REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 2-A-13

Subject: Nanotechnology Safety and Regulation (Resolution 512-A-12)

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Referred to: Reference Committee E (Lawrence K. Monahan, MD, Chair)

INTRODUCTION

Resolution 512-A-12 introduced by the California Delegation and referred by the House of Delegates asked:

> That our American Medical Association: (1) recognize both the benefits and the potential risks to public health and the environment from the widespread use of nanoparticles; and (2) endorse responsible regulation of existing or new nanoparticles prior to their introduction in industrial or consumer products, such as, but not limited to, standardized research, toxicologic testing, biomonitoring and product labeling.

Nanotechnology is the science of manipulating matter at the nanoscale (i.e., dimensions of 1-100 nanometers) to create new and unique materials and products. Nanoparticle components are present in materials such as polymers, electronics, paints, batteries, sensors, fuel cells, solar cells, coatings, computers and display systems. Nanoparticles are also found in other consumer products such as cosmetics and pharmaceuticals. Concerns have been raised, suggesting that nanoparticles could have undesirable effects on the environment and unintended effects on human health. Nanomaterials also present challenges to the policy and risk assessment process, in part because no clear answer exists to the question of where they fit within current regulatory and policy guidance and frameworks. This report offers a brief overview of the current uses of nanotechnology, potential effects on human health and the environment, and regulation of nanomaterials. Several comprehensive reports on nanotechnology and its regulation are available as additional resources.[1-6]

METHODS

Literature searches were conducted in the PubMed database for English-language articles using the search terms “nanotechnology,” “nanoparticle,” and “nanomaterial” along with the terms “health” and “environment.” Additionally, a Google search was conducted using the same search terms. Several comprehensive reports on nanotechnology and its regulation were consulted.[1-6]

NANOPARTICLE TECHNOLOGY

As mentioned, nanotechnology is the understanding and control of matter at dimensions of approximately 1-100 nanometers.[4] For comparison, a sheet of paper is about 100,000 nanometers

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thick, a human hair is about 80,000 nanometers thick, the protein hemoglobin is about 5.5 nanometers in diameter, and the DNA double helix is about 2.5 nanometers in diameter.[1,7] Nanoscale materials often have properties that differ from those of conventionally scaled materials.[8] These differences may include altered magnetic properties, electrical or optical activity, structural integrity, or chemical or biological activity.[1] The altered properties of nanoscale materials are largely due to the increased surface area per mass, which allows a greater amount of the nanoparticle to come in contact with its surroundings and induce reactivity.[7]

Commercial Application of Nanotechnology

Over 800 commercial products and applications of nanoparticle-based materials exist.[9] Selected examples are:

- nanoscale polymer composites that make baseball bats, tennis rackets, motorcycle helmets, automobile bumpers, luggage, and power tool housings more lightweight, stiff, durable, and resilient;
- surface treatments of fabrics that help to resist wrinkling, staining, and bacterial growth and provide lightweight ballistic energy deflection in personal body armor;
- nanoscale materials in cosmetic products that provide better coverage and absorption, increase antioxidant and antimicrobial properties, and filter UV light;
- nano-engineered materials in automotive products such as high-powered rechargeable battery systems, thermoelectric materials for temperature control, lower-rolling-resistance tires, high-efficiency/low-cost sensors and electronics, thin-film smart solar panels, and fuel additives and improved catalytic converters for cleaner exhaust and extended range;
- nanomaterials in computing, communications, and other electronics applications provide faster, smaller, and more portable systems that can manage and store larger amounts of information; and,
- nanocomposites in food containers minimize carbon dioxide leakage out of carbonated beverages, or reduce oxygen inflow, moisture outflow, or the growth of bacteria to keep food fresh and safe for longer periods of time.

Medical Applications of Nanotechnology

Nanotechnology is being widely applied in many facets of health care.[9,10] For example, quantum dots (semi-conducting nanocrystals) show unique optical and electronic properties like size-tunable light emission, simultaneous excitation of multiple fluorescence colors, high signal brightness, and long-term photostability. These properties have enhanced both in vitro and in vivo biological imaging, and are being used to image sentinel lymph nodes, tumor-specific receptors, malignant tumor detectors, and tumor immune responses.[11]

In oncology, nanoparticulate antineoplastic drugs can better target tumors and reduce the systemic toxicity associated with their conventional counterparts. Liposomal doxorubicin (doxorubicin encapsulated in a liposome) is preferentially directed away from sites at which the non-encapsulated form would cause cardiac and gastrointestinal toxicity, and instead exits the circulation where tumor growth has disrupted capillaries.[12]

In another example, nanoparticle-based hydrogels used as wound dressings have been introduced. Nanoscale inorganic particles have been added to hydrogels as reinforcing agents, improving the strength, elasticity, absorptive capability, and barrier properties of the wound dressing.[13]

NANOPARTICLES AND HUMAN HEALTH

Since humans are routinely exposed to a number of materials containing nanoparticles, concerns exist about how such exposure affects human health. The increased surface-to-volume ratio of nanoparticles creates an increased potential for reactivity, and their small size may facilitate uptake into and between various cells or cell components allowing for transport to other parts of the body. In addition to surface-to-volume ratio and size, the shape, solubility, and surface chemistry of nanoparticles may affect human tissue and cells.[1,5]

Little is currently known about the long-term effects of exposure to engineered nanoparticles, but cell culture and animal studies have begun to offer clues. Complicating the effort to characterize effects is the number of different nanoparticles and applications, each of which may affect cells differently. Data on the cellular effects of nanoparticles come mostly from *in vitro* cell culture nanotoxicology studies. Interactions between the nanoparticle and the cell can be chemical, including the production of reactive oxygen species, dissolution and release of toxic ions, and disturbance of the electron/ion cell membrane transport activity; or physical, including disruption of membrane integrity and stability, transport processes, protein conformation and folding, and protein aggregation.[14] Intracellularly, some nanoparticles appear to target mitochondria, sometimes affecting function and leading to apoptosis.[14-17] Often, nanoparticles end up in lysosomes, which carry out the cell's digestion and excretion activities, although it is not known whether or how those processes are affected.[14,18,19] Some nanoparticles are small enough to enter the nuclear space through pores in the nuclear envelope, and have been shown to induce DNA damage.[14,20,21] At the protein level, the ability of nanoparticles to affect protein folding has been shown to interfere with cell signaling processes and to result in aggregations or amyloid-like structures.[14,22-24]

In vivo studies are necessary to examine routes of exposure and how cellular effects translate to tissue and organ function in complex multi-cellular organisms like humans. Studies using animal models have demonstrated that the organs most commonly exposed to nanoparticles are the lungs, skin, and gut; nanoparticles gain access to the systemic circulation by inhalation, direct contact, and ingestion, respectively.[14,25] Transport throughout the body has been demonstrated, though in very small quantities; biodistribution studies have shown low concentrations of nanoparticles in the liver, spleen, heart, brain and central nervous system.[14] It is not yet clear to what extent nanoparticles bioaccumulate in organs, nor at what rate they are excreted.[14] In tissues exposed to nanoparticles, inflammation has been observed, but the mechanisms resulting in inflammation are unclear.[14,26]

No known studies to date have examined the effects of real-world exposures in humans, i.e., exposure levels that an average human being would experience in day-to-day life. Cell culture and animal studies have used exposure levels that are thought to be far greater than those experienced by an average person. From current research findings, no evidence exists of adverse changes in human health as a result of the use of nanoparticles currently on the market.[27] However, the known adverse health effects of ultrafine particulate matter (dust and pollutants), which is also nanoscale-sized, suggests that the effect of engineered nanoparticles on human health warrants rigorous scientific study.[14]

NANOPARTICLES AND THE ENVIRONMENT

In addition to concerns about potential direct human health effects of nanoparticles, concerns exist about the potential of nanomaterials to adversely affect the environment. In free form, nanoparticles can be released in the air or water during production or as a waste byproduct of

production, and ultimately accumulate in the soil, water, plant, or animal life. In fixed form, where they are part of a manufactured substance or product, nanoparticles will ultimately have to be recycled or disposed of as waste. Toxicity of nanoparticles to microorganisms, aquatic invertebrates, and some terrestrial organisms has been described,[28] but similar to studies on human exposure, it is not known whether the acute experimental exposure levels accurately reflect potential toxicity from real-world exposure levels. Few nanotoxicity studies have been reported for plants.[28]

A challenge in evaluating risk associated with the manufacture and use of nanomaterials is the diversity and complexity of the types of materials available and being developed, as well as the vast potential uses of nanomaterials.[2] Improvements in standard protocols for environmental risk assessments are needed and is an area of active study for the Environmental Protection Agency (EPA) and other research groups.[2,29] While potential nanoparticle hazards are a focus of attention, the use of some nanomaterials has led to the development of new environmental sensors and remediation technologies that may provide new tools for preventing, identifying, and solving environmental problems.[2]

OVERSIGHT AND REGULATION OF NANOTECHNOLOGY PRODUCTS

Existing statutes and responsibility to protect the health of the public provide a foundation for the FDA's regulation and oversight of nanomaterials. The FDA has not adopted a regulatory definition of "nanomaterial;" instead, it has taken a broadly inclusive approach to considering whether products contain nanomaterials or involve nanotechnology.[30] The Agency recently issued a draft guidance for industry suggesting that several factors be considered when determining whether products include nanomaterials or otherwise involve nanotechnology.[31] For example:

1) Has the product or material been engineered to occur in the nanoscale range (as opposed to naturally occurring in the nanoscale range)?
2) Is one dimension of the product or material less than 100 nanometers?
3) Does the product or material exhibit properties that are attributable to its dimensions?[28]

The FDA's approach to regulating nanomaterials consists of the following attributes:[30,32]

- Product-focused and science-based: Assessments take into account the effects of the nanomaterial(s) in the context of each product and its intended use.
- Follows legal standards for different product classes: Food and drug products will be regulated according to their corresponding standards criteria. For example, foods are evaluated for safety, while drugs are evaluated for safety and effectiveness.
- Attention to nanomaterials is incorporated into pre-market review procedures: For products required to undergo premarket review (new drugs, biologics, food additives, color additives, certain devices, and certain new ingredients in dietary supplements), review procedures include attention to whether the use of nanomaterials suggests the need for additional data on safety and effectiveness.
- Consultation when pre-market review authority does not exist: For products not required to undergo pre-market review (most dietary supplements, cosmetics, and food), FDA encourages manufacturers to consult with it before bringing nanomaterial products to the market. The consultation serves the purpose of reviewing safety information and designing necessary post-marketing oversight.
- Post-market monitoring: FDA will monitor the marketplace for nanomaterial products and will take action as needed to protect consumers.

- Industry responsibility: Regardless of whether or not a product is subject to pre-market review, manufacturers must use all information possible to ensure that their product meets all applicable safety standards.
- Collaboration with domestic and international regulatory counterparts: FDA works with other U.S. agencies[8] to contribute to and coordinate overarching policy on nanotechnology; and with foreign regulatory counterparts to share information on nanotechnology products.
- Technical advice and guidance: FDA will offer technical advice and guidance to help industry meet its obligations to ensure that nanomaterial products are safe.

The EPA has the obligation and mandate to protect human health and safeguard the environment. Its goal of better understanding and addressing potential risks from exposure to nanoscale materials and products is carried out in a number of its Offices:[2]

- Office of Pollution Prevention and Toxics: Administers a voluntary program for the evaluation of nanomaterials and reviews nanomaterial premanufacture notifications under the Toxic Substances Control Act.
- Office of Air and Radiation/Office of Transportation and Air Quality: Reviews nanomaterial registration applications.
- Office of Pesticide Programs: Reviews potential nanoscale pesticides for exposure and hazard profiles on a case-by-case basis.
- Office of Solid Waste and Emergency Response: Investigates the use of nanoscale materials for environmental remediation.
- Office of Enforcement and Compliance Assurance: Evaluates existing statutory and regulatory frameworks to determine the enforcement issues associated with nanotechnology.

In 2000, the National Nanotechnology Initiative (NNI) was created as a central point of communication, collaboration, and cooperation for the 26 Federal agencies involved in nanotechnology research and regulatory activities. The mission of the NNI is to expedite the discovery, development and deployment of nanoscale science and technology to serve the public good, through a program of coordinated research and development aligned with the missions of the participating agencies.[33] NNI invests heavily in research projects that examine the safe use of nanomaterials, in turn acting as a resource to the FDA, EPA, and other regulatory agencies.[4]

CONCLUSIONS AND AMA POLICY CONSIDERATIONS

Nanotechnology has demonstrated great benefit in the improvement of consumer products and applications. Very little is known about how nanomaterials affect human health and the environment, but preliminary research has shown that acute exposure to nanoparticles can affect cellular behavior and may be toxic to some components of the environment. More detailed research is needed to examine how real-world exposure levels affect human health and the environment. In the meantime, regulation of products or applications that include nanomaterials will occur on a case-by-case basis, using science-based methods to evaluate the balance of benefits and risks. AMA policy is strongly supportive of the FDA's mission to protect the health of the public, and of the EPA's efforts to ensure that the public is protected from environmental pollution.

RECOMMENDATION

The Council on Science and Public Health recommends that the following statement be adopted in lieu of Resolution 512-A-12, and that the remainder of the report be filed.

Our American Medical Association: (a) recognizes the benefits and potential risks of nanotechnology; (b) supports responsible regulation of nanomaterial products and applications to protect the public's health and the environment; and (c) encourages continued study on the health and environmental effects of exposure to nanomaterials. (New HOD Policy)

Fiscal note: No significant fiscal impact

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