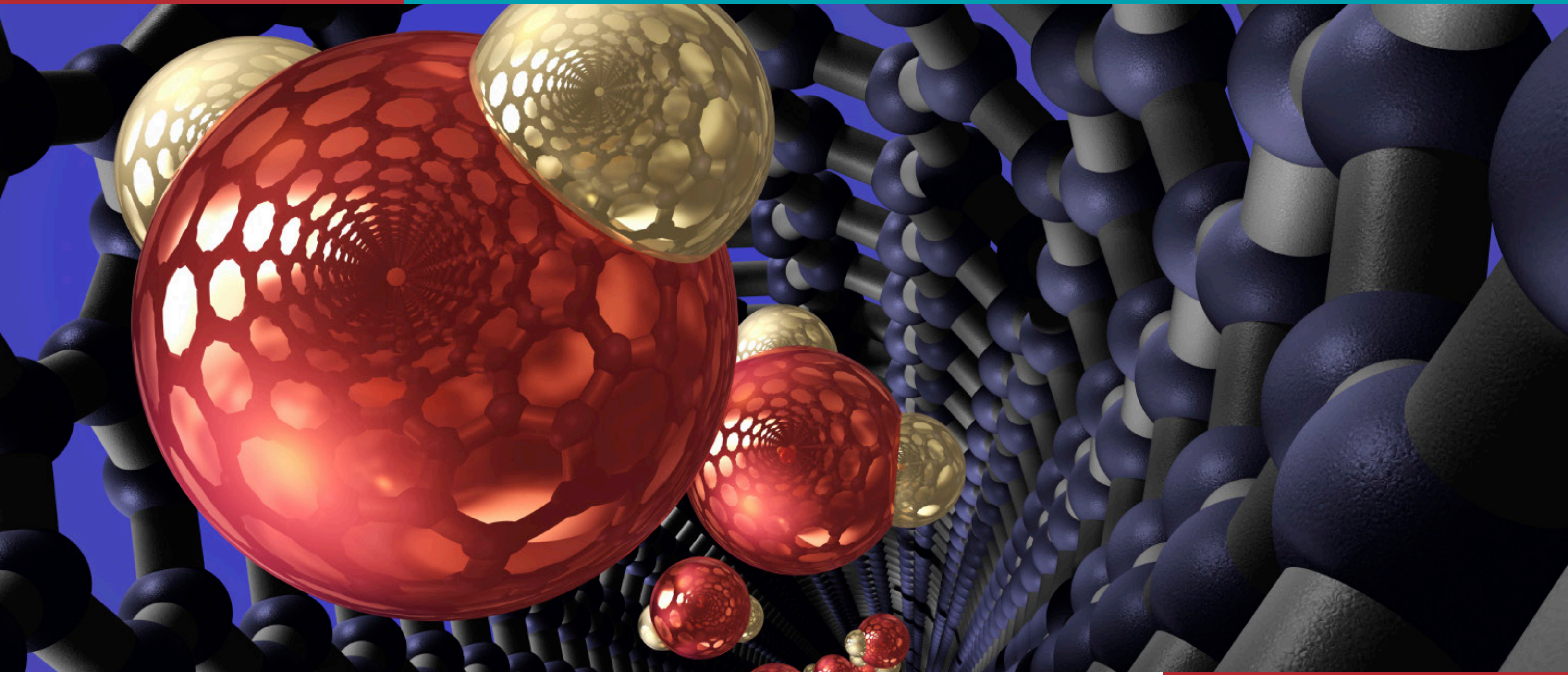
Nanotechnology and Environmental Health Laboratories:

White Paper



APRIL 2015

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES™

This publication was developed under Assistance Agreement No. 83483301 awarded by the US Environmental Protection Agency. It has not been formally reviewed by EPA. The views expressed in this document are solely those of APHL; EPA does not endorse any products or commercial services mentioned in this publication. This publication was funded 100% with federal funds; $1,000,000 in federal funds supported this program.

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Acknowledgements

The Association of Public Health Laboratories and the Environmental Laboratory Sciences Committee gratefully acknowledges the following individuals for their contributions:

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Heidi Grecsek, PerkinElmer

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Executive Summary

In 1959, Dr. Richard Feynman gave a speech to the American Physical Society titled, “There’s Plenty of Room at the Bottom.” In those remarks, Dr. Feynman suggested, “Atoms on a small scale behave like nothing on a large scale, for they satisfy the laws of quantum mechanics. So, as we go down and fiddle around with the atoms down there, we are working with different laws, and we can expect to do different things.”[1] Dr. Feynman was exactly right — materials on a small scale behave differently than their large-scale counterparts, and today, purposefully engineered nanomaterials are being used in an increasing number of materials and processes. In the decades since his speech, the “nanotechnology” industry that Dr. Feynman forecasted has emerged and developed exponentially.

This white paper provides a “primer” to public and environmental health laboratorians and professionals interested in nanotechnology. To summarize the entire field in one paper is impossible. Instead, what follows is a high-level overview of selected topics that includes references to point the reader to additional information. The paper addresses topics such as toxicity, laboratory methods, exposure, regulations and more. However, this paper only scratches the surface of the field of nanotechnology and should be viewed as a starting point only. Every day, new information, materials and experiments provide more information on the field. Readers are encouraged to find the latest information on the topic(s) of interest to develop detailed knowledge of the field.

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[1] Richard P. Feynman. 1959. There’s Plenty of Room at the Bottom. Remarks to the American Physical Society. Retrieved March 12, 2014, from http://www.pa.msu.edu/~yang/RFeynman_plentySpace.pdf.

Introduction

Unfortunately, there is no one, universally accepted definition of nanotechnology, nanomaterial or nanoscience. This paper will rely on the definition provided by the National Nanotechnology Initiative (NNI), a research collaborative comprising 20 US federal agencies: “Nanotechnology is science, engineering and technology conducted at the nanoscale, which is about 1 to 100 nanometers. Nanoscience and nanotechnology are the study and application of extremely small things and can be used across all the other science fields, such as chemistry, biology, physics, materials science and engineering.”[2] Therefore, when considering nanotechnology, note that it generally addresses purposefully-engineered particles, and is an application used across other disciplines.

A nanometer is one-billionth (10^{-9}) of a meter. For perspective, a nanometer is approximately 100,000 times smaller than the diameter of a human hair (see Figure 1).[3] Nanomaterials, then, are materials with one dimension less than 100 nanometers in length, and nanoparticles are nanomaterials with at least two dimensions less than 100 nanometers in length.

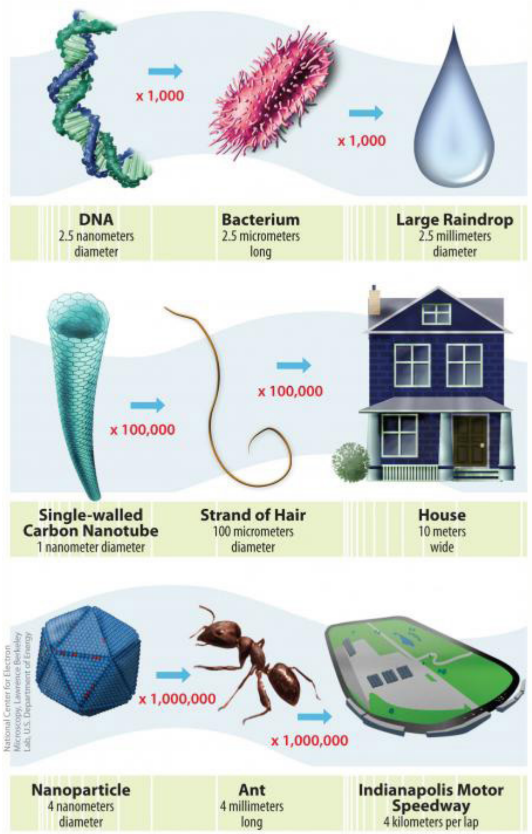

Figure 1: The Scale of Things[4]

Over a decade after Dr. Feynman’s speech (see the Executive Summary), Professor Norio Taniguchi coined the term “nanotechnology” while studying ultraprecision machining. However, it was not until 1981, with the development of the scanning tunneling microscope that scientists could “see” individual atoms, signaling the start of modern nanotechnology.[5] Nanoparticles are found everywhere — both in nature and in a variety of products. They are produced from forest fires (and other types of combustion), volcanic ash, dust storms, ocean spray, and have been found in glazes of pottery from the 9th century in Mesopotamia. These glazes are the earliest examples of man-made (or anthropogenic) nanoparticles, while the other examples are naturally-occurring.

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[2] What is Nanotechnology? National Nanotechnology Initiative. Retrieved March 11, 2014, from, http://www.nano.gov/nanotech-101/what/definition.

[3] Nanomaterials. National Institute of Environmental Health Sciences. Retrieved March 11, 2014, from https://www.niehs.nih.gov/health/topics/agents/sya-nano/.

[4] Size of the Nanoscale. National Nanotechnology Initiative. Retrieved July 8, 2014, from http://nano.gov/nanotech-101/what/nano-size.

[5] What is Nanotechnology? National Nanotechnology Initiative. Retrieved March 11, 2014, from, http://www.nano.gov/nanotech-101/what/definition.

Nanoparticles can be made from almost any type of material. Commonly used nanoparticles come from carbon, silver, titanium and silicon. "Engineered nanomaterials can be produced either by milling or lithographic etching of a large sample to obtained nanosized particles (an approach often called 'top-down'), or by assembling smaller subunits through crystal growth or chemical synthesis to grow nanoparticles of the desired size and configuration (an approach often called 'bottom-up')."[6]

The unique phenomena associated with nanoparticles result from surface area and particle size (see Figure 2). At the nanoscale, quantum effects control the properties of the particle. For example, particle size can affect the color of a suspension of nanoparticles:

> *The color of the light, based on its wavelength, will vary with the size of the nanosized crystal or the type of crystal. Smaller particles of a particular crystal emit light of shorter wavelengths (towards the blue end of the visible light spectrum) and larger particles emit light of longer wavelengths (towards the red end).*

Other properties like electrical conductivity, melting point, and chemical reactivity also change as a function of particle size. By controlling the particle size it is possible to control the properties of the material. For example, nanosize silver has antimicrobial characteristics not seen with aggregated silver particles.

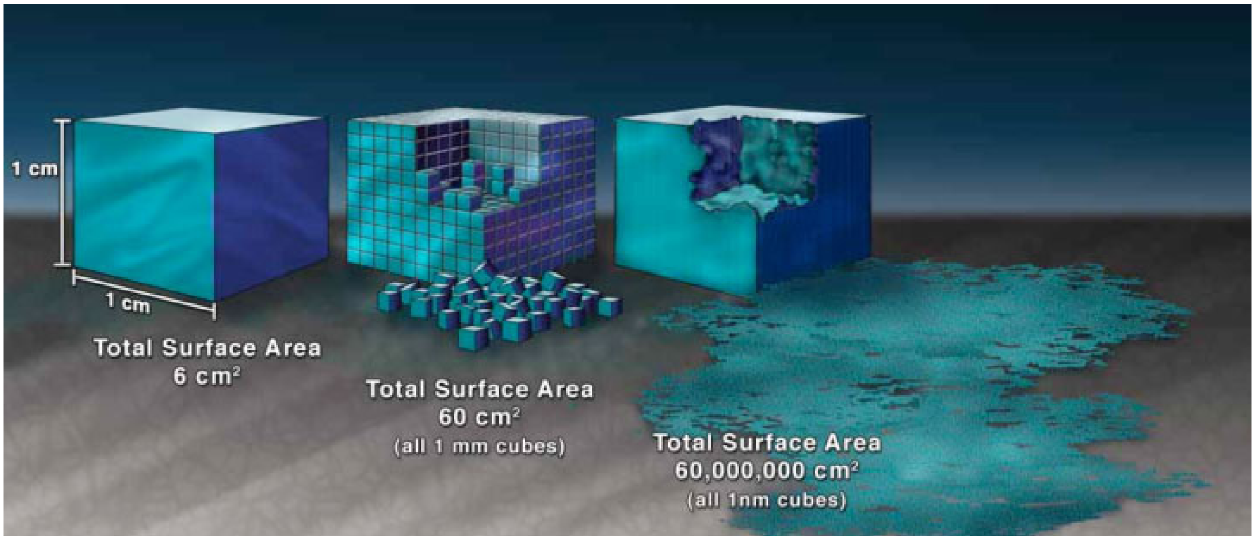

Figure 2: Surface Area of Nanomaterials[8]

As explained by the NNI:

> *Nanoscale materials have far larger surface areas than similar masses of larger-scale materials. As surface area per mass of a material increases, a greater amount of the material can come into contact with surrounding materials, thus affecting reactivity. A simple thought experiment shows why nanoparticles have phenomenally high surface areas. A solid cube of a material 1 cm on a side has 6 square centimeters of surface area, about equal to one side of half a stick of gum. But if that*

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[6] Classification, Definitions, Properties, Hazards, Risks and Toxicology of Nanoparticles and Nanotechnology. AZnano.com. Retrieved March 11, 2014, from http://www.azonano.com/article.aspx?ArticleID=1694.

[7] What's So Special About the Nanoscale. National Nanotechnology Initiative. Retrieved July 8, 2014, from http://www.nano.gov/nanotech-101/special.

> *volume of 1 cubic centimeter were filled with cubes 1 mm on a side, that would be 1,000 millimeter-sized cubes (10 x 10 x 10), each one of which has a surface area of 6 square millimeters, for a total surface area of 60 square centimeters — about the same as one side of two-thirds of a 3" x 5" note card. When the 1 cubic centimeter is filled with micrometer-sized cubes — a trillion (10^{12}) of them, each with a surface area of 6 square micrometers—the total surface area amounts to 6 square meters, or about the area of the main bathroom in an average house. And when that single cubic centimeter of volume is filled with 1-nanometer-sized cubes — 10^{21} of them, each with an area of 6 square nanometers — their total surface area comes to 6,000 square meters. In other words, a single cubic centimeter of cubic nanoparticles has a total surface area one-third larger than a football field.*[8]

Estimates predicted that nanomaterials will be a $2.4 trillion business by 2015.[9] They are found in products ranging from clothing and donuts to paints and sunscreens. Future applications may include targeted medicines, removing pollutants from water, nanoscale biochips, tissue regeneration and others not yet conceived.

The rest of this paper will provide information to help in the understanding of the public health issues surrounding nanoparticles and nanomaterials. The sections below focus on purposefully-engineered nanomaterials and not those naturally occurring (e.g. clays) or incidentally created (e.g. combustion products).

Exposure to Nanoparticles

Exposure to nanomaterials and nanoparticles can happen through a variety of routes. Known or intentional exposure can happen via the workplace, such as in factories, or through consumer products like sunscreens. Exposure may also occur unintentionally through unknown components of commercially-available items, such as food packaging, or through releases into air, soil and water. Not all routes of exposure are known at this time, and as more is learned about the mobility of nanoparticles, the number of possible routes of exposure may increase.

Consumer Products

The use of nanomaterials in consumer products is expected to dramatically increase over the next few years. This growth will have a significant impact on products found in commerce. There are currently several hundred companies in the United States alone developing or manufacturing nano-enabled products.[10] Already, a number of household products currently use nanomaterials to enhance their performance. As of 2007, the National Science

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[8] What's So Special About the Nanoscale. National Nanotechnology Initiative. Retrieved March 11, 2014, from http://www.nano.gov/nanotech-101/special.

[9] NaturalNano Expects to Benefit as Global Market for Nanotechnology-Enabled Products to Reach US$2.4 Trillion by 2015. Global Newswire. Retrieved March 5, 2014 from http://globenewswire.com/news-release/2011/05/09/446643/221320/en/NaturalNano-Expects-to-Benefit-as-Global-Market-for-Nanotechnology-Enabled-Products-to-Reach-US-2-4-Trillion-by-2015.html.

[10] EmTech Research. 2005. 2005 Nanotechnology Industry Category Overview. Ann Arbor, MI: EmTech Research (a division of Small Times Media).

Foundation estimated that up to $70 billion worth of nanotechnology-enabled products were sold in the United States annually, and that number is predicted to grow explosively.[11]

The Woodrow Wilson Center and Virginia Tech University's Project on Emerging Nanotechnologies created an inventory of nanotechnology-based consumer products: http://www.nanotechproject.org/cpi/. This inventory uses public input to identify consumer products made with or containing nanomaterials, including geographic information when available or appropriate.[12]

According to the Consumer Products Inventory developed by the Project on Emerging Nanotechnologies, there are over 1,600 manufacturer-identified products containing nanoparticles.[13] "Nanoparticles are now being used in the manufacture of scratchproof eyeglasses, crack-resistant paints, anti-graffiti coatings for walls, transparent sunscreens, stain-repellent fabrics, self-cleaning windows and ceramic coatings for solar cells. Nanoparticles can contribute to stronger, lighter, cleaner and "smarter" surfaces and systems.

Nanoparticles of titanium oxide used in sunscreens, for example, have the same chemical composition as the larger white titanium oxide particles used in conventional products for decades, but nanoscale titanium oxide is transparent, not white. Nanoparticles of antimony-tin oxide incorporated into a coating provide scratch-resistance and offer transparent protection from ultra-violet radiation, not seen with larger size particles.[14]

A recent article in the journal *Environmental Science & Technology* describes research into the effects of titanium nanoparticles in sunscreens estimated that there were about four kilograms of nanoparticles released into the water by bathers, and that the nanoparticles promoted the formation of hydrogen peroxide, which negatively impacted the phytoplankton.[15]

Public exposure to consumer products, whether intentional (such as through sunscreens or antimicrobial products) or unintentional (via coatings or sealants), may occur via various routes, including orally, dermally and through inhalation. Because of the widespread application of nanomaterials in a variety of products, it is also likely that the population exposed to nanoscale materials in consumer products is representative of the entire population, and not restricted to a particular age, sex, ethnic background or disease condition. In June 2014, the FDA released draft guidance on the use of nanomaterials in regulated products, including food and cosmetics.[16]

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[11] The future of nanotechnology: A Rice Q&A with the NSF's Mike Roco. Rice University. Retrieved March 11, 2014, from http://news.rice.edu/2007/04/04/the-future-of-nanotechnology-a-rice-qa-with-the-nsfs-mike-roco/.

[12] Nanowerk also publishes a catalog of Nanotechnology Products, Applications & Instruments available at: http://www.nanowerk.com/nanotechnology/nanomaterial/products_a.php.

[13] Project on Emerging Nanotechnologies. Consumer Products Inventory. Retrieved September 15, 2014 from, http://www.nanotechproject.org/cpi/.

[14] European Commission, Health and Consumer Protection Directorate-General. The appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies. 2006. Retrieved September 15, 2014, from http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003b.pdf.

[15] Sánchez-Quiles, D., Tovar-Sánchez, A. Sunscreens as a Source of Hydrogen Peroxide Production in Coastal Waters. Environmental Science & Technology 201448 (16), 9037-9042.

[16] US Food and Drug Administration. FDA Issues Three Final Guidances Related to Nanotechnology Applications in Regulated Products, Including Cosmetics and Food Substances. Retrieved September 15, 2014 from, http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm301093.htm.

Pharmaceutical Exposure

Potential uses for nanotechnology in the healthcare sector reside mainly in pharmaceutical applications for drug, gene and protein delivery. Basic components of cells such as DNA, RNA and proteins are of nanometer size; hence it is useful to explore how nanomaterials may interact with these biological components to influence treatment results. Important nanomaterials are polymeric nanoparticles, lipid-based systems, albumin nanoparticle, metal nanoparticles, dendrimers, nanocrystalline material, carbon nanotube, quantum dots and biological systems such as gene- and protein-based therapy.

Advancements in nanotechnology applications can address issues with current drug delivery systems. For example, one potential application is using dendrimers — globular polymeric nanostructures that can be easily tailored — for drug delivery. Dendrimers provide spherical architecture and polyvalency at the nanoscale level and are incrementally grown in approximately nanometer steps from one to over 10 nm.[17]

Dendrimers offer many unique features not found in traditional polymers, for example:[18] (a) well-defined, high density, polyvalent exo-presentation of peripheral functionality, (b) the ability to systematically introduce appropriate hemispherical/quadrant differentiated periphery group combinations to produce optimum features, (c) low viscosity and (d) nano-container properties suitable for nano-reactor or controlled release of encapsulated agents. Dendrimer nanoconstructs with controllable pharmacokinetics, drug entrapment and release rates, and targeting properties recommend them as an advanced drug-delivery system.[19] Applications utilizing nanostructures such as dendrimers in nanopharma have potential in formulation development, drug/gene delivery and targeting. Drugs can be entrapped physically by non-covalent interaction, or chemically by covalent coupling, thus solubilized for different drugs such as indomethacin, simvastatin, flurbiprofen, ibuprofen, vitamin D3, vitamin E and camptothecin.[20,21,22,23,24,25,26,27] These dendrimer-drug complexes enhance dissolution to achieve higher bioavailability.[28] The spherical architecture of dendrimers can entrap a labile drug and enhance the stability as demonstrated with resveratrol.[29]

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[17] Tomalia DA. Birth of a new macromolecular architecture: dendrimers as quantized building blocks for nanoscale synthetic polymer chemistry. Progress in Polymer Science. 2005; 30(3-4):294–324.

[18] Petersson B. Hyperbranched polymers: unique design tools for multi-property control in resin and coatings Pigment & Resin Technology. 1996; 25(4):4-14.

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[20] Asthana A, Chauhan AS, Diwan PV, Jain NK. Poly(amidoamine) (PAMAM) dendritic nanostructures for controlled site-specific delivery of acidic anti-inflammatory active ingredient. AAPS PharmSciTech. 2005; 6(3):E536-42.

[21] Chauhan AS, Diwan PV, Jain NK, Tomalia DA. Unexpected in vivo anti-inflammatory activity observed for simple, surface functionalized poly(amidoamine) dendrimers. Biomacromolecules. 2009; 10(5):1195-202.

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[23] Chauhan AS, Sridevi S, Chalasani KB, Jain AK, Jain SK, Jain NK, et al. Dendrimer-mediated transdermal delivery: enhanced bioavailability of indomethacin. Journal of controlled release : official journal of the Controlled Release Society. 2003;90(3):335-43. Epub 2003/07/26. PubMed PMID: 12880700.

[24] Chauhan AS, Svenson S. Formulations Containing Hybrid Dendrimers. 2007:WO/2007/149500.

[25] Chauhan AS, Svenson S, Reyna L, D.A. T. Solubility enhancement propensity of PAMAM nanoconstructs Materials Matters- Nanomaterials issue. 2007;2: 24-6.

[26] Kulhari H, Pooja D, Prajapati SK, Chauhan AS. Performance evaluation of PAMAM dendrimer based simvastatin formulations. International journal of pharmaceutics. 2011;405(1-2):203-9.

[27] Svenson S, Chauhan AS. Dendrimers for enhanced drug solubilization. Nanomedicine (Lond). 2008;3(5):679-702. Epub 2008/09/27.

[28] Gu L, Wu Z, Qi X, He H, Ma X, Chou X, et al. Polyamidomine dendrimers: an excellent drug carrier for improving the solubility and bioavailability of puerarin. Pharmaceutical development and technology. 2013;18(5):1051-7.

[29] Chauhan AS, Gerhardt, A.G., Newenhouse, E. Dendrimer Nanostructure Based Resveratrol Formulations. USPTO. 2013;US Provisional Patent 61959344.

Finally, physicians are able to use targeted medicine to treat infections such as Methicillin-resistant *Staphylococcus aureus* (MRSA)[30] and chronic illnesses such as cancer[31,32] on the cellular and subcellular levels. Information surrounding potential toxicity of these particular nanoparticles has been limited to date.[33]

Toxicity

As nanotechnology becomes more pervasive in day-to-day life, it raises concerns regarding the potentially-toxic effects on human and environmental health. Many federal agencies are working on answering this question. The Centers for Disease Control and Prevention (CDC), through its National Institute for Occupational Safety and Health (NIOSH), dedicates a website to those that produce and use nanotechnology.[34] The Occupational Safety and Health Administration (OSHA) recognizes the new-ness of the field and the potential effects of exposure as not yet fully understood; for now, they direct individuals to what standards currently apply (the general industry standard). The Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), the United States Department of Agriculture (USDA), and the United States Geological Survey (USGS) are some of the other agencies attempting to address concerns related to the effects of exposure to nanotechnology on humans and the environment. Regulatory information from selected agencies is included in Section 7.

Human Health Toxicity

Concerns related to the human health impacts of nanoparticles range from minimal to significant. In some cases, no two resources provide the same perspective on this topic. And while a number of agencies are evaluating the impact of nanoparticles on humans and the environment, to date their full toxicological impact remains unclear.

Nanomaterials can permeate transdermal routes due to their small size and possibly through interactions with the dermal components such as fat and proteins. Moreover these tiny substances can be exposed to internal mucosal membranes via nose, eye or mouth. Their small size can help them enter respiratory systems, including the lungs. Research on carbon nanotubes and their structure indicates that they behave similar to asbestos, leading to concerns regarding the toxicological effects on humans, specifically mesothelioma.[35]

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[30] Smith, Abbie. 2012. Treating MRSA with nanotechnology and nanomedicine. Global Healthcare. Retrieved March 11, 2014 from http://www.healthcareglobal.com/healthcare_technology/treating-mrsa-with-nanotechnology-and-nanomedicine.

[31] Nanotechnology. National Cancer Institute at the National Institutes of Health. Retrieved March 11, 2014 from http://www.cancer.gov/researchandfunding/extramural/cancercenters/accomplishments/nanotechnology.

[32] NCI Alliance for Nanotechnology in Cancer. National Cancer Institute Alliance for Nanotechnology in Cancer. Retrieved March 11, 2014 from http://nano.cancer.gov.

[33] Maynard, Robert L. 2012. Nano-technology and nano-toxicology. Journal of Emerging Threats. Retrieved March 11, 2014 from http://www.eht-journal.net/index.php/ehtj/article/view/17508/22521.

[34] Nanotechnology. CDC. Retrieved March 12, 2014, from http://www.cdc.gov/niosh/topics/nanotech/.

[35] Poland, Craig A., Duffin, Rodger, et al. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. Nature Nanotechnology 3, 423-428 (2008). Retrieved February 14, 2014 from http://www.nature.com/nnano/journal/v3/n7/abs/nnano.2008.111.html.

Other nanoparticles may show physiological toxicity as they can cross physiological barriers[36] including the blood-brain barrier[37] and placental barrier.[38]

A recent study from MIT and the Harvard School of Public Health presents evidence that some nanoparticles can negatively impact DNA. The researchers focused on silver, zinc oxide, iron oxide, cerium oxide and silicon dioxide using a high-throughput DNA screening assay.[39] The actual effects in the body are difficult to determine because of the complexity of biological systems.[40]

Environmental Toxicity

Nanotechnology is a double-edged sword for the environment. On the one hand, it can possibly harm environments due to unknown properties of, and interactions by, nanomaterials in nature. Nanoparticles can form different kinds of molecular assembly units depending upon the environment, and can easily leach from containment and cause harm to ecosystems. For example, nanomaterials may be small enough to pass through landfill liners and into underlying soil and water.

A report in *Nature* indicates that buckyballs (carbon-60 nanospheres) can travel through soil, and are available for uptake by earthworms. Such availability may help these nanoparticles gain access to higher orders and humans.[41]

Moreover, some nanoparticles can be easily made airborne and adhere to surfaces; this elevates the chances of toxicity to humans and the environment. Studies show that exposures to on-road particle mixtures have negative impacts on the pulmonary and cardiovascular system in compromised, older rats.[42,43] Studies also suggest that engineered nanoparticles accumulate in the organs of laboratory animals, are taken up by cells and have potential to get into food sources.[44] Researchers from NASA and the DuPont Haskell

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[36] Hogan, J. 2003. How safe is nanotech? Special Report on Nano Pollution, New Scientist, Vol. 177, No. 2388, p. 14.

[37] Nano's Troubled Waters: The Latest toxic warning shows nanoparticles cause brain damage in aquatic species and highlights need for a moratorium on the release of new nanoparticles. 2004. ETC Group. Retrieved March 12, 2014, from http://online.sfsu.edu/rone/Nanotech/nanobraindamage.htm. See also, Nano-Devices that Cross Blood-Brain Barrier Open Door to Treatment of Cerebral Palso, Other Neuologic Disorders: Studies in rabbits hold promise for people. 2012. Nanotechnology Now. Retrieved March 12, 2014, from http://www.nanotech-now.com/news.cgi?story_id=44990.

[38] Wick, P., Malek, A., Manser, P., Meili, D., Maeder-Althaus, X., Diener, L., Diener, P., Sizch, A., Krug, H., von Mandach, U. Barrier Capacity of Human Placenta for Nanosized Materials. 2009. Environ Health Perspect. Mar 2010; 118(3): 432–436. Retrieved March 12, 2014 from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2854775/. See also, Keelan, J. Nanotoxicology: Nanoparticles versus the placenta. 2011. Nature Nanotechnology 6, 263–264 (2011). Retrieved March 12, 2014, from http://www.nature.com/nnano/journal/v6/n5/full/nnano.2011.65.html.

[39] Ge, J., Cohen, J., Pyrgiotakis, G., Engelward, B.P., Demokritou, P. High-Throughput Screening Platform for Engineered Nanoparticle-Mediated Genotoxicity Using CometChip Technology, Christa Watson. ACS Nano20148 (3), 2118-2133.

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http://www.sciencedirect.com/science/article/pii/S0300483X11004872.

[41] Brumfiel, G. 2003. A Little Knowledge...,. Nature, Vol. 424, no. 6946, 17 July 2003, p. 246.

[42] Elder, A.; Gelein, R.; Finkelstein, J.; Phipps, R.; Frampton, M.; Utell, M.; Kittelson, D.; Watts, W.; Hopke, P.; Jeong, C.-H.; Kim, E.; Liu, W.; Zhao, W.; Zhuo, L.; Vincent, R.; Kumarathasan, P.; Oberdörster, G. Exposures of Aged, Compromised Rats. Inhalation Toxicology, Volume 16, Supplement 1 to issue 1, Supplement 1/2004, pp. 41-53(13).

[43] D. Kittelson; W. Watts; J. Johnson; M. Remerowk; E. Ische; G. Oberdörster; R. Gelein; A. Elder; P. Hopke; E. Kim; W. Zhao; L. Zhou; C.-H. Jeong. On-Road Exposure to Highway Aerosols, 1. Aerosol and Gas Measurements. Inhalation Toxicology, Volume 16, Supplement 1 to issue 1, Supplement 1/2004, pp. 31-39(9).

[44] Brown, D. 2002. Nano litterbugs? Experts See Potential Pollution Problems. Small Times Magazine. March 15, 2002. Retrieved March 11, 2014 from http://online.sfsu.edu/rone/Nanotech/NANO%20LITTERBUGS.htm

laboratory reported that the effects of nanotubes on the lungs of rats produced a more toxic response than quartz dust.[45]

Paradoxically, nanoparticles can be useful to the environment, for example iron nanoparticles that effectively detoxify a wide variety of common environmental contaminants, such as chlorinated organic solvents, organochlorine pesticides and PCBs from groundwater.[46] Similarly, nanomaterials show promise for water and air filtration using thin film polymers or metals.[47]

Nanomaterial Toxicity Management

Nanomaterial toxicity can be managed by (1) predicting the hazard of the nanomaterial through existing knowledge; (2) using materials with less hazardous properties; (3) curtailing exposure of hazardous material; and (4) safer disposal of nanomaterials.[48] The EPA presented a white paper for future regulation of nanotechnology, and promotes pollution prevention and identification of new nanotechnologies to support environmentally-beneficial approaches such as green energy and green manufacturing.[49] Recently EPA issued a proposed rule to require reporting and recordkeeping on certain chemical substances when they are manufactured or processed as nanoscale materials.[50]

EPA encourages research on identification and detection of nanomaterials along with an assessment of its effect on human and ecological conditions. Existing nanomaterials should be extensively studied to develop a tool for risk assessment.[51] A cross-EPA research group fosters information sharing on nanotechnology science and policy issues.[52] Adequate nanotechnology training activities for scientists and experts are critical to understanding nanotoxicity issues and addressing mitigation efforts.

Toxicity Modeling and Bioaccumulation

There is limited information on the impacts of nanomaterials on ecologically-relevant species. In order to predict the potential impact of nanomaterials on the environment, there needs to be a biological modeling approach that examines the properties of natural and artificial nanomaterials that have toxic potential to impact populations. While researchers use different modeling systems, the toxicity of a variety of nanomaterials on the aquatic model species *Daphnia sp.* helps to make predictions about the impact of current and

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[45] Hogan, J. 2003. How safe is nanotech? Special Report on Nano Pollution, New Scientist, Vol. 177, No. 2388, p. 14.

[46] Zhang, W. Nanoscale Iron Particles for Environmental Remediation: An Overview. Journal of Nanoparticle Research. Issue: Volume 5, Numbers 3-4 , pp. 323 - 332.

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[48] Gibbs, L. 2004. Nanotechnology: Safety and risk management overview (presentation). Retrieved March 11, 2014, from http://www.nnin.org/sites/default/files/people/Lawrence%20Gibbs.pdf.

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[51] Nanotechnology & Nanomaterials Research. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/oppt/nano/.

[52] Research Coordination Team. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/nanoscience/rp_leads.htm.

future nanomaterials. These studies show that nanomaterial core structure influences toxicity: smaller particles tend to be more toxic than larger aggregates found in the complex environmental matrices.[53]

One of the key factors in determining the potential toxicity of nanomaterials is the extent to which these particles reach tissues within an organism and accumulate. Recent studies examined the uptake and release of gold particles in the filter feeder microbial model systems. Health exposure and toxicity is associated with the time of retention in biological systems and clearance of the particle from the gut. While the sublethal impacts of nanomaterials are as or more important than their toxicity, certain nanomaterials have a greater influence on the behavior of critical freshwater invertebrates. The extent of the impact of nanomaterial on behavior and physiology is influenced by the chemical structure and composition of the nanomaterial.[54]

Studies of the response of immune systems to nanomaterials may provide an understanding of how these materials can affect the biology of an organism. Recent studies assessing the immune reaction of aquatic vertebrates to *in vitro* exposure of macrophages to engineered nanomaterials showed feasibility of such physiological models in fish species native to the US. The outcome of such studies may create a mechanism to test other types of nanomaterials by developing immunological testing procedures, including the development of genomic biomarkers, to evaluate the exposure effects.[55]

Ecological Impacts

Nanoparticles may impact environmental and ecological systems through adsorption, entrapment, aggregation, complexation, degradation, reactivity and mobility into other environmental compartments. The lack of available information on the potential health and environmental risks of nanomaterials is being addressed by a number of organizations, including the National Science Foundation, EPA and academic researchers. For example, the Nanotechnology in City Environments (NICE) program at Arizona State University's Center for Nanotechnology in Society is investigating using gold nanoparticles to detect methylmercury in water and fish.[56]

Water

Wastewater

It is not surprising that nanoparticles used in consumer products will end up in wastewater. A review article in *Environmental Science: Processes and Impacts* indicates that most of the nanoparticles in wastewater will end up in the sludge, which is then disposed in landfills. Residual nanoparticle concentration will be in the tens of parts per billion range for

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[53] Lovern, S, Klaper, R. 2006. Daphnia magna mortality when exposed to titanium dioxide and fullerene nanoparticles. Environmental Toxicology and Chemistry. Volume 25 (4): 1132-1137.

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[55] Laboratory of Dr. Rebecca Klaper. School of Freshwater Sciences. Retrieved March 11, 2014, from http://home.freshwater.uwm.edu/klaperlab/environmental-implications-of-nanotechnology.

[56] Detecting Methylmercury in Water and Fish with Gold Nanoparticle Sensors. Center for Nanotechnology in Society, Arizona State University. Retrieved March 26, 2014 from http://nice.asu.edu/nano/detecting-methylmercury-water-and-fish-gold-nanoparticle-sensors.

treated wastewater, and in the parts per million range in the sludge.[57] The paper goes on to explain, "…the effect of metallic and metal oxide [nanoparticles (NPs)] on waste/wastewater treatment and sludge digestion is highly dependent on aerobic and anaerobic conditions."[58]

Much work has been done on the fate of silver nanoparticles, and work by Doolette, et al indicates that:

> *Silver NPs were transformed to Ag-S phases during activated sludge treatment (prior to anaerobic digestion). Transformed AgNPs, at predicted future Ag wastewater concentrations, did not affect nitrification or methanogenesis. Consequently, AgNPs are very unlikely to affect the efficient functioning of wastewater treatment plants. However, AgNPs may negatively affect sub-dominant wastewater microbial communities.*[59]

The Water Environment Research Foundation also has information available on the effects of silver nanoparticles on wastewater treatment.[60] Similar work has been done on copper nanoparticles and activated sludge. Chen, et al show that high concentrations of copper nanoparticles (30 to 50 ppm) increase surface charge and decrease hydrophobicity, thereby reducing floc formation.[61]

Finally, nanoparticles can also be used in wastewater treatment.[62,63,64] Nanoscale zero-valent iron is effective in removing classes of pollutants like bacteria, metals and organic compounds. The instability of iron in the zero oxidation state causes it to be very effective as a reducing agent.[65] There is innovative research about the use of magnetic nanoparticles in wastewater treatment for removal of metals[66] and other contaminants.[67] Although silver nanoparticles raise some toxicity concerns, there are also applications in wastewater treatment.[68]

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[57] Yang, Z. and Hu. 2013. Impact of Metallic and Metal Oxide Nanoparticles on Wastewater Treatment and Anaerobic Digestion. Environ. Sci.: Processes Impacts, 2013, 15, 39, retrieved 8/12/14 from http://pubs.rsc.org/en/content/pdf/article/2013/em/c2em30655g DOI: 10.1039/c2em30655g.

[58] Ibid, p. 45.

[59] Doolette et al. 2013. Transformation of PVP coated silver nanoparticles in a simulated wastewater treatment process and the effect on microbial communities. Chemistry Central Journal. 2013, 7:46, retrieved 8/12/14 from http://journal.chemistrycentral.com/content/7/1/46.

[60] Water Environment Research Foundation. Identifying the Effects of Silver Nanoparticles on Wastewater Treatment. Retrieved August 22, 2014 from http://ww2.werf.org/AM/Template.cfm?Section=Home&TEMPLATE=/CM/ContentDisplay.cfm&CONTENTID=17761.

[61] Chen, H., Zheng, X., Chen, Y., Li, M., Liu, K., et al. 2014. Influence of Copper Nanoparticles on the Physical-Chemical Properties of Activated Sludge. PLoS ONE 9(3): e92871. doi:10.1371/journal.pone.0092871 Retrieved August 12, 2014 from http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0092871.

[62] Future Medicine. Applications of Nanoparticles for Water Quality. 2013. doi: 10.4155/9781909453074, eISBN (PDF): 978-1-909453-07-4. Retrieved August 12, 2014 from http://www.futuremedicine.com/doi/book/10.4155/9781909453074.

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[67] Lakshmanan, R. Application of Magnetic nanoparticles and reactive filter materials for wastewater treatment. 2013. Retrieved August 12, 2014 from http://www.diva-portal.org/smash/get/diva2:665773/FULLTEXT01.pdf.

[68] Daniel, S.C.G. K., Malathi, S., Balasubramanian, S., Sivakumar, M. and Sironmani, T. A. Multifunctional Silver, Copper and Zero Valent Iron Metallic Nanoparticles for Wastewater Treatment, in Application of Nanotechnology in Water Research (ed

Drinking Water

Water treatment is one of the main strategies to prevent the ingestion of harmful contaminants, including nanoparticles, from drinking water.[69] Drinking water treatment provides a barrier to contaminant exposure via ingestion of drinking water. However, the occurrence of nanoparticle breakthrough into finished water after traditional coagulation/flocculation/sedimentation and membrane filtration is likely to happen as larger industries dispose of nanoparticle-containing products. Neither of which is typically the case for naturally-occurring nanoparticles.

The EPA sets guidelines for the total organic carbon (TOC) removal by coagulation based on initial TOC and alkalinity to monitor effective drinking water treatment for natural organic material (NOM) removal.[70] Water treatment plants use turbidity and TOC as surrogate measures for NOM and contaminant removal. The use of low-pressure membrane (LPM) filtration was found to be efficient over traditional treatment.[71] The Comprehensive Environmental Assessment (CEA) approach used by EPA includes a product life-cycle perspective with the risk assessment allowing an estimate of the fate and transport processes, exposure-dose characterization, and indirect as well as direct ecological and human health impacts due to water-mediated nanoparticle exposure.[72] Future routine monitoring of nanoparticles in public water system (source and finished water) by available analytical methods in the public health laboratories (PHLs) would allow timely identification, estimate concentration, risk assessment and intervention strategies for nanoparticle exposure in humans, plants and animals.

Ingestion of nanoparticles via drinking water may pose a potential direct effect on human health or an indirect risk due to release of metal ions from the nanoparticles. Human exposure to metal nanoparticles or metal nanoparticle ions via ingestion of drinking water can result in adverse effects including kidney damage, increased blood pressure, gastrointestinal inflammation, neurological damage and cancer.[73,74] Cell uptake, cytotoxicity, and DNA damage due to nanoparticle exposure have also been reported during in vitro nanoparticle studies.[75,76,77] While the ingestion of metal nanoparticles has also been reported to lead to DNA damage, the consequences of increased metal burdens, DNA damage and liver toxicity are not yet fully understood.[78]

A. K. Mishra). 2014. doi: 10.1002/9781118939314.ch15. Retrieved August 12, 2014 from http://onlinelibrary.wiley.com/doi/10.1002/9781118939314.ch15/summary.

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[72] US Environmental Protection Agency. 2012. Research to Support Comprehensive Environmental Assessments of Nanomaterials. Retrieved October 24, 2014, from http://www.epa.gov/nanoscience/quickfinder/risks.htm.

[73] US Environmental Protection Agency. 2013. Drinking Water Contaminants. Retrieved June 17, 2013, from http://water.epa.gov/drink/contaminants/index.cfm#List.

[74] Abbott Chalew TE, Schwab KJ. 2013. Toxicity of commercially available engineered nanoparticles to Caco-2 and SW480 human intestinal epithelial cells. Cell Biol Toxicol 29(2):101–116.

[75] Abbott Chalew TE, Schwab KJ. 2013. Toxicity of commercially available engineered nanoparticles to Caco-2 and SW480 human intestinal epithelial cells. Cell Biol Toxicol 29(2):101–116.

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[78] Sharma, V., Singh, P., Pandey, A.K., Dhawan, A. 2012. Induction of oxidative stress, DNA damage and apoptosis in mouse

Surface Water

Like drinking water and wastewater, the impacts of nanomaterials on surface water are largely unknown. Nanomaterials have several pathways for entering surface water systems, including runoff from soil applications (see below), discharges from wastewater systems (see above), and direct discharge and disposal from industrial sites and consumer products. Once released into water, nanomaterials can undergo a number of transformations, including degradations, agglomerations and dissolution, among others.[79]

Unfortunately, the fate and transport, and consequently the resulting toxicity of nanomaterials in water are not well understood at this time. Researchers understand that most metal-nanoparticles are hydrophilic, but have low solubility. But, other hydrophobic materials, such as carbon nanotubes and fullerenes, do not dissolve so much as form stabilized suspensions.[80] Moreover, predictions concerning toxicity and water interactions are complicated further when accounting for surface coatings.[81]

Most believe that nanomaterials will affect all levels of aquatic organisms from coating algae to accumulating in the respiratory systems of vertebrates. Additionally, untreated nanomaterials are "likely to accumulate in benthic sediments," an additional area of research need.[82]

Modeling predicts high-volume production nanomaterials at the following concentrations in surface water following expected fate under natural conditions:[83]

• Silver (Ag)	0.088-10,000 ng/L
• Titanium Dioxide (TiO_2)	21-10,000 ng/L
• Zinc Oxide (ZnO)	1-10,000 ng/L
• Carbon-based (nanotubes/fullerenes)	0.001-0.8 ng/L

The wide range associated with the predictive concentrations is due largely to transformations that individual particles may undergo as well as the complex environmental matrices that may be encountered in various aquatic systems.[84] As other nanomaterials move into high-volume production, this list may need to be expanded as research dictates. For detecting nanomaterials in water, light-scattering techniques are the most common methods.[85]

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liver after sub-acute oral exposure to zinc oxide nanoparticles. Mutat Res 745(1–2):84–91.

[79] Batley, G., Kirby, J., McLaughlin, M. Fate and Risks of Nanomaterials in Aquatic and Terrestrial Environments. Accounts of Chemical Research. 854-862:2013 Vol. 46, No. 3.

[80] Batley, G., Kirby, J., McLaughlin, M. Fate and Risks of Nanomaterials in Aquatic and Terrestrial Environments. Accounts of Chemical Research. 854-862:2013 Vol. 46, No. 3.

[81] Batley, G., Kirby, J., McLaughlin, M. Fate and Risks of Nanomaterials in Aquatic and Terrestrial Environments. Accounts of Chemical Research. 854-862:2013 Vol. 46, No. 3. Of particular note, a Center for Environmental Implications of Nanotechnology (CEINT) operates at each of Duke University (http://www.ceint.duke.edu/) and the University of California Los Angeles (http://www.cein.ucla.edu/new/index.php) to study these and related issues.

[82] Batley, G., Kirby, J., McLaughlin, M. Fate and Risks of Nanomaterials in Aquatic and Terrestrial Environments. Accounts of Chemical Research. 854-862:2013 Vol. 46, No. 3.

[83] Maurer-Jones, M.A., Gunsolus, I.L., Murphy, C.J., Haynes, C.L. Toxicity of Engineered Nanoparticles in the Environment. Anal. Chem. 2013, 85, 3036-3049.

[84] Maurer-Jones, M.A., Gunsolus, I.L., Murphy, C.J., Haynes, C.L. Toxicity of Engineered Nanoparticles in the Environment. Anal. Chem. 2013, 85, 3036-3049.

[85] Maurer-Jones, M.A., Gunsolus, I.L., Murphy, C.J., Haynes, C.L. Toxicity of Engineered Nanoparticles in the Environment. Anal. Chem. 2013, 85, 3036-3049.

However, like in soil, drinking water and wastewater, nanomaterials are showing beneficial uses. For example, anchoring nano-valent iron onto materials such as carbon, silica gel and other membranes shows potential for remediating polluted stream systems.[86] Additionally, nanofilm reactors show similar promise with water remediation of methyl tert-butyl ether (MTBE).[87]

Plants and Soil

Several recent publications attempt to characterize the interactions between terrestrial plants and engineered nanomaterials. Many of these studies explore the implications of nanomaterial absorption, translocation, accumulation and biotransformation within plants and specifically food crops.[88]

Collectively, this rapidly-growing literature demonstrates that nanomaterials can exert either positive or negative effects on terrestrial plants at the physiological, biochemical and genetic level.[89] Much of this literature evaluates nanomaterial effects on photosynthesis, oxidative stress/antioxidative enzyme activity, radical scavenging, gene expression and biomolecule (DNA, protein, carbohydrates, fatty acid, lignin) modification within plants. A major shortcoming with the existing knowledge base is the fact that much of the work conducted to date focuses on short exposures during germination or early growth stages. There is a near complete lack of understanding of the long-term risks and benefits associated with nanomaterial exposure and use. With only 30 published studies on fully mature plants, important questions on the long-term effects of nanomaterial in plants remain unknown.[90]

Exposure Pathways for Plants

There are a number of pathways that expose plants to nanomaterials. The primary pathway is the application of biosolids, which are rich in organic matter and nutrients, as an agricultural amendment. About 60% of the biosolids produced in the US are applied on more than 70 million acres of agricultural fields. Biosolids contain nanomaterials; up to 45% of the nanomaterial entering wastewater treatment facilities may result from biosolid application to soil.[91] Given the nature of repeated applications in agricultural settings, nanomaterial accumulation in soil over time is a concern.

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[86] Nowack, B., Becheli, T. Occurrence, behavior and effects of nanoparticles in the environment. Environmental Pollution, 150 (2007) 5-22.

[87] Nowack, B., Becheli, T. Occurrence, behavior and effects of nanoparticles in the environment. Environmental Pollution, 150 (2007) 5-22.

[88] Ma, X.; Geiser-Lee, J.; Deng, Y.; Kolmakov, A. 2010. Interactions between engineered nanoparticles (ENPs) and plants: phytotoxicity, uptake and accumulation. Sci. Total Environ. 408:3053-3061. Rico, C. M.; Majumdar, S.; Duarte-Gardea, M.; Peralta-Videa, J. R.; Gardea-Torresdey, J. L. 2011. Interaction of nanoparticles with edible plants and their possible implications in the food chain. J. Agric. Food Chem. 59:3485-3498. Miralles, P.; Church, T. L. Harris, A.T. 2012. Toxicity, uptake, and translocation of engineered nanomaterials in vascular plants. Environ. Sci. Technol. 46:9224-9239. Remedios, C.; Rosario, F.; Bastos, V. 2012. Environmental nanoparticles interactions with plants: morphological, physiological, and genotoxic aspects. J. Bot. doi:10.1155/2012/751686. Gardea-Torresdey, J.L.; Rico, C.M.; White, J.C. 2014. Trophic transfer, transformation, and impact of engineered nanomaterials in terrestrial environments. Environ. Sci. Technol. 48:2526–2540.

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[91] Keller, A. A.; Lazareva, A. 2013. Predicted releases of engineered nanomaterials: from global to regional to local. Environ. Sci. Technol. Lett. dx.doi.org/10.1021/ez400106t.

A second significant exposure pathway involves nano-containing agrichemicals such as pesticides, fertilizers and other soil amendments. Collectively, these products often offer improved crop yield and reduced cost.[92] The application of nanotechnology in agriculture is particularly attractive to developing countries because of the potential to enhance soil fertility and yield, thereby adding to efforts combatting hunger, malnutrition and child mortality.

A third nanomaterial exposure pathway for plants is through the soil remediation approaches based on nanotechnologies. For example, nano-zero-valent iron is effective for the remediation of several organic and inorganic pollutants.[93] Additional routes by which plants may be exposed to nanomaterial include atmospheric deposition, spillage, wastewater reuse and surface runoff.

Nanomaterial Accumulation in Plants

While exposure to nanomaterials may have direct phytotoxic effects on plants, the public health-related concern from these effects is likely minimal. However, the accumulation of nanomaterial from soils or other media into plant tissues, followed by intra-plant translocation to various vegetative, edible and reproductive structures is of significant concern. In fact, one relatively consistent finding when reviewing the literature on plant-nanomaterial interactions is the significantly greater levels of element accumulation observed in plants when exposure is in nanoparticle form.

For example, silver nanoparticle accumulation in zucchini shoots was nearly five-times greater than with equivalent bulk (non-nano) particles.[94] Similar findings were observed with soybean exposed to silver.[95] Dozens of other studies report similar findings. Unfortunately, the accumulation and translocation of carbon nanomaterials, such as fullerenes, multi-/single-wall carbon nanotubes or graphene nanostructures, remains largely unexplored, due primarily to the lack of adequate analytical tools to characterize nanomaterial presence. The few existing studies that are available report somewhat contradictory findings on topics such as uptake and transfer, edible/reproductive tissues and complete exclusion from plant tissues.[96] Scientists' understanding of nanomaterial uptake and disposition within plants is an active area of research. Similarly, science needs a mechanistic understanding of the key processes under realistic exposure scenarios.

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[92] Gogos, A., Knauer, K., and Bucheli, T.D. 2012. Nanomaterials in plant protection and fertilization: Current state, foreseen applications, and research priorities. J. Agric. Food Chem. 60:9781-9792.

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[96] Gardea-Torresdey, J.L.; Rico, C.M.; White, J.C. 2014. Trophic transfer, transformation, and impact of engineered nanomaterials in terrestrial environments. Environ. Sci. Technol. 48:2526–2540.

Trophic Transfer

A primary concern with nanomaterial fate and effects is the potential for biomagnification in food chains that may include humans (see Figure 3). In spite of this fundamental concern, very few studies address the potential trophic transfer of nanomaterial under environmentally-relevant conditions.[97]

Figure 3: Trophic Transfer in the Food Chain

One group in Kentucky published three papers on the trophic transfer of nanoparticle silver in several food chains.[98] Two of the studies reported both trophic transfer and biomagnification; the third reported 100-fold decreases in silver content along the food chain. Preliminary work at the Connecticut Agricultural Experiment Station (CAES) suggests similar variability in the transfer of select metal oxide nanoparticles. Collectively, although these findings are far from conclusive, the results demonstrate the potential and perhaps probable trophic transfer of nanomaterials in terrestrial systems. They raise the likelihood of human exposure through dietary uptake as an issue in need of rapid and intense investigation.

Secondary Effects in Soil & Plants

Nanomaterials may also have secondary or indirect effects that could subsequently compromise public health. For example, work at CAES shows that exposure to nanomaterials such as fullerenes, functionalized and non-functionalized nanotubes, and silver may significantly alter the availability and accumulation of co-contaminants such as weathered organochlorine pesticide residues.[99] Although some nanomaterials seem to reduce uptake into plants, others seem to actively promote contaminant uptake and translocation. Another important aspect of nanomaterial-plant interactions involves the responses of important soil or endophytic bacteria to nanomaterial exposure and how that may influence important symbioses.[100] Separately, the impact of nanomaterial on the nutrient content of edible plant tissues is largely unknown. However, a handful of studies conducted under varied conditions has shown that nanomaterial exposure may alter protein, carbohydrate, fatty acid, phenol and lignin content of select crops.

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[97] Gardea-Torresdey, J.L.; Rico, C.M.; White, J.C. 2014. Trophic transfer, transformation, and impact of engineered nanomaterials in terrestrial environments. Environ. Sci. Technol. 48:2526–2540.

[98] Judy, J. D.; Unrine, J. M.; Rao, W.; Bertsch, P. M. 2012. Bioaccumulation of gold nanomaterials by Manduca sexta through dietary uptake of surface contaminated plant tissue. Environ. Sci. Technol. 46:12672-12678.

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Needs Related to Plants and Soil

Although it is clear that food crops may be exposed to and impacted by nanomaterial exposure, there is very limited understanding of the extent of nanomaterial accumulation in food and the resulting implications on human health. Several important gaps exist:[101]

- Predictive quantitative models that can accurately describe nanomaterial fate and disposition within agricultural soils
- Development of assessment assays that can accommodate the unique nature of nanoparticles
- Nanomaterial evaluation with a focus on actual particles and formulations that will or already are seeing widespread use in consumer products and agriculture
- Long-term exposure investigations into nanomaterial-interactions with plants under different conditions (e.g. concentration, media, duration/frequency of application)
- Evaluation of the potential for nanomaterial trophic transfer within terrestrial food chains
- Characterization of important secondary and indirect effects on plants from nanomaterial exposure

Air

Overall, natural and incidental sources produce nanoparticles that appear in both the ambient and indoor air environment; that is to say, purposefully-engineered nanoparticles are not typically used in atmospheric applications. Road traffic is a major source of carbon or soot particles as exhaust is released from gasoline internal combustion engines, diesel engines and as non-exhaust emissions result from tire degradation, brake linings and catalytic converters. Stationary sources such as incinerators and power plants burning natural gas, oil or coal also emit nanoparticles into the atmosphere during combustion. Volcanic eruptions, forest fires, soil dust, sea salt from tide action and plant pollen all produce or contain nanoparticles. Nanoparticles in the atmosphere exist as a combination of carbon, minerals, metals and salts, ice, acids including sulfuric and nitric, viruses and pollen.[102,103,104,105]

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[101] Gardea-Torresdey, J.L.; Rico, C.M.; White, J.C. 2014. Trophic transfer, transformation, and impact of engineered nanomaterials in terrestrial environments. Environ. Sci. Technol. 48:2526–2540.

[102] Biswas, P. and Wu, C-Y. Nanoparticles and the Environment. Journal of the Air and Waste Management Association, 2005, 55, 708-746.

[103] Nowack, B., and Bucheli, T.D. Review Occurrence, behavior and effects of nanoparticles in the environment. Environmental Pollution 150 (2007) 5-22.

[104] Nanoparticles In The Atmosphere Retrieved August 18, 2014 from http://www.nanocap.eu/Flex/Site/Download047b.pdf?ID=4445.

[105] Shi, J.P, Evans, D.E., Khan, A.A, Harrison, R.M. Sources and concentration of nanoparticles ((10nm diameter) in the urban atmosphere. Atmospheric Environment 35 (2001) 1193-1202.

Nanoparticles identified in indoor air primarily come from tobacco smoke and cooking, but are also generated from gas burners, electric heating elements, vacuum cleaner emission, candles, wood-burning fireplaces and other sources.[106] Nanoparticles also develop in the atmosphere via nucleation, the photochemical process in which molecular clusters form during the transition from aerosol vapors to liquid to solid. These solid particles can continue to grow through vapor condensation and coagulation.[107,108,109]

The chemical composition of nanoparticles in the atmosphere is highly variable, and includes numerous inorganic anions, sulfates, nitrates, ammonium and chloride among others. Chemical content of nanoparticles can serve to identify emission sources, for example zinc has been identified in smoke particles from municipal waste incineration, selenium and sulfur from coal combustion, nickel and vanadium from oil combustion.[110,111]

Regarding health and environmental impacts, the World Health Organization estimates that nanosized particles can influence conditions such as climate change, atmospheric chemistry and human health in a variety of ways.[112] Specifically, human health may be impacted by the inhalation of these fine particles more deeply into respiratory systems and via translocation into the nervous, brain and circulatory systems.[113] Unfortunately, there is limited information concerning the toxicological profiles of nanoparticles, as well as a lack of understanding of the epidemiological impacts on humans. And, despite the existence of limited studies addressing combustion-formed carbon particles and the aerosol behavior of such nanoparticles, overarching studies into this topic are still lacking.[114]

Food

Nanoparticles are widely used in food processing (e.g. flavor or odor enhancers, food texture or quality improvement, as gelation or thickening agents), in food packaging (e.g. detecting/sensing pathogens, UV-protection, stronger and more impermeable polymer films, and film/food containers with antimicrobial attributes), and in nutrient supplements (e.g. nutraceuticals with higher stability and bioavailability). However, the use of these products in foods and food production is minimally regulated.[115]

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[106] Biswas, P. and Wu, C-Y. Nanoparticles and the Environment. Journal of the Air and Waste Management Association, 2005, 55, 708-746.

[107] Biswas, P. and Wu, C-Y. Nanoparticles and the Environment. Journal of the Air and Waste Management Association, 2005, 55, 708-746.

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[115] Duncan, TV. 2011. Applications of nanotechnology in food packaging and food safety: Barrier materials, antimicrobials and sensors. J. Colloid and Interface Sci. 363:1–24. See below for further discussions on regulation.

The ability to create and manipulate on the nanoscale is driving an increased use of engineered nanomaterials (ENMs) throughout the food production continuum from farm to consumer. The potential for better and healthier food products is at odds with legitimate concerns by consumers and scientists as to how ENMs may impact environmental and public health. There is very little research on the potential adverse health impacts of exposure to ENMs, largely because use of ENMs in food production is so new. Research is needed on the potential adverse health effects of exposure to nanomaterials at the nano-bio interface. Exposure studies are needed to determine how ENMs move in the environment, if and how they accumulate, the types and quantities of ENMs humans are currently exposed to, and what the fate of these materials are in our bodies and the environment. Sound approaches on how to measure the ecotoxicity of ENMs do not currently exist. This is cause for concern given the pace of expanding use of ENMs in food production and other applications.[116]

Regardless of public health concerns centered on ENMs in food, nanotechnology applications in agricultural and food production is on track to realize revolutionary advances in a very short span of time. A few already identified include:[117]

- Development of nanotechnology-based foods with lower calories and less fat, salt, and sugar while retaining flavor and texture
- Nanoscale vehicles for effective delivery of micronutrients and sensitive bioactives
- Re-engineering of crops, animals, and microbes at the genetic and cellular level
- Nanobiosensors for detecting pathogens and toxins in foods
- Identification systems for tracking animal and plant materials from origination to consumption
- Nanoscale films for food packaging and contact materials that extend shelf life, retain quality and reduce cooling requirements

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[116] Chen, H., James, N., Hotze, M. 2014. ACS Select on Nanotechnology in Food and Agriculture: A Perspective on Implications and Applications. J. Agri. Food Chem. 62:1209 – 1212.

[117] Nanowerk. Food Nanotechnology. Retrieved August 26, 2014, from http://www.nanowerk.com/nanotechnology-in-food.php. See also: European Food Safety Authority. Nanotechnology. Retrieved August 26, 2014, from http://www.efsa.europa.eu/en/topics/topic/nanotechnology.htm.

Laboratory Methods

Laboratory equipment manufacturers PerkinElmer and ThermoFisher are evaluating analytical techniques for detecting nanomaterials. Table 1 summarizes the different characteristics of nanomaterials and the effective analytical equipment used for detection. Because of their unique properties and ubiquitous use, carbon fullerenes are addressed in more detail below.

In addition to ICP-MS methods, a more refined approach for measuring nanoparticles involves the use of single-particle inductively coupled plasma–mass spectrometry (spICP-MS). This method allows for detecting, counting and sizing metal nanoparticles. For example, spICP-MS can theoretically detect and count gold nanoparticles near 5 nm. However, this method has only been tested in the laboratory and its accuracy in "real world" samples has not been determined.[119]

The Analysis of Fullerenes in Environmental Samples

Fullerenes are robust and versatile molecules of pure carbon (i.e. C_{60}) with unique physico-chemical properties (see Figure 4). A variety of applications use these sphere-like structures, including drug delivery, electronic products, sensors and photonic devices, and as coating, pigments or cosmetic products. Based on their potential use, environmental concentrations of engineered fullerenes in the United Kingdom were predicted to be around 0.30 µg/L in water.[120] However, lower concentrations are expected in European surface waters (0.003 and 0.021 ng/L) when sedimentation is included.[121]

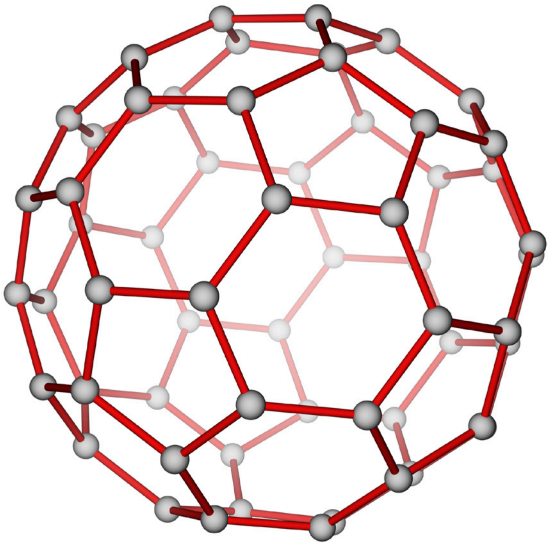

Figure 4: A Carbon-60 Fullerene

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[120] Boxall, A.B.A.; Chaudry, Q.; Sinclair, C.; Jones, A.; Aitken, R.; Jefferson, B.; Watts, C. 2007. Report by the Central Science Laboratory (CSL) York for the department of the Environment and Rural Affairs (DEFRA), United Kingdom.

[121] Gottschalk, F.; Sonderer, T.; Scholzm, R.W.; Nowack, B. 2009. Modeled Environmental Concentrations of Engineered Nanomaterials (TiO2, ZnO, Ag, CNT, Fullerenes) for Different Regions. Environ Sci Technol. 43, 9216-9222.

Table 1: Nanomaterial characteristics and applicable analytical technologies technique[118]

TECHNIQUE	NANO-OBJECT PARAMETERS												
	Abbreviation	Concentration	Size	Size Distribution	Surface Charge	Surface Area	Shape	Agglomeration	Crystallinity	Chemical Properties	Mechanical Properties	Thermal Properties	Electrical Properties
Acoustic Spectroscopy	–	✓	✓	✓									✓
Atomic Force Microscopy	AFM		✓	✓		✓	✓	✓			✓		
Aerosol Particle Mass Analyzer	AMS	✓											
Brunauer-Emmett-Teller	BET					✓							
Condensation Particle Counter	CPC	✓											
Differential Electric Mobility Analyzing System	DMAS	✓	✓	✓									
Differential Scanning Calorimetry	DSC											✓	
Dynamic Light Scattering	DLS	✓	✓	✓									
Electron Back-Scatter Diffraction	EBSD								✓				
Electron Energy Loss Spectroscopy	EELS									✓			
Energy Dispersive X-ray Spectrometry	EDX/ EDS	✓											
Flurorescence Spectroscopy	FL	✓	✓					✓		✓			
Fourier Transform Infrared Spectroscopy/ Imaging	FTIR									✓			
Induced Grating Method	IG		✓	✓				✓					
Inductively Coupled Plasma — Mass Spectrometry and Single Particle ICP-MS	ICP-MS	✓	✓	✓				✓		✓			
Laser Diffraction	–		✓	✓				✓					
Particle Tracking Analysis	PTA	✓	✓	✓	✓			✓					

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[118] Adapted and updated from: Salamon, A., Courtney, P, & Shuttler, I. 2010. Nanotechnology and Engineered Nanomaterials: A Primer. PerkinElmer. Retrieved March 11, 2014, from http://shop.perkinelmer.com/Content/Manuals/GDE_NanotechnologyPrimer.pdf.

TECHNIQUE	NANO-OBJECT PARAMETERS												
	Abbreviation	**Concentration**	**Size**	**Size Distribution**	**Surface Charge**	**Surface Area**	**Shape**	**Agglomeration**	**Crystallinity**	**Chemical Properties**	**Mechanical Properties**	**Thermal Properties**	**Electrical Properties**
Quartz Microbalances	QCM		✓							✓			
Raman Spectroscopy/ Imaging	--		✓						✓	✓			
Scanning Electron Microscopy	SEM		✓	✓			✓						
Secondary Ion Mass Spectrometry	SIMS	✓	✓	✓			✓	✓	✓				
Selected Area Electron Diffraction	SAED								✓				
Small Angle X-Ray Scattering	SAXS		✓	✓			✓	✓					
Static Light Scattering Photometer	SLS	✓	✓	✓									
Thermogravimetric Analysis	TGA		✓							✓		✓	
Transmission Electron Microscopy	TEM		✓	✓			✓	✓	✓				
X-ray Diffraction	XRD			✓					✓				
X-ray Photoelectron Spectroscopy	XPS				✓	✓				✓			

An essential aspect of environmental risk assessment is the development of analytical tools that enable studying the behavior and occurrence of fullerenes in natural environmental samples at low concentrations. Fullerenes can be exclusively composed of carbon or carry additional functional groups. The purely carbon-based fullerenes exhibit very low solubility in water (e.g. $C_{60}<10^{-9}$ mg/L),[122,123] but have the ability to form stable aggregate clusters with nanoscale dimensions upon contact with water.[124,125]

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[122] Jafvert, C. T.; Kulkarni, P. P. 2008. Buckminsterfullerene's (C60) Octanol Water Partition Coefficient (Kow) and Aqueous SolubilityEnviron. Sci. Technol. 42, 5945–5950.

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[125] Isaacson, C. W.; Bouchard, D. J.; Asymmetric Flow Field Flow Fractionation of Aqueous C60 Nanoparticles with Size Determination by Dynamic Light Scattering and Quantification by Liquid Chromatography Atmospheric Pressure Photo-Ionization Mass Spectrometry. Chromatogr, A. 2010. 1217, 1506–1512.

Several analytical methods focusing on the analysis of fullerenes in environmental samples have been reported in the literature.[126,127,128,129,130,131] Reversed phase liquid chromatography can be employed for the chromatographic separation of fullerenes, but other techniques such as asymmetric flow field flow fractionation and non-aqueous capillary electrophoresis are on the rise.[132] Although liquid chromatography coupled with ultraviolet detection (LC-UV) can be used for the analysis of fullerenes, liquid chromatography coupled to mass spectrometry (LC-MS) is the most commonly used technique for the determination and characterization of fullerenes and substituted fullerenes in complex environmental matrices.

Different ionization techniques, like electrospray ionization (ESI), atmospheric pressure ionization (APCI) and atmospheric pressure photoionization (APPI) can be applied, however, negative APPI seems favorable in terms of sensitivity.[133] The combination of ultra-high performance liquid chromatography (uHPLC) with high-resolution mass spectrometry is the technique of choice due to the high sensitivity and selectivity demonstrated as well as its capacity to work in a non-targeted approach.[134] This strategy enables the detection of transformation products of fullerenes or other new products not expected during the experimental design and possibly not reported before.

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[126] Farré, M.; Pérez, S.; Gajda-Schrantz, K.; Osorio, V.; Kantiani, L.; Ginebreda, A.; Barceló, D. J. 2010. First determination of C60 and C70 fullerenes and N-methylfulleropyrrolidine C60 on the suspended material of wastewater effluents by liquid chromatography hybrid quadrupole linear ion trap tandem mass spectrometry. Hydrol. 383, 44−51.

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[129] Pycke, B. F. G.; Halden, R. U.; Benn, T. M.; Westerhoff, P.; Herckes, P. 2011. Strategies for quantifying C60 fullerenes in environmental and biological samples and implications for studies in environmental health and ecotoxicology. Trends Anal. Chem. 30, 44−57.

[130] Pycke, B. F. G.; Halden, R. U.; Benn, T. M.; Westerhoff, P.; Herckes, P. 2011. Strategies for quantifying C60 fullerenes in environmental and biological samples and implications for studies in environmental health and ecotoxicology. Trends Anal. Chem. 30, 44−57.

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[134] Kolkman, A.; Emke, E.; Bäuerlein, P.S.; Carboni, A.; Tran, D.T.; ter Laak, T.L.; van Wezel, A.P.; de Voogt, P. 2013. Analysis of (Functionalized) Fullerenes in Water Samples by Liquid Chromatography Coupled to High-Resolution Mass Spectrometry. Anal Chem. 85, 5867-5874; Núñez, O.; Gallart-Ayala, H.; Martins, C. P.; Moyano, E.; Galceran, M. T. 2012. Atmospheric Pressure Photoionization Mass Spectrometry of Fullerenes. Anal. Chem. 84, 5316−5326; See also: Van Wezel, A.; Moriniere, V.; Emke, E.; ter Laak, T.; Hogenboom, C. 2011. Quantifying summed fullerene nC60 and related transformation products in water using LC LTQ Orbitrap MS and application to environmental samples. Environ Internat., 37, 1063-1067.

Applications for Nanotechnologies in Laboratories

Nanotechnology has application in virtually all fields. Initial commercialization in this field occurred with nanoscale versions of conventional materials including silica, alumina, titanium dioxide, and metals such as gold and silver.[135] Later, manufacturers synthesized new nanomaterials such as nanotubes, quantum dots, lipid-based systems, nanoparticles and dendrimers. Healthcare industries are expected to capitalize widely on nanotechnology use through pharmaceuticals (drug and gene delivery, nano-drugs), biotech industries, clinical and diagnostic laboratories, medical product and other health care applications such as diagnostics, genomic, imaging and personal care products.[136]

Pathogen Identification

From food intoxication and contaminated water, to hospital-acquired diseases and pandemics, infectious agents are still a major healthcare problem throughout the world. Despite advancements in pathogen identification, some of the gold-standard diagnostic methods have limitations, including laborious sample preparation, bulky instrumentation and slow data readout. In addition, first-responder and point-of-care applications need new field-deployable diagnostic modalities. Apart from being compact, these sensors must be sensitive, specific robust and fast, in order to facilitate detection of the pathogen, even in remote rural areas.

Unique properties of nanomaterials could be used for the detection of infectious agents in complex matrices like blood, soil and body fluids. Gold nanoparticles and their plasmonic shifts to iron oxide nanoparticles and changes in magnetic properties have been used for the detection of pathogens, toxins, antigens and nucleic acids with impressive detection thresholds. Additionally, nanotechnology is achieving rapid determination of bacterial drug susceptibility and resistance using novel methods, such as amperometry and magnetic relaxation. These promising techniques may encourage the adoption of nanotechnology-based diagnostics for the diagnosis of infectious diseases in diverse settings throughout the globe, preventing epidemics and safeguarding human and economic wellness.[137]

Identifying Antibiotic Resistance

Antibiotic-resistant microbial pathogens are a challenging and complex problem. Development of ultrasensitive sensor technology for detection of infectious bacterial pathogens as well as new approaches to treatment is a very urgent issue for public health, food safety, and the world economy. Nanotechnology-based assays like bacteria conjugated to gold nanoparticles may have enormous potential for rapid, on-site pathogen detection including those for food production in order to avoid the distribution of contaminated products.[138]

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[135] Nanomaterials-Worldwide market challenges & opportunities. Research & Markets. Retrieved March 11, 2014, from http://www.researchandmarkets.com/reportinfo.asp?report_id=1095445&tracker=related.

[136] World Nanomaterials Market. ReportLinker. Retrieved March 11, 2014, from http://www.reportlinker.com/p0185325/World-Nanomaterials-Market.html.

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A recent proteomic study showed the diagnosis of β-lactam resistance using shotgun proteomics and LC-nano-electrospray ionization ion trap mass spectrometry platform for the rapid diagnosis of wild type and resistant strains that would be useful for the medical treatment of microbial strains found during hospital-associated infections (HAI).[139] Genotypic applications often use single nucleotide polymorphisms (SNPs) and their associated phenotypes, including human disease diagnostics, pathogen detection, and identification of genetic traits impacting agricultural practices, both in terms of food quality and production efficiency. While validation of SNP associations in large-scale cohorts is currently impeded by the technical challenges and the high cost inherent in analyzing large numbers of samples, nano-particle based genotyping platforms deliver better accuracy in genotyping compared to the similar systems.[140]

Clinical Applications

Nanotechnology has tremendous potential in clinical laboratory diagnostics as it could enable diagnosis at the molecular level. Nanomaterials, such as gold nanoparticles, quantum dots, and nanobiosensors will extend the limits of current molecular diagnostics and enable point-of-care diagnosis as well as the development of personalized medicine. While the potential diagnostic applications are virtually unlimited, most current applications are in the areas of biomarker research, cancer diagnosis and the detection of infectious microorganisms.[141] As molecular techniques become mainstream, magnetic nanoparticles could offer fast, simple, reliable, environmentally friendly and high quality nucleic acid extractions.[142]

Nanoparticles are robust in diverse clinical settings, and substantially more affordable than traditional PCR enzymes. Consequently, the potential clinical and field-based use of magnetic nanoparticles in the multiplexed identification of microbial pathogens and other disease-related biomarkers via a single, deployable instrument in clinical samples would likely be efficient and cost effective. One example of this is the rapid and sensitive detection of an intracellular pathogen like those found in human peripheral leukocytes.[143]

Genomic Applications

As emerging biological and chemical contaminants (e.g. nanomaterials, pharmaceuticals, microbes and associated toxins) impact ecological and human health, it is critical to be innovative in applying genomic applications to better understand the complexity of the relationship between the environment and human health. The application of functional genomic technologies to clinical diagnostic, public health and ecological research would be

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a powerful tool in understanding the effect of such contaminants and toxins on human and environmental health.[144,145]

Post-genomics nanotechnology is gaining momentum from proteomics and metabolomics, to nanoproteomics and personal genomics. These advances also catalyze other novel post-genomics innovations, leading to convergences between omics and nanotechnology. Post-genomics life sciences and biomedicine applications for nanotechnology include developing:

- immunosensors for inflammatory, pathogenic and autoimmune markers for infectious and autoimmune diseases
- amplified immunoassays for detection of cancer biomarkers
- methods for targeted therapy and automatically adjusted drug delivery systems in stroke and brain injury studies[146]

In this way, nanotechnology compliments proteomics through different applications, including nanoporous structures, functionalized nanoparticles, quantum dots and polymeric nanostructures. However, these applications are still in the early growth phases.

Nanotechnology and nanoscopy are a strong driving force for advancing genomic mapping approaches, allowing both better manipulation of DNA on the nanoscale and enhanced optical resolving power for analysis of genomic information. During the past few years, epigenetic studies also adopted these techniques. The principle for these studies is the use of advanced optical microscopy for the detection of fluorescently-labeled epigenetic marks on long, extended DNA molecules. The complex composition of the genome has made it an ideal system to study single-molecule optical mapping. The optical-based mapping of DNA approach has been instrumental in highlighting genomic variation and contributed significantly to the assembly of many genomes including the human genome.[147]

The development of RNA therapeutics utilizing nanotechnology has potential for cancer treatment. Due to specialized physicochemical properties of the therapeutic RNA nanoparticles, they are ideal for delivery of siRNA, miRNA, ribozymes, or riboswitches; fluogenenic RNA; and targeted use of RNA aptamers. RNA nanoparticles are advantageous for in vivo applications as well due to their uniform nano-scale size, precise stoichiometry, polyvalent nature, low immunogenicity, low toxicity and target specificity. Thus they possess potential for use as a substitute for expensive endosome trapping for cancer treatments.[148]

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As nanoproteomics becomes more accessible it will likely lead to further breakthroughs in personalized and targeted medicine. Omics-based nanomedicine could also be attributed to the use of nanotechnology in the advancement of personalized oncology.[149] Micro-machined biosensors, such as injectable needle biosensors, are nanotech devices that employ electrical detection. These devices are being developed as ultrasensitive, real-time, and localized sensors to overcome some of the current limitations of biosensors for drug screening and for studying various intracellular signaling pathways.[150] Finally nanotechnology has potential applications for next generation sequencing and microarrays that may advance biomedical research and thus transform the field of laboratory sciences.[151]

Nanomedicines

Nanomedicine is an emerging field that integrates nanotechnology, biomolecular engineering, life sciences and medicine. Nano-scale structures and devices are compatible in size with proteins and nucleic acids in living cells. Therefore, the design, characterization and application of nano-scale probes, carriers and machines will likely provide greater opportunities for achieving better control of biological processes, and dramatic improvements in targeted disease detection, therapy and prevention.

Applications of nanomolecule-based drug delivery can potentially revolutionize current systems for complex diseases like cancer, as well as brain, infectious, skin and cardiovascular diseases. There are numerous reports on dendrimeric particles for cancer diagnosis and treatment (see above).[152] This technology successfully increased the aqueous solubility of drugs such as camptothecin and paclitaxel.[153]

Complex nano-constructs show increased half-life of olyvalent dendrimer-methotrexate as a folate receptor-targeted cancer therapeutic.[154] Dendrimer-drug delivery to tumor tissue is attained by either passive or active targeting. Passive targeting is achieved by enhanced permeation and retention effect by using leaky tumor vasculature. Tumor-specific targeting ligands such as folic acid, transferrin, and antibodies can be attached on the dendrimer surface for tumor targeting of drug in the body. The spherical architecture of nanomolecule-based drug delivery systems like dendrimers was also explored to entrap small imaging molecules such as gadolinium for increased blood circulation leading to enhanced MRI images.[155] This technology can be used to create multifunctional nanodevices for

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[150] Esfandyarpour, R., Esfandyarpour, H., Harris, J.S., Davis, R.W. 2013. Simulation and fabrication of a new novel 3D injectable biosensor for high throughput genomics and proteomics in a lab-on-a-chip device.

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simultaneous imaging and treatment of cancer.[156] Additionally, nano-sized doses of bee, snake and scorpion venom show early promise as a cancer treatment.[157]

One of the challenges in nanomedicine and drug delivery is crossing transmembrane barriers. A dendrimer-indomethacin complex showed enhancer permeation and superior pharmacokinetic profile for the drug,[158] while cationic structures used as a transfection agent for the gene delivery.[159] Because of the biocompatibility and *in-vivo* disposition potentials of specialized nanoparticles, surface chemistry, core, and charge,[160,161] molecules like dendrimers exhibit distinct pharmacokinetic and pharmacodynamic profiles, which help to design on-demand systems for drug delivery in specific medical applications.[162]

Recent advances in nanomedicine also include the development of nanoparticle-based probes for molecular imaging, nano-carriers for drug/gene delivery, multifunctional nanoparticles for theranostics, and molecular machines for biological and medical studies, including engineered nucleases for genome editing.[163]

Lab on a Chip

The advent of nanotechnology is allowing laboratories to shrink, i.e., "lab-on-a-chip."[164] This technology allows a broad spectrum of diagnostic testing on-site. Currently most useful for medical screening, this technology has ever-increasing application[165] for other biological and chemical screenings.[166]

EPA's evaluation of lab-on-chip (LOC) for sensory and high-sample throughputs includes diagrams and other information concerning design and function. The principle, environmental use of LOC focuses mainly on sensor technology, both with chemicals and radionuclides (using microcantilevers). In addition, carbon nanotubes are showing promise with gas-sensing applications. As more is learned about the function of nanomaterials, expect LOC technology to improve and become more widespread.[167]

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[160] Kaminskas, L.M., Boyd, B.J., Porter, C.J. 2011. Dendrimer pharmacokinetics: the effect of size, structure and surface characteristics on ADME properties. Nanomedicine (Lond). 2011;6(6):1063-84.

[161] Dendrimer-Based MRI Contract Agents. National Characterization Laboratory. 2006. Retrieved March 11, 2014, from http://ncl.cancer.gov/120406.pdf.

[162] Barrett, T., Ravizzini, G., Choyke, P.L., Kobayashi, H. 2009. Dendrimers in medical nanotechnology. IEEE engineering in medicine and biology magazine. Engineering in Medicine & Biology Society. 2009;28(1):12-22.

[163] Tong, S., Fine, E.J., Lin, Y., Cradick, T.J., Bao, G. Nanomedicine: Tiny Particles and Machines Give Huge Gains. Ann Biomed Eng. Ann. Biomed. Eng. 2014 Feb; 42(2):243-59.

[164] Alok, J. The incredible shrinking laboratory or "lab-on-a-chip." 2011. The Guardian. Retrieved March 11, 2014, from http://www.theguardian.com/science/2011/nov/28/incredible-shrinking-laboratory-lab-chip.

[165] Medintz, I. Using nanotechnology to improve lab on a chip devices. 2012. J Biochips Tiss Chips 2:e117. doi: 10.4172/2153-0777.1000e117. Retrieved March 11, 2014, from http://www.omicsonline.org/2153-0777/2153-0777-2-e117.php?aid=9488.

[166] Lab on a chip videos. AZ.nano. Retrieved March 11, 2014, from http://www.azonano.com/nanotechnology-videos.aspx?cat=19.

[167] Lab-on-a-chip. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/radiation/docs/cleanup/nanotechnology/chapter-3-lab-on-a-chip.pdf.

Regulatory and Policymaking

To date, the United States has taken little firm regulatory action regarding nanotechnology. While a number of administrative agencies conduct research and investigations into nanomaterials, there is not yet an enforceable regulatory structure in place.[168]

Agencies including the EPA, National Institute for Occupational Health and Safety (NIOSH), and the FDA, all have roles in nanotechnology research and regulation. In addition to individual agency efforts, the National Nanotechnology Coordinating Office (NNCO), and the National Nanotechnology Initiative (NNI), help coordinate and organize US government activities regarding nanotechnology.[169]

Environmental Protection Agency

Through many of its offices, EPA is leading the research effort regarding the environmental impacts and benefits of nanotechnology. No fewer than three separate offices are conducting nano-related research, all with a different focus. However, outside of the requirements found in the Toxic Substances Control Act (TSCA) for notices of a new chemical substance or manufacturing, and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) regarding product labeling, EPA is not regulating nanotechnology use or disposal.[170]

Toxic Substances Control Act (TSCA)

The Office of Chemical Safety and Pollution Prevention leads the bulk of EPA's work regarding nanomaterials research.[171] This work includes chemical registrations and other data submissions under the Toxic Substances Control Act. Because EPA considers nanomaterials "chemical substances," they are subject to the registration requirements in TSCA before manufacturing or introducing into commerce.[172] EPA has a number of tools to gather information on nanomaterials, including:

- Premanufacture notices (PMN) — specific information provided to EPA before manufacturing a new chemical substance[173]
- Significant New Use Rules (SNUR) — 0a regulatory determination that an existing chemical is being used in a new way, including new environmental or health impacts[174]

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[168] A full list of the federal agencies involved with nanotechnology issues can be found at the National Nanotechnology Initiative's site: http://nano.gov/partners. For the purposes of this Paper, only those agencies with direct oversight with environmental health will be discussed.

[169] The NNI released a draft strategic research plan in late 2013. Strategic Plan. National Nanotechnology Initiative. 2013. Retrieved March 11, 2014, from http://www.nano.gov/sites/default/files/2014_nni_strategic_plan_-_draft_for_public_comment_locked.pdf.

[170] The requirements under FIFRA and TSCA are applicable to all new pesticides and chemicals, and do not apply to nanomaterials uniquely.

[171] Control of nanoscale materials under the Toxic Substances Control Act. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/oppt/nano/. See also Fact sheet for nanotechnology under the Toxic Substances Control Act. Retrieved March 11, 2014, from http://www.epa.gov/oppt/nano/nano-facts.htm.

[172] New Chemicals. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/oppt/newchems/index.htm.

[173] New Chemicals. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/oppt/newchems/index.htm.

[174] TSCA Section 5 Significant New Use Rules. US EPA. Retrieved March 11, 2014, from http://epa.gov/oppt/existingchemicals/pubs/sect5a2.html.

- Information Gathering Rules—EPA's record keeping requirements[175]
- Test Rules—EPA's authority to require manufacturers test existing chemicals[176]

To date, the EPA relies largely on pre-manufacture notices and significant new use rules to gather information on nanomaterials. In fact, EPA issued a number of SNURs for nanomaterials focusing mainly on carbon nanotubes.[177] A complicating factor for a PMN is that they only apply to "new" chemicals, based on chemical composition. Consequently, if a chemical appears in the Chemical Substances Inventory,[178] the nanoscale counterpart may not need a PMN before manufacturing or placing into commerce. EPA is working to address this potential gap via the SNUR process.[179] EPA is currently developing administrative Information Gathering and Testing rules applicable to nanomaterials.[180]

Pesticides

Similar to the requirements under TSCA, the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) also requires registration of new pesticide products.[181] The EPA has a number of information-gathering tools under FIFRA to compel data from pesticide manufacturers.

Under Section 6(2)(a), EPA can obtain existing information regarding the nanoscale products in registered products already on the market. Conversely, EPA can use Section 3(c)(2)(B) to proactively request additional information concerning pesticides, including those containing nanomaterials.[182] The EPA is using both of these tools to obtain information on nanomaterials in pesticides and related products. Note, however, these requirements only apply to active ingredients of pesticides, and does not apply to inactive or inert portions of the compound. Should a nanomaterial component of a pesticide be inactive, FIFRA may not apply.

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[175] General information gathering authority. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/opptintr/chemtest/pubs/sect8a.html.

[176] Data development (testing). US EPA. Retrieved March 11, 2014, from http://www.epa.gov/opptintr/chemtest/pubs/data.html.

[177] EPA proposes snur for 37 chemical substances, including 14 nanomaterials. 2013. Nano and Other Emerging Technologies Blog. Retrieved March 11, 2014, from http://nanotech.lawbc.com/2013/02/articles/united-states/federal/epa-proposes-snurs-for-37-chemical-substances-including-14-nanomaterials/.

[178] TSCA chemical substance inventory. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/oppt/existingchemicals/pubs/tscainventory/index.html.

[179] Control of nanoscale materials under the Toxic Substances Control Act. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/oppt/nano/.

[180] Control of nanoscale materials under the Toxic Substances Control Act. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/oppt/nano/.

[181] Regulating pesticides that use nanotechnology. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/pesticides/regulating/nanotechnology.html. See also: Pesticide registration program. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/pesticides/factsheets/registration.htm.

[182] Regulating pesticides that use nanotechnology. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/pesticides/regulating/nanotechnology.html.

Other EPA Efforts

Other EPA offices[183] are researching nanomaterials for a variety of other reasons, including risk assessment,[184] life cycle assessment,[185] environmental and human health impacts (termed "sustainability" by EPA),[186] and exposure assessment.[187] The majority of these activities reside in EPA's Office of Research and Development's National Exposure Research Laboratory (NERL) and the National Risk Management Research Laboratory (NRMRL). A list of EPA's research publications concerning nanotechnology is available through the Office of Research and Development.[188]

Finally, the EPA has released nano-specific resources over the last several years. In 2007, EPA issued its own White Paper concerning nanotechnology,[189] and a set of research priorities in 2009.[190]

Worker Protection

Two federal entities have significant influence on worker protection standards. NIOSH is the research arm of the CDC primarily concerned with workplace exposure. The Occupational Health and Safety Administration (OSHA) is the regulatory body tasked with monitoring and enforcing applicable worker safety standards.

National Institute for Occupational Safety and Health

NIOSH engages in research concerning workplace exposure to nanomaterials. Principally related to inhalation concerns, NIOSH released a series of resources associated with worker protection. However, unlike EPA or OSHA, NIOSH does not have a regulatory or enforcement mission, and is instead focused on research. NIOSH is considering a number of topics regarding nanotechnology, including:[191]

- Worker exposure to nanomaterials during manufacturing
- Occupational health implications of nanomaterials, including effects on humans
- Engineering controls and personal protective equipment

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[183] Nanotechnology & nanomaterials research. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/nanoscience/.

[184] Nanomaterials: Research to support comprehensive environmental assessments of nanomaterials. US EPA. Retrieved March 11, 2014, from http://cfpub.epa.gov/ncea/CFM/nceaQFind.cfm?keyword=Nanomaterials.

[185] Nanotechnology. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/nrmrl/std/nanotech.html.

[186] Green chemistry and nanotechnology. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/nrmrl/std/green_chem_nano.html.

[187] Research focuses on potential exposure to nanomaterials. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/nanoscience/quickfinder/exposure.htm.

[188] Nanotechnology research publications. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/nanoscience/publications-overview.htm.

[189] Nanotechnology White Paper. 2007. US EPA. Retrieved March 11, 2014, from http://www.epa.gov/osa/pdfs/nanotech/epa-nanotechnology-whitepaper-0207.pdf.

[190] Nanomaterial research strategy. 2009. US EPA. Retrieved March 11, 2014, from http://epa.gov/nanoscience/files/nanotech_research_strategy_final.pdf (June 2009).

[191] Nanotechnology. CDC. Retrieved March 11, 2014, from http://www.cdc.gov/niosh/topics/nanotech/. See also NIOSH's 10 Critical Topic Areas: http://www.cdc.gov/niosh/topics/nanotech/critical.html.

To begin addressing these and related issues, NIOSH creates and collects a wide variety of reports and resources.[192] These include guidance on issues such as engineering controls for nanomaterials,[193] medical screening and hazard surveillance[194] and field research.[195] NIOSH also maintains a wide variety of publications associated with workplace safety and nanotechnology. Like EPA, NIOSH has a strategic plan for nanomaterial research.[196] NIOSH last updated the plan in 2010, and again in 2012, releasing it in draft for 2013-2016.[197]

Occupational Safety and Health Administration (OSHA)

OSHA a related worker protection agency, is also taking an interest in nanotechnology issues.[198] Like NIOSH, OSHA is interested in the occupational health effects of nanomaterials on the workforce,[199] and specifically focuses on the application of General Industry Standards on nanotechnology manufacture and research.[200] Unlike NIOSH, OSHA does have enforcement authority should it find a violation of worker protection standards.

Food and Drug Administration

FDA regulates a wide variety of products that may contain nanomaterials, including food, food packaging, cosmetics, and drug or drug delivery systems.[201] Consequently, FDA is accumulating information on the use of nanomaterials in these products. While there has not been direct regulation to date, FDA is releasing guidance materials,[202] factsheets,[203] and since 2006, maintains a task force[204] to consider regulatory approaches for nanomaterials falling within FDA's authority. FDA's efforts are guided by its "2013 Nanotechnology Regulatory Science Research Plan."[205] The Plan aims to coordinate leadership at FDA on nanomaterial issues while addressing scientific needs, categories, and goals.

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[192] Nanotechnology: guidance and publications. CDC. Retrieved March 11, 2014, from http://www.cdc.gov/niosh/topics/nanotech/pubs.html.

[193] Current strategies for engineering controls in nanomaterial production and downstream handling processes. 2013. CDC. Retrieved March 11, 2014, from http://www.cdc.gov/niosh/docs/2014-102/.

[194] Current intelligence bulletin 60: interim guidance for medical screening and hazard surveillance for workers potentially exposed to engineered nanoparticles. 2009. CDC. Retrieved March 11, 2014, from http://www.cdc.gov/niosh/docs/2009-116/.

[195] NIOSH nanotechnology field research effort. 2008. CDC. Retrieved March 11, 2014, from http://www.cdc.gov/niosh/docs/2008-121/.

[196] Strategic plan for NIOSH nanotechnology research and guidance. 2009. CDC. Retrieved March 11, 2014, from http://www.cdc.gov/niosh/docs/2010-105/.

[197] Protecting the nanotechnology workforce: NIOSH nanotechnology research and guidance strategic plan 2013-2016. 2012. CDC. Retrieved March 11, 2014, from http://www.cdc.gov/niosh/docket/review/docket134B/pdfs/ProtectNanoWk.pdf (cited only for existence, not for substantive information).

[198] Nanotechnology. OSHA. Retrieved March 11, 2014, from https://www.osha.gov/dsg/nanotechnology/nanotechnology.html.

[199] Health Effects and workplace assessments and controls. OSHA. Retrieved March 11, 2014, from https://www.osha.gov/dsg/nanotechnology/nanotech_healtheffects.html.

[200] OSHA standards. OSHA. Retrieved March 11, 2014, from https://www.osha.gov/dsg/nanotechnology/nanotech_standards.html.

[201] Nanotechnology. FDA. Retrieved March 11, 2014, from http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm.

[202] FDA Issues two draft guidances related to nanotechnology application in cosmetics and food substances. 2012. FDA. Retrieved March 11, 2014, from http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm301093.htm.

[203] Fact Sheet: Nanotechnology. 2012. FDA. Retrieved March 11, 2014, from http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm300914.htm.

[204] Nanotechnology task force. FDA. Retrieved March 11, 2014, from http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm2006658.htm.

[205] 2013 Nanotechnology regulatory science and research plan. FDA. Retrieved March 11, 2014, from http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm273325.htm.

Regarding specific programs, FDA has nanomaterial efforts underway in eight different offices, including the Office of the Commissioner, Center for Biologics Evaluations and Research, Center for Drug Evaluation and Research, Center for Food Safety and Applied Nutrition, and National Center for Toxicological Research.[206]

Secondary Sources of Information

In addition to the research and regulatory effort underway in the United States, Europe has also taken a significant interest in the environmental, health and safety issues related to nanotechnology. Although beyond the scope of this White Paper, information from Europe may provide additional context and information regarding nanomaterial health and safety.

Two resources may be particularly useful:

1. The European Commission (part of the governing structure of the European Union) is responsible for chemical regulation.[207] Through the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation, the European Union is taking steps towards nanomaterial regulation.[208]
2. A US-based law firm closely follows European regulation of nanomaterials. The "Nano and Other Emerging Chemical Technologies Blog" may be a good resource for up-to-date developments and activities by governments concerning the regulation of nanomaterials.[209]

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[206] Current nanotechnology programs at FDA. FDA. Retrieved March 11, 2014, from http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm309672.htm.

[207] Nanotechnology. European Commission. Retrieved March 11, 2014, from http://ec.europa.eu/nanotechnology/index_en.html.

[208] REACH and nanomaterials. European Commission. Retrieved March 11, 2014, from http://ec.europa.eu/enterprise/sectors/chemicals/reach/nanomaterials/index_en.htm.

[209] Nano and other emerging chemical technologies blog. Bergeson & Campbell, P.C. European Commission. Retrieved March 11, 2014, from http://nanotech.lawbc.com/.

Opportunities for Public Health Laboratories

Nanomaterials will impact public health laboratories in a number of ways, mostly connected to the exposure, toxicity, release and therapeutic issues discussed above. That said, there are opportunities for public health and environmental laboratories to affirmatively enter the nanomaterial discussion via applied research with qualified partners.

Academic Partnerships and Applied Research in Public Health and Environmental Laboratories

Nanotechnology, said to be the “next big thing,” has immense potential. However, it is important to balance harnessing the benefits of nanotechnology with toxicological concerns. The transformation from bench to the bedside or mass industry usage needs more collaborative efforts. Critical issues include:

- The effect and interaction of natural and engineered nanomaterials on living and environmental factors
- The stability of nanomaterials
- Large scale manufacturing of nanoparticles/nanomaterials
- Building better understanding of nanotechnology among researchers
- Relaying information about nanotechnology to the public and the media

Nano-Periodic Table

With the advent of new nanomaterials, there are efforts to prepare a nano-periodic table to find patterns and rules pertaining to nanomaterials (see Figure 5).[210] Atom mimicry provided the first working premise and rationale for understanding the relationships and behavior of well-defined picoscale atomic-elements as we describe them in our traditional chemistry paradigm. This atom mimicry with structure control is well demonstrated in the two major nanomaterial categories: hard nano-matter (i.e., metal nanocrystals) and soft nano-matter (i.e., dendrimers). Intrinsic nano-periodic property patterns have been noted for a variety of nano-modules that appear to fulfill criteria for nano-elements, as well as their use for the synthesis of corresponding nano-compounds. Therefore, expect nano-elements to manifest totally different periodic patterns and emerging properties than those observed for traditional atoms.

While nanomaterial periodic property patterns are observed for both soft and hard nano-matters, a deeper understanding of these patterns will likely allow future understanding of such nano-periodic property patterns. Moreover, such patterns may inspire the initiation of appropriate new concepts, theories and rules that, with experimental confirmation, would allow prediction of properties or behavior patterns for a wide range of nanomaterials. Understanding such nano-periodic property patterns arising from chemical/physical/energy perturbations and their interactions with biological/environmental systems should be expected to provide invaluable information for designing more effective nano-device function as well as for defining reasonable nanomaterial risk/benefit parameters.

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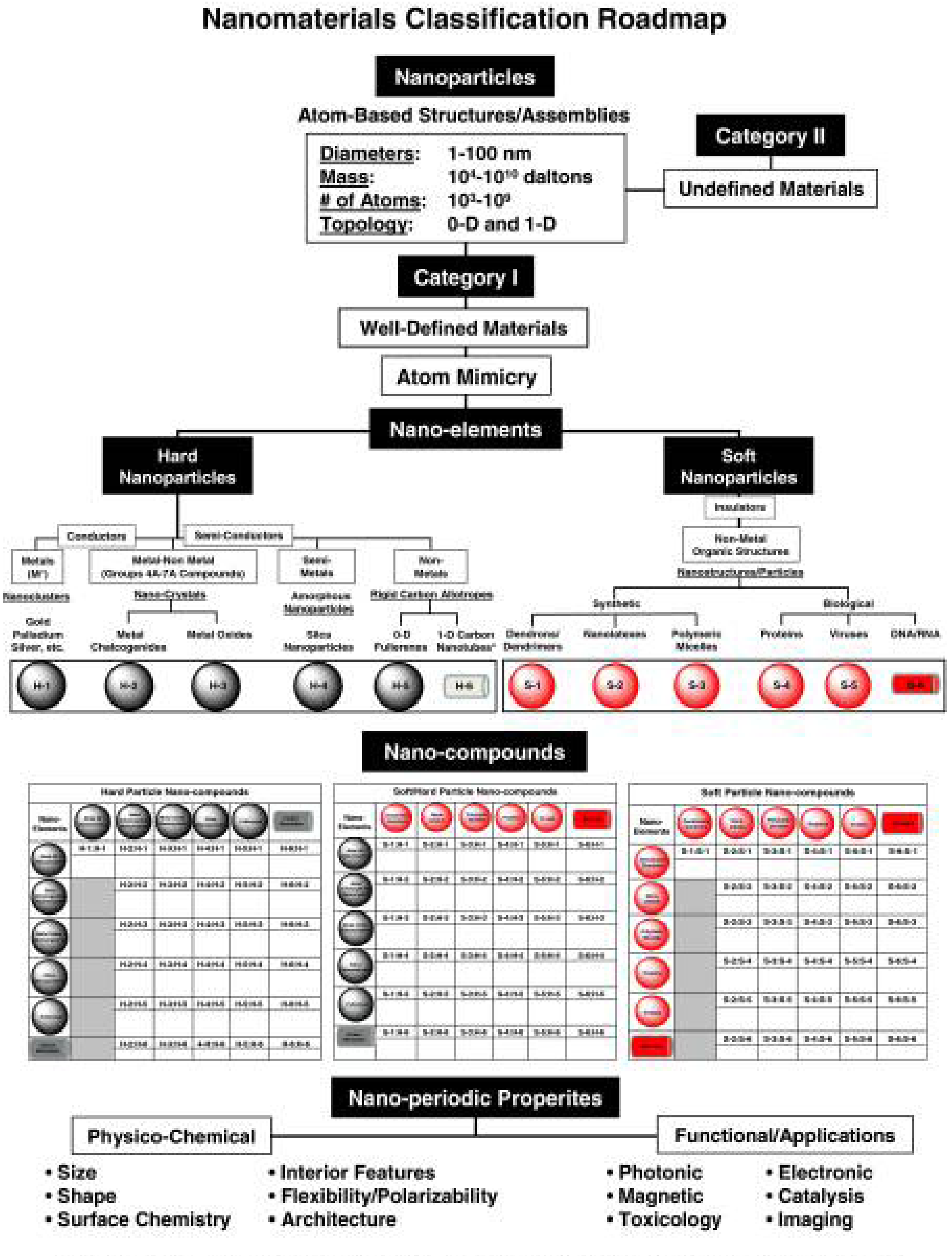
[210] Periodic Patterns, Relationships and Categories of Well-Defined Nanoscale Building Blocks. National Science Foundation. 2007. Retrieved August 18, 2014 from http://www.nsf.gov/crssprgm/nano/GC_Charact08_Tomalia_nsf9_29_08.pdf.

Figure 5: Nanomaterials Classification Roadmap[211]



* The arm chair architectural form of carbon nanotubes can exhibit metal-like conducting properties (Fig. 37)

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[211] Tomaia, D.A. In quest of a systematic framework for unifying and defining nanoscience. J. Nanopart. Res. 2009. Retrieved August 18, 2014 from http://openi.nlm.nih.gov/detailedresult.php?img=2988219_11051_2009_9632_Fig7_HTML&req=4.

Advances in the rapidly progressing field of nanotechnology will have a tremendous impact on several disciplines such as materials, electronics and medicine. Despite the potential impact of nanotechnology, and the abundance of funds, there is a paucity of serious, published research into the ethical, legal, social and public health implications of nanotechnology.

There is danger of derailing nanotechnology if the study of ethical, legal and social implications does not catch up with the speed of scientific development or industrial use.[212] Public perceptions of emergent technologies like genomics and nanotechnology are increasingly important to understand;[213] recent studies show concerns about nanotechnology development, perceptions of informed citizens, and the reasoning basis in relation to applications of nanotechnology. Concerns about managing risks, as well as medical and industrial uses of nanotechnology, point to the need for better nanoscience understanding at institutions of higher learning.[214] Interdisciplinary, basic and applied research partnerships amongst academic, industry, government and public health agencies would likely lead to better understanding and management of the field of nanotechnology.

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[212] For more information on the ethical issues associated with nanotechnology and emerging technologies, see the Ethics + Emerging Sciences Group at California Polytechnic University, available at: http://ethics.calpoly.edu/index.htm (last visited March 6, 2014).

[213] Mnyusiwalla, A. Daar, A., Singer, P. Mind the gap: science and ethics in nanotechnology. 2003. Nanotechnology Volume 14 Number 3. Retrieved March 11, 2014, from http://iopscience.iop.org/0957-4484/14/3/201.

[214] Macoubrie, J. 2006. Nanotechnology: public concerns, reasoning and trust in government. Public Understanding of Science vol. 15 no. 2 221-241.

Conclusion

Nanotechnology will continually evolve and change as more is learned. Readers are encouraged to continually update their resources in order to maintain current information in this fast-moving field. In addition,“unknowns” are already being identified and a number are highlighted in the topic-specific sections above.

The impact on and for environmental and public health laboratories will similarly change and evolve as the field does. To be sure, there will be benefits to laboratories in the form of more powerful analysis, more efficient field devices, and remediation potential for environmental contamination. However, there will also be increased burdens for laboratories as they will have to be equipped to search for, and find, nanoparticles in air, soil, water and people. With the industry moving faster than the science, laboratories will face the burden of keeping up. A necessary, but not easy task.

Association of Public Health Laboratories

The Association of Public Health Laboratories (APHL) is a national nonprofit dedicated to working with members to strengthen laboratories with a public health mandate. By promoting effective programs and public policy, APHL strives to provide public health laboratories with the resources and infrastructure needed to protect the health of US residents and to prevent and control disease globally.

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