

# Nanotechnology: Safety Issues

**KATHLEEN KENWRIGHT, LINDA L WILLIFORD PIFER**

**ABBREVIATIONS:** FDA= Federal Drug Administration; MSDS= material safety data sheets; ASR= analyte specific reagents; NIOSH = National Institute for Occupational Safety and Health, NIST = National Institute of Standards and Technology; OTC = over-the-counter; NIL= National Information Library; FTC= Federal Trade Commission; CDER= Center for Drug Evaluation and Research; EPA= Environmental Protection Agency; NST= Center for Nanoscale Science and Technology; NTF= Nanotechnology Task Force; PEN = Project on Emerging Technologies.

**INDEX TERMS:** nanomaterials; nanoproducts; nano-emulsions; nanoparticles; Nanotechnology Task Force; Project on Emerging Technologies; Center for Nanoscale Science and Technology, nanotechnology safety

**LEARNING OBJECTIVES:**

1. List the “watchdog” organizations and agencies that intend to improve oversight of the safety of nanotechnology development and research.
2. Describe potential personal risks posed by nanotechnology.
3. Differentiate between speculation about nanomaterial safety and data-supported “facts”.
4. List products that contain nanoparticles.
5. Identify sources of information concerning safety of handling nanotechnology products in the clinical laboratory.

**Clin Lab Sci 2010;23(2);122**

*Kathleen Kenwright, MS, MT,MP(ASCP) SI , University of Tennessee Health Science Center, Memphis, TN 38163*

*Linda L. Williford Pifer, Ph.D.,SM(ASCP), GS(ABB), University of Tennessee Health Science Center, Memphis, TN 38163*

*Address for Correspondence: Kathleen Kenwright, MS, MT,MP(ASCP), SI, Assistant Professor , Department of Clinical Laboratory Sciences, University of Tennessee Health Science Center, 930 Madison Avenue, Suite 672, Memphis, TN, 38163, 901-448-6338., kkenwig@uthsc.edu*

**The Current Ubiquity of Nanotechnology**

Is nanotechnology safe for humans? Nanoproducts are everywhere. There are currently over 1000 nanotechnology-based consumer products on the market.<sup>1,2</sup> An inventory of nanoengineered products is maintained by the Project on Emerging Nanotechnologies (PEN) and published on their web site (Table 1).<sup>1</sup>

**Table 1.** Examples of nanoengineered products.

Home	Electronics	Automotive	Adults/Children
Food Containers	iPod Nano®	Oil	XBOX 360®
Cutting Boards	iPhone®	Air filters	Stuffed animals
Sheets	Camera lenses	Cleaners	Pacifier
Towels	Organic light emitting diode	Wax	Sunscreen
Fabric Softener	Computer processor chips	Paint finish	Clothing

Some products boldly declare nanotechnology in their advertising such as Bionic Joint Support™ “...it’s worth taking advantage of a nanosphere liposomal delivery system”<sup>3</sup>; other manufacturers use nanoparticles but choose not to advertise the fact. Employment of nanoengineered particles in manufacturing is increasing at an enormous rate, but reporting the use of nanomaterials is voluntary. Maynard and Rejeski say these voluntary efforts have been unsuccessful.<sup>4</sup> The US Environmental Protection Agency (EPA) stated that “approximately

90% of the different nanoscale materials likely to be commercially available were not reported".<sup>4,5</sup>

Consumers are exposed to nanoparticles daily, without even realizing it, from natural sources as they are present in soot and many living and non-living entities in nature. Nanoparticles such as titanium dioxide (TiO<sub>2</sub>) and zinc oxide are used in sunscreens and cosmetics. Titanium dioxide is also used as a food additive to whiten creamy products such as salad dressings, and it is used in candies and non-dairy creamers.<sup>6</sup> Nanomaterials are internalized by ingestion of food, medication or supplements that contain microparticles (Figure 1). Silicates and aluminosilicates are added to food products as an adsorbent to prevent caking. The average person ingests approximately 1012 submicron-sized particles each day in the form of food additives.<sup>6</sup>



Figure 1. Medications and Supplements

### Exposure to Nanomaterials

There are four routes of possible exposure to nanomaterials: skin contact, respiratory exposure, needle injection, and oral contact.<sup>7</sup> Safety issues concerning nanotechnology will affect everyone, either as consumers using products containing nanomaterials, as patients being treated or tested (*in vivo*) with nanoparticles, occupational hazards, and even innocent bystanders who breathe the air that may contain nanoparticles.

What safeguards are in place and what agencies are responsible for monitoring the safety of nanomaterials available in the public venue? The Nanotechnology Task Force (Task Force) was formed in 2006 by the Food and Drug Administration (FDA). One of the

functions of the Task Force is to evaluate any specific problems that may arise from using nanoscale materials contained in FDA-regulated products. This would cover FDA-cleared reagents in the laboratory, but may not cover the use of research reagents, analyte specific reagents (ASRs), or products containing nanomaterials used in paints, coatings, and other products in use beyond the venue of the clinical laboratory.

The FDA places the responsibility for safety of over-the-counter dietary supplements upon the manufacturer. The FDA has post-marketing power and responsibility which includes "...monitoring safety, e.g., voluntary dietary supplement adverse event reporting, and product information, such as labeling, claims, package inserts, and accompanying literature." The Federal Trade Commission (FTC) regulates dietary supplement advertising.<sup>8</sup> The Office of Nonprescription Products' Center for Drug Evaluation and Research (CDER) serves as a "watchdog" that oversees OTC's proper labeling and risks vs. benefits issues.<sup>9</sup> These are primarily "post-marketing" powers, which are usually not applicable prior to sale.

### Nanotechnology Safety in the Laboratory

Laboratory professionals may once again face an unforeseen safety hurdle. Will gloves typically worn in the lab protect against reagents that contain nanoparticles (Figure 2)? If nanoparticles cross the glove barrier will they penetrate the skin or remain on the surface? If they penetrate the skin, will the particles migrate to various organ systems and tissues or remain at the site of penetration?<sup>10</sup> Does evidence exist that they may perhaps be teratogenic, mutagenic, or carcinogenic?

At present, Material Safety Data Sheets (MSDSs) regarding nanomaterials are a work in progress, and toxicology data are accumulating and continually being sought. Examples of these may be found on the website of the College of Engineering at the University of Illinois (Urbana-Champaign).<sup>11</sup> A web-based Nanoparticle Information Library (NIL) is currently being established by NIOSH. The goals include collection of information on health and safety issues available on a national and international level for those working with nanomaterials.<sup>12</sup> This data base includes

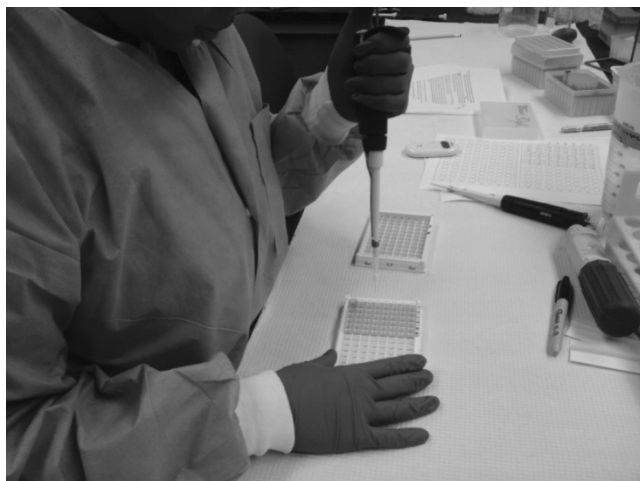


Figure 2. MLS working in laboratory.

composition of nanomaterials, methods for producing them, particle size, surface area and morphology, including "...scanning, transmission, or other electron micrographic images".<sup>12</sup> In addition, the Center for Nanoscale Systems at Harvard University maintains safety and training information as well as MSDS's on its website.<sup>13</sup>

Since both clinical laboratory scientists and the lay public have concerns about potential risks posed by skin contact with nanomaterials, this issue presents an ideal venue in which to explore the controversy. The cosmetology industry states that evidence suggests that the nanoemulsions sometimes used in milk products, cosmetics or sunscreens do not cross the skin barrier, even when conditions such as psoriasis exist.<sup>14</sup> Nohynek, Dufour and Roberts concluded that the current abundance of evidence "...suggests that nanomaterials used in cosmetic preparations or sunscreen pose no risk to human skin or human health."<sup>10</sup> They point out that sunscreen is extremely important in the prevention of skin cancer, which has reached a virtual epidemic status in the EU, US and Australia.<sup>10</sup> Here again, we must sift through the data to determine any risk posed by nanomaterials in sunscreen weighed against potential benefit derived from nanomaterials present in these products. However, to accomplish this meaningfully, reproducible data must be presented.

A thoughtful analysis by M. Berger asserts that absolute proof of skin-applied nanomaterial's inability to

penetrate healthy human skin and the safety of these products has not been substantiated to everyone's satisfaction. He states that the controversy arises from an "...incomplete scientific picture created by a lack of relevant research", and points out that sunburn might increase the risk for nanoparticle skin penetration.<sup>15</sup> Berger also describes research by Baroli, et al. underway at the University of Rochester Medical Center that addresses this issue, and their studies indicate that metallic nanoparticles were able to penetrate the hair follicle and stratum corneum of human skin<sup>16</sup>. She states that "...nanoparticles were unable to permeate the skin." She further indicates that this presents early evidence that rigid nanoparticles can "...passively reach the viable epidermis through the SC lipidic matrix".<sup>17</sup> Clearly, the jury is still "out" on this issue.

### Nanotechnology and Regulatory Agencies

There are many unanswered questions but, fortunately, numerous U.S. and international governmental agencies have been investigating the use of nanomaterials. The primary questions on the table are these: Are laboratory professionals at risk? As consumers, are we at risk? The U.S. Environmental Protection Agency (EPA), the National Institute of Occupational Health and Safety (NIOSH), the National Institute of Environmental Health and Safety, the CDC and the National Toxicology Program are all working to identify and eliminate hazards.

NIOSH asks how could workers be exposed to these particles in the industrial use or manufacturing of nanomaterials and how will nanomaterials impact the various systems of the human body, or will they?<sup>18</sup> Vladimir Murashov, PhD, Special Assistant to the NIOSH Director, and John Howard, MD, former NIOSH director, published the "six essential features for proactive management of occupational safety and health risks in emerging industries such as nanotechnology"<sup>19</sup> in the 2009 issue of *Nature Nanotechnology*. These six features include "qualitative risk assessment; the ability to adapt strategies and refine requirements; an appropriate level of precaution; global applicability; the ability to elicit voluntary cooperation by companies; and stakeholder involvement".<sup>19</sup>

### Potential Health Risks of Nanomaterials

The greatest potential health threat to humans by nanoparticles appears to be by inhalation.<sup>7</sup> The conclusion of DR Johnson, et al. in “Potential for Occupational Exposure to Engineered Carbon-based Nanomaterials in Environmental Laboratory Studies” was that “Engineered nanomaterials can become airborne...” under certain circumstances, indicating that “laboratory workers may be at increased risk of exposure to engineered nanomaterials”<sup>20</sup>. However, these “laboratory workers” are those at the research and development stage, and does not necessarily include those who work with finished, FDA-approved diagnostic kits or devices.

Recently it was reported that seven workers in a Chinese printing factory who worked with nano particles developed pleural granulomas.<sup>21</sup> All seven had 30 nanometer-sized particles in their lungs. Two of the workers died. This case is complicated by the fact that the workers were working in a small non ventilated area. Experts cannot positively conclude that their symptoms were because of the nano sized particles or by inhaling chemical fumes.

In a 2007 review, “Nanotechnology Safety Concerns Revisited”, Stern and McNeil<sup>7</sup> detail several rat and human studies on radiolabeled nanoparticle systemic distribution, and conclude, based upon available data, that the respiratory tract “...represents a formidable barrier to the systemic exposure of some nanoparticles”.<sup>22</sup> However, experimental investigations continue, as they should.

Another concern about nanotechnology is that nanoparticles may pose risks to the environment. Researching these potential effects are subject to multiple difficulties, including standardization of experimental conditions, how to assess long-term chronic effects, the presence of contaminants and other sources of error, and the fact that the rat model may/may not be predictive of human exposure outcomes.

Clinical laboratory scientists are very well trained to handle biohazardous and chemically hazardous materials; many have worked with radioactive materials, formaldehyde, and other chemical hazards over the

years. Monitors for exposure and environmental/engineering safety controls have been introduced. Just as monitors were in place to determine the quantity of radiation exposure sustained by technologists, one wonders if such monitors or other protective devices will become necessary for the use of diagnostic nanomaterials. Since at this time, none have been employed or recommended, it appears unlikely that that this will occur. Since clinical laboratory scientists are handling “finished” test kits, it is more likely that if there is a risk, that it will be experienced by those who prepare nanomaterials for inclusion in these reagents.

### Federal Guidance and Nanotechnology

For guidance, we must rely upon the FDA, NIOSH, OSHA, CDC and the various other governmental and professional agencies dedicated to health and safety in the laboratory, in other work places and in the environment at large. Material Safety Data Sheets, which are currently under development, will provide guidance.

In conclusion, there are many troubling concerns. Summer Johnson, the executive managing editor of NT-MDT<sup>23</sup>, likens nanotechnology to the American “wild west”, as well as the next industrial revolution. She emphasizes the information explosion that we are experiencing in nanotechnology. It is incredibly difficult to “keep up” with all of the data simultaneously. It actually becomes a concern that we are inundated with such an information torrent, that we could be deluged and drowned in the flood. As a bioethicist, she opines that “There is no single governmental agency given dominion to regulate nanotechnology and regulate its progress”.<sup>23</sup> She knowledgeably expresses concerns about the potential (and proven) fraud in this exciting new technology. We must remember that only data, not opinion, must be seriously accepted.

### What is the Truth about Nanotechnology?

What constitutes what we “believe” as scientific evidence? Only the data tell the entire story, as it is revealed by experimental results, and it changes quite constantly, depending on current trends in research, reproducibility of data, and publication. Research findings must be reproducible and consistent before “belief” and trust can be achieved in a rational manner.

The ultimate truth is “out there”, according to the past popular television show “The X-Files”, but finding it is always challenging. Be careful what you believe. A single report or two do not constitute hard evidence. They are only “flags” indicating areas of interest and possible concern, but are not necessarily the “bottom line” of the facts at the end of the day. Science struggles forward laboriously, and these news reports are helpful, but are usually not the total truth until they are tried and true. Trends are “easy”, solid facts are not. Research findings must be reproducible and consistent before “belief” and trust can be achieved in a rational manner. Only if “the glove fits”, we must invest conviction (acceptance/belief). Whenever profit is at stake, absolute truth may be compromised. Virtually everyone who is technologically inclined must want to embrace this new “singularity”, but as always, we must be critical in a positive sense of what we hear, read and see. Optimism and caution must be the watchwords. We are entering a “Brave New World” and, as usual, technology is at the front line. As they said on the old hit television program “Hill Street Blues”, “Be careful out there!” In conclusion, it is evident that a great deal of progress has been made. However, maintaining (and keeping pace with) current detailed health and safety information in this rapidly expanding technology will undoubtedly be extremely challenging.

REFERENCES

1. Nanotechproject.org. The Project on Emerging Technologies, Washington, DC. Available from <http://www.nanotechproject.org/inventories/consumer/browse/products/> [cited Oct 10, 2009].
2. Schulte PA, Schubauer-Berigan MK, Mayweather C, et al. Issues in the development of epidemiologic studies of workers exposed to engineered nanoparticles. *J Occup Environ Med* 2009. Mar doi: 10.1097/JOM.0b013e3181990c2c. PubMed PMID: 19225418.
3. Life Enhancement Products, Inc. Bio Joint Product. Available from <http://www.life-enhancement.com/product.asp?ID=616#desc>. 2009 [cited Oct 11, 2009].
4. Maynard A, Rejeski D. Too small to overlook. *Nature* 2009. doi: 10.1038/460174a
5. Nanoscale Materials Stewardship Program. Interim Report (US Environmental Protection Agency, 2009).
6. Lomer MC, Thompson RP, Powell JJ. Fine and ultrafine particles of the diet: influence on the mucosal immune response and association with Crohn's disease. *Proc Nutr Soc* 2002; 61:123–30.
7. Stern ST, McNeil SE. Nanotechnology safety concerns revisited. *Toxicol Sci* 2008;101:4–21. PMID 17602205 doi:10.1093/toxsci/kfm169.
8. Food and Drug Administration. Dietary Supplements. Available from <http://www.fda.gov/Food/DietarySupplements/default.htm>. Jun18, 2009 [cited Oct 13, 2009].
9. Food and Drug Administration. Available from <http://www.fda.gov/AboutFDA/CentersOffices/cder/ucm093452.htm>. Office of Nonprescription Products, Nov 10, 2009 [cited Dec 2, 2009].
10. Nohynek GJ, Dufour EK, Roberts MS. Nanotechnology, cosmetics and the skin: is there a health risk? *Skin Pharmacol Physiol* 2008. doi: 10.1159/000131078. PMID: 18523411
11. College of Engineering, University of Illinois at Urbana-Champaign. Available from: <http://mntl.illinois.edu/CleanroomMSDS.htm>. [cited Oct 13, 2009].
12. National Institute for Occupational Safety and Health. Atlanta. Available from: <http://www.cdc.gov/niosh/topics/nanotech/NIL.html>. Aug 28, 2009 [cited Oct 13, 2009].
13. Center for Nanoscale Systems, Harvard University. Available from <http://www.cns.fas.harvard.edu/safety/index.php>. Cambridge Massachusetts c2009 [cited Oct 13, 2009].
14. Butz T. No evidence for nanoparticle penetration into living skin. *Proceedings of European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC)*, Barcelona, Spain 2005. Available from <http://www.colipa.eu/nanotechnology.html?sid=49&smid=115>. [cited Oct 6, 2009].
15. Berger M. Sunburn increases risk of nanoparticle skin penetration. Available from: <http://www.nanowerk.com/spotlight/spotid=6838.php>. Nanowerk Aug 20, 2008. [cited Oct 8, 2009].
16. Berger M. Nanopenetration of human skin-a double edged sword. Available from <http://www.nanowerk.com/spotlight/spotid=1820.php>. Nanowerk Apr 24,2007 [cited 2009 Oct 8].
17. Baroli B, Ennas MG, Loffredo F, et al. Penetration of metallic nanoparticles in human full-thickness skin. Available from <http://www.nature.com/jid/journal/v127/n7/abs/5700733a.html>. *J Invest Dermatol* 2007: 1701–12; doi: 10.1038/sj.jid.5700733.
18. Natural Institute for Occupational Safety and Health (NIOSH), Atlanta. Available from: <http://www.cdc.gov/niosh/topics/nanotech/NIL.html>. Oct 19, 2009 [cited Dec 3, 2009].
19. Murashov V, Howard J. Essential features for proactive risk management. doi:10.1038/nnano.2009.205. *Nature Nanotechnology* 2009 August; [cited 2009 Oct 6].
20. Johnson DR, Methner MM, Kennedy AJ, Stevens JA. Potential for occupational exposure to engineered carbon based nanomaterials in environmental laboratory studies. *Environmental Health Perspectives*. Forthcoming 2009.
21. Gilbert N. Nanoparticle safety in doubt. Available from: <http://www.nature.com/news/2009/090818/full/460937a.html> *Nature News* Aug 2009 [cited Oct 11, 2009]
22. Oberdorster G, Sharp Z, Atudorei V, et al. Extra pulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats, Part A. *J Toxicol Environ Health* 2002; 65:1531–43.
23. Johnson S. The wild west of nanotechnology. Available from: <http://www.nanotech-now.com/columns/?article=297> *Nanotechnology Now*. Apr 25, 2009 [cited Oct 6, 2009].