

# Understanding Risk Assessment of Nanotechnology

By *Trudy E. Bell*

## I. Why small particles are a big story

For decades, scientists have anticipated from theory that if they could manipulate individual molecules, they could engineer materials with electronic, optical, and other properties not observed in bulk—and open new frontiers in electronics,<sup>1</sup> medicine, and consumer products.<sup>2</sup> Rather as cells use a few amino acids to assemble proteins with a wide range of characteristics and functions, nanotechnology may make it possible to design and engineer materials at the molecular level to have specific properties. “There is plenty of room at the bottom” is an often-quoted prophetic quip of the late Caltech physicist Richard A. Feynman in 1959.<sup>3</sup>

Half a century later, the promise of nanotechnology is becoming reality—not only in the lab but already in some commercial consumer products ranging from sunscreens to self-cleaning windows. More exciting are possibilities of targeted cancer therapies, where a tumor may be eradicated without making the rest of the body sick.<sup>4</sup> Environmental researchers are investigating the use of engineered nanoscale materials (engineered nanomaterials for short<sup>5</sup>) to purify or desalinate water, to improve energy efficiency, or to clean up hazardous wastes.<sup>6</sup> Indeed, people are starting to talk about engineered nanomaterials as a completely new class of materials, and nanotechnology as being a new industrial revolution—as significant to the twenty-first century as the first industrial revolution was to the nineteenth century and the information-technology revolution was to the twentieth.

But with such a revolutionary new technology come questions

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about occupational, consumer, and environmental safety and health. If engineered nanomaterials have physical properties different from their bulk counterparts, might they also pose new risks to human health in their manufacture, use, and disposal?

As yet, no one knows. Current data basically suggest “it depends.” But researchers both in government and private industry are keen to find out.<sup>7</sup>

First, toxicity itself can be useful. Indeed, it is highly sought for certain applications, such as cancer therapies. (Also, keep in mind that often toxicity depends on dose and administration: even table salt is toxic in high doses.)

Second, if toxicity is known, handling and packaging procedures can be devised to mitigate risks of undesired exposure in manufacturing processes, as is routinely done in industries using hazardous materials. Safe-handling procedures for engineered nanomaterials may need to differ from those now used for larger micrometer-sized particulates—especially important for nanomanufacturing workers.<sup>8</sup> Questions have also been raised about the safety of engineered nanomaterials in consumer products or in implantable medical devices, or to plants and animals in the environment after disposal.<sup>9</sup>

Third, nanotechnology developers are heeding a lesson in *perceived* risk from an unrelated high-tech field: consumer resistance that arose at the introduction of crops and products using genetically modified organisms (GMOs). In part, that resistance arose because biotech companies introduced GMO products without much open discussion of legitimate questions and concerns in the general public, with the result that the public felt it had to accept risks to health and environment while benefits were limited to increased profits for large agribusiness. The result was widespread public mistrust and suspicion. Wanting to avoid a similar fate (especially given that concern and calls for regulation already have been expressed in some quarters<sup>10</sup>), nanotech developers are pursuing what they call “responsible development,” i.e., directing research towards potential negative impacts of nanomaterials, as well as toward beneficial applications.<sup>11</sup>

This backgrounder has three purposes: to sketch essential basics of the physics and biology of engineered nanomaterials (and, for that matter, also natural and incidental nanoparticles),

to highlight key issues and resources, and—most importantly—to warn about contradictory findings and pitfalls of logic and to suggest insightful questions before conclusions are drawn.

## II. Uncertain terms

**Disagreement on classification.** According to the National Academies, a distinction is made between three types of nanoscale particles (often abbreviated in the literature as “NSPs”): natural, incidental, and engineered. Natural nanoparticles occur in the environment (volcanic dust, lunar dust, magnetotactic bacteria, mineral composites, etc.). Incidental nanoparticles, sometimes also called waste or anthropogenic particles, occur as the result of manmade industrial processes (diesel exhaust, coal combustion, welding fumes, etc.). Both natural and incidental nanomaterials may have irregular or regular shapes. Engineered nanomaterials most often have regular shapes, such as tubes, spheres, rings, etc.

Engineered nanomaterials can be produced either by milling or lithographic etching of a large sample to obtain nanosized particles (an approach often called “top-down”), or by assembling smaller subunits through crystal growth or chemical synthesis to grow nanomaterials of the desired size and configuration (an approach often called “bottom-up”). The specific production technique may or may not influence human health risk.<sup>12</sup>

Recent questions about toxicity are directed at engineered nanomaterials. Nonetheless, the literature about natural and incidental nanoparticles is helpful, because more is known about them (in part, because of research on smog, welding fumes, coal dust, and ultrafine aerosols<sup>13</sup>), and because information about their behavior can be helpful for understanding the behavior of engineered nanomaterials.

Also according to the National Academies, nanoscale materials—whether engineered or natural—so far seem to fall into four basic categories.<sup>14</sup> The group currently with the largest number of commercial nanomaterials is the metal oxides, such as zinc or titanium oxides, which are used in ceramics, chemical polishing agents, scratch-resistant coatings, cosmetics, and sunscreens. A second significant group is nanoclays, naturally occurring plate-like clay particles that strengthen or harden materials or make them flame-retardant. A third group is nanotubes, which are used in coatings to dissipate or minimize static electricity (e.g., in fuel lines, in hard disk handling trays, or in automobile bodies to be painted electrostatically). The last group is quantum dots, used in exploratory medicine or in the self-assembly of nanoelectronic structures. But be aware: not every official source finds the same categorization useful. For example, the U.S. Environmental Protection Agency divides engineered nanomaterials into carbon-based materials (nanotubes, fullerenes), metal-based materials (including both metal oxides and quantum dots), dendrimers (nano-sized polymers built from branched units of unspecified chemistry), and composites (including nanoclays).<sup>15</sup>

**Disagreement on definition.** Most U.S. and British nanotech experts define nanomaterials as materials smaller than 100

nanometers (nm)—that is, 0.1 micrometer or micron ( $\mu\text{m}$ )—in any one dimension. Thus, a fiber thinner than 100 nm would be considered a nanomaterial even if it were several micrometers long. This definition, however, is not universal. In Japan, particles between 50 and 100 nm are classed as “ultrafines” and only those below 50 nm in one dimension are considered genuine NSPs.<sup>16</sup> That being said, even some U.S. government agencies also use the term “ultrafines” to describe particles under 100 nm<sup>17</sup> (although usually in the context of only natural or incidental nanoparticles—seldom referring to engineered nanoparticles). To resolve such confusion, ISO, IEC, ANSI, ASTM, and other national and international standards bodies are now discussing the standardization of terminology, metrology, characterization, and approaches to safety and health.<sup>18</sup>

Just how small is 1 nm? It’s about one hundred-thousandth the diameter of a human hair (which is 50 to 100  $\mu\text{m}$ ). More usefully, 1,000 nm (1  $\mu\text{m}$ ) is about the size of a bacterium, about the limit of what is visible through most light microscopes. In contrast, 100 nm is about the size of a virus, a tenth the size of a bacterium. NSPs, like viruses, are invisible even through the best light microscope, because they are smaller than wavelengths of light (which range from about 700 nm in the red to 400 nm in the violet); they can be imaged only with some higher-resolution instrument such as a scanning electron microscope. 1 nm is about the size of a single sugar molecule.<sup>19</sup>

**Four anticipated generations.** Already, scientists are talking in terms of generations of engineered nanomaterials. First-generation is passive nanostructures, such as individual particles, coatings, etc.—types of engineered nanomaterials already incorporated into some consumer products. Second-generation is nanostructures that perform an active function, such as transistors or sensors, or that react in an adaptive way; many are under development. Third-generation engineered nanomaterials might be three-dimensional systems that could self-assemble or be used to target drug delivery to specific parts of the body, anticipated to be developed about 2010. Fourth generation is anticipated to be molecular structures by design.<sup>20</sup>

## III. The surprising physics of engineered nanomaterials

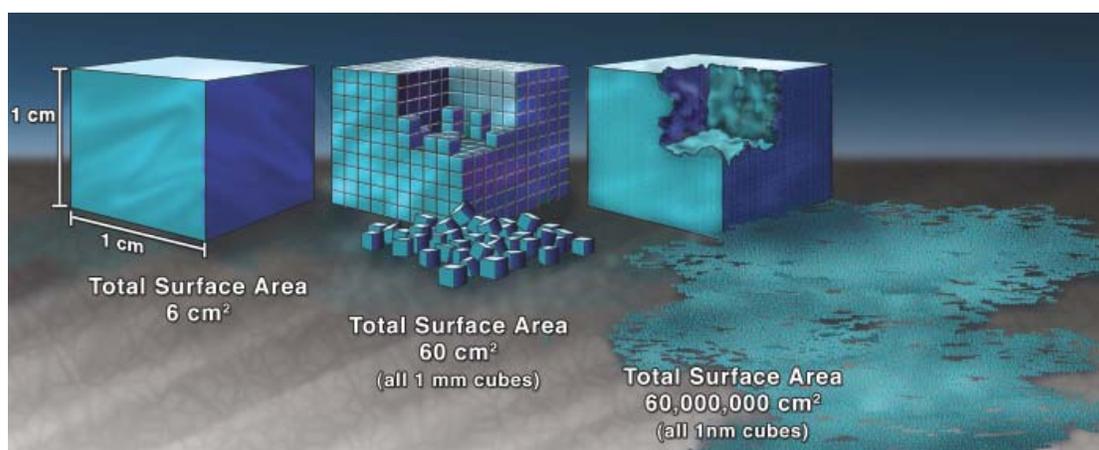
**Size matters.** At the nanoscale, fundamental mechanical, electronic, optical, chemical, biological, and other properties may differ significantly from properties of micrometer-sized particles or bulk materials.

One major reason is surface area. Surface area counts because most chemical reactions involving solids happen at the surfaces, where chemical bonds are incomplete. The surface area of a cubic centimeter of a solid material is 6 square centimeters—about the same as one side of half a stick of gum. But the surface area of a cubic centimeter of 1-nm particles in an ultrafine powder is 6,000 square meters—literally a third larger than a football field. (See Figure 1, above.)

Thus, collections of NSPs with their enormous surface areas can be exceptionally reactive (unless a coating is applied), because

### Figure 1. Surface Area Diagram

A simple thought experiment shows why nanoparticles have such phenomenal surface area per unit volume. A solid cube of a material 1 cm on a side—about the size of a sugar cube—has 6 square centimeters of surface area, about equal to one side of half a stick of gum. But if that 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. The total surface area of the 1,000 cubes adds up to 60 square centimeters—about the same as one side of two-thirds of a 3 x 5 notecard—because one must count the surface areas of all the millimeter cubes even in the interior of the original volume. But when that single cubic centimeter of volume is filled with cubes 1 nanometer on a side—yes,  $10^{21}$  of them, each with an area of 6 square nanometers—their total surface area comes to 60 million square centimeters or 6,000 square meters. In other words, a single cubic centimeter of cubic nanoparticles has a total surface area a third again larger than a football field!



[Source: Trudy E. Bell; graphics courtesy of Nicolle Rager Fuller]

more than a third of their chemical bonds are at their surfaces. For example, even though silver has been used as an effective bactericide for many years, nanoscale silver has greatly enhanced effectiveness, a finding that has inspired several companies to design reusable water-purification filters using nanoscale silver fibers.<sup>21</sup>

At what size do a material's properties start changing? Is it a gradual transformation as one proceeds from large to small, or is there a threshold below which the properties abruptly change? Both may be true, actually. Quantum-size effects begin to significantly alter material properties (such as transparency, color of fluorescence, electrical conductivity, magnetic permeability, and other characteristics) whenever they dominate thermal effects, which for many materials is around 100 nm.<sup>22</sup> For electronic properties, quantum-size effects increase inversely with decreasing particle size. Yet, for some materials, other distinct properties become pronounced at particular sizes—for example, gold nanoparticles have greatly increased catalytic properties at 3 nm. Characterizing material effects at different sizes is a hot area of basic research.

**Shape matters.** Engineered nanomaterials with the identical chemical composition can have a variety of shapes (including spheres, tubes, fibers, rings, and planes). Moreover, every one of these shapes may have different physical properties, because the pattern of molecular bonds differ even though they are composed of the same atoms.

For example, until 1985, it was believed that pure carbon came in only two crystalline forms: graphite (whose hexagonal crystal lattice lies in a two-dimensional plane) or diamond (whose cubic crystal lattice extends in all three dimensions). That

year, hollow cages of 60 carbon atoms in a soccerball shape were first made in the laboratory (and also independently discovered in distant stars and in combustion byproducts)—a new crystalline form of carbon so significant it was recognized by the Nobel Prize in Chemistry in 1996.<sup>23</sup> The new form, quite stable, was named a buckyball or fullerene after the architect Richard Buckminster Fuller, inventor of the geodesic dome of the same shape. Since then, stable fullerenes of 70, 74, and 82 carbon atoms have also been synthesized. (See Figure 2, next page)<sup>24</sup>

Similarly, titanium dioxide ( $\text{TiO}_2$ ) has been synthesized in NSPs of at least two different shapes and crystalline structures, each of which may have different toxicities. Although titanium dioxide is normally opaque white—indeed, is used to make white paints—as engineered nanoparticles, its optical qualities change, allowing it to become transparent. Yet it still effectively blocks ultraviolet light, a combination of properties attractive to makers of cosmetics and sunscreens.

**Other properties matter.** Other material properties that may be more important than just size include charge, crystal structure, surface coatings, residual contamination depending on method of synthesis, and tendency of individual nanoparticles to aggregate into larger clumps.<sup>25</sup>

## IV. Hazard, risk, and other terms of art

If the physical properties of NSPs are so different from bulk materials, what might be the implications for toxicology and the risk of human exposure? First, some essential definitions:

**Hazard, risk, exposure, dose.** Several everyday words have specific meanings in the fields of risk analysis, toxicology, or occupational safety and health.



**Figure 2. Structures of Diamond, Graphite and Buckminsterfullerene<sup>23</sup>**

Carbon and some other elements (including sulphur, tin, and oxygen) are found in multiple structural forms, called allotropes, which have significantly different properties. For example, in crystalline form, pure carbon is found as graphite (very soft), diamond (very hard), and various sizes of Buckminsterfullerenes (depending on the number of carbon atoms).

[Source: [http://home.att.net/~cat6a/allot\\_carbon-1.htm](http://home.att.net/~cat6a/allot_carbon-1.htm)]

“Hazard” is the potential to cause harm; it is an intrinsic property of a material. Sulfuric acid, for example, is a hazardous material by virtue of its chemistry. Nothing can change that, short of altering its chemistry to become something else.

“Risk” is the likelihood of harm occurring; it is a combination of a hazard with the probability of exposure and the magnitude and frequency of doses. Risks, unlike hazards, can be managed and minimized: a hazardous material poses low risk if the chances of exposure and the magnitude and frequency of the dose that might be received through that exposure are low. Leaving an unlabeled paper cup of concentrated sulfuric acid on a kitchen counter poses high risk because the chance of exposure and the potential dose are high; but the same acid, if properly labeled and locked in a chemistry lab to which only trained personnel have access, poses minimal risk.<sup>26</sup>

“Exposure” is a combination of the concentration of a substance in a medium multiplied by the duration of contact. For example, dilute sulfuric acid that splashes and is quickly washed off is a low-exposure dose that may only redden the skin; concentrated sulfuric acid allowed to sit on skin is a high-exposure dose that likely will cause serious burns.

“Dose” is the amount of a substance that enters a biological system and can be measured as a systemic dose, the total amount taken up by the biological system, or as the amount in a specific organ (skin, lung, liver, etc.). And herein lie more unanswered questions.

**Questions about dosimetry.** Up to now, exposure to dust and toxic doses have been measured in terms of mass per unit volume, commonly milligrams per cubic meter. However, even very low concentrations of NSPs—whether natural, incidental, or engineered—in the air represent a phenomenal number of particles, as is well known from measurements of ultrafine pollutants. Exposing lab rats to 100-nm titanium dioxide particles has evoked the same amount of pulmonary inflammation as a *10 times greater* mass of larger (1–2.5- $\mu\text{m}$ ) particles. In fact, in at least some cases, the amount of inflammation seems to be better correlated to particle surface area of administered NSPs than to their mass.<sup>27</sup> Thus, some

toxicologists are now wondering whether surface area would be a better measure of dose for NSPs than mass. Until researchers know which counts most, many investigators are starting to specify both in their papers.

## V. The surprising toxicology of nanoparticles

**Size matters.** Size may have another crucial biological consequence: *where* nanoparticles end up in the body.<sup>28</sup>

A complex of physical factors such as aerodynamics, gravity, and mass causes the largest inhalable dust particles to deposit primarily in the nose and throat. Any toxic effects occur at that site (for example, nasal cancers due to wood dust). Smaller particles are deposited in upper airways and are expelled by the “mucosiliary escalator,” the fingerlike cilia and the mucous lining of the trachea and bronchial tubes, which together move particles up into the throat and nose, where they are coughed, sneezed, blown out, or swallowed. Any toxic effects usually result from absorption through the gut (lead poisoning for example).

The next smallest particles penetrate deeper into the alveolar region (where oxygen and carbon dioxide are exchanged in and out of the blood) and are usually cleared when alveolar macrophages (special monocytic scavenger cells in the lungs) engulf the particles and carry them away. But if a high concentration of NSPs is inhaled, the sheer number of particles—especially if they do not agglomerate—can overwhelm those clearance mechanisms, and they can penetrate to different parts of the respiratory tract. Toxic effects are usually due to killing of the macrophages, which causes chronic inflammation that damages lung tissue (asbestosis and silicosis are examples).

At sizes less than 100 nanometers, inhaled particles begin to behave more like gas molecules and can be deposited anywhere in the respiratory tract by diffusion. Like gases, NSPs—whether natural, incidental, or engineered—simply because of their “nanoscopic” size, can pass through the lungs into the bloodstream and to be taken up by cells, within hours reaching potentially sensitive sites such as bone marrow, liver, kidneys, spleen, and heart.

As particles become small compared to the size of a cell, they can begin to interact with the molecular machinery of the cell. The central nervous system’s olfactory bulb (where aromatic molecules are detected) seems to be able to absorb NSPs smaller than 10 nm from the nasal cavity—which then can travel along axons and dendrites to cross the blood-brain barrier.

Inhalation is not the only route into the body. When ingested, NSPs can end up in the liver, spleen, and kidneys. When touched, NSPs in the range of 50 nm and smaller tend to penetrate the skin more easily than larger particles (although other aspects such as charge and surface coatings of the particles are also important), sometimes, being taken up by the lymphatic system and localizing in the lymph nodes. (See Figure 3, next page.)

By the same token, the mucosiliary escalator is also not the only way out of the body. There is evidence suggesting that nanoparticles could be excreted through urine.<sup>29</sup> However,

excretion routes for nanoparticles (urine, feces, sweat) are likely to vary depending on exposure route, size, charge, surface coating, chemical composition, and many other factors.

For incidental exposure, all this uptake of NSPs into internal organs could be of concern. But for therapeutic exposure, it is exciting, as it suggests that engineered nanomaterials can be used to target therapies to specific organs, even ones normally quite difficult to reach (such as the brain).

So far, results from different investigators are more suggestive than definitive. More research needs to be done on methods of administration, means of uptake, and on the body's clearance mechanisms. Also, when nanometer-sized particles are generated, they collide randomly with each other and with other particles, and tend to aggregate or agglomerate into larger particles. The distribution of particles sizes will depend on the density of nanometer particles at the point of generation. One of the early priorities for nanotechnology health research is to gain a better understanding of the particle sizes that are likely to be associated with the production of engineered nanoparticles.

Still, size is not the only thing that matters for potential toxicity.

**Shape matters.** Although the shapes of NSPs also give them unique properties, under the Toxic Substances Control Act (TCSA) engineered nanoparticles may not be viewed as new compounds unless they have a unique composition.<sup>30</sup> For example, TiO<sub>2</sub> nanoparticles are handled the same way with respect to regulation as bulk TiO<sub>2</sub>, even though the two forms have different properties.<sup>31</sup>

Some studies show that the materials having the same composition but of different shapes as well as sizes have different toxicities—moreover, not with a linear relationship as one might expect. For example, one study showed that nanoparticles 50 to 130 nm across of quartz-crystalline silica (a substance known to be toxic) were *less* toxic than 1.6- $\mu$ m particles—but that 10-nm particles were actually *more* toxic.<sup>32</sup> But route of entry into the body as well as dose also affect toxicity. The lesson? No one should generalize from just a few studies.

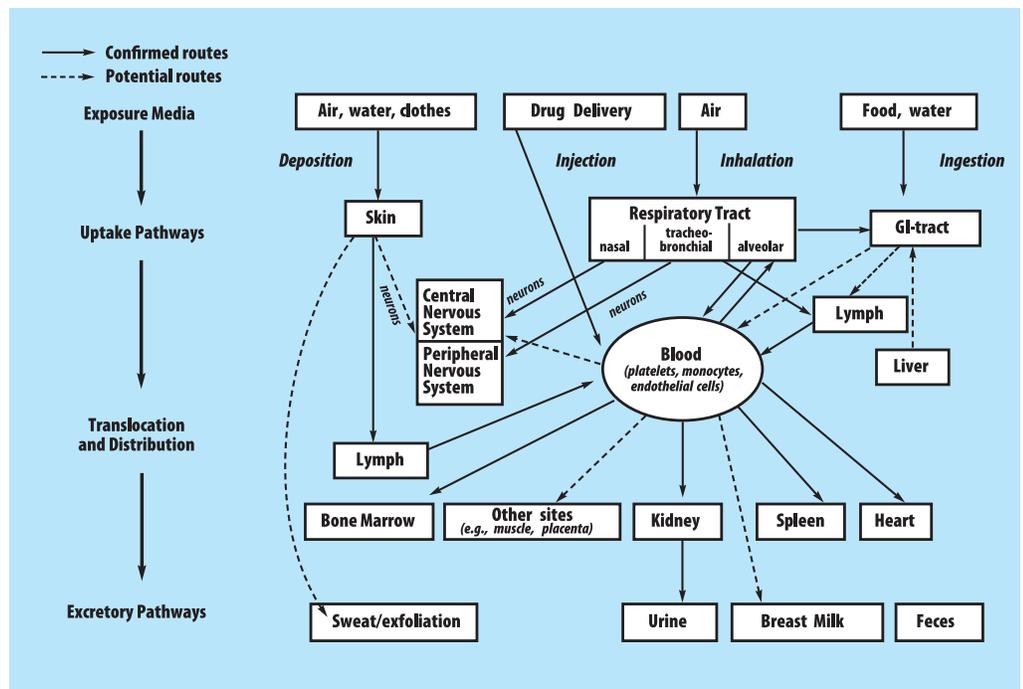
**Purity matters.** Bulk carbon in macroscopic components is medically useful because it is not poisonous to or rejected by the body. Yet, some researchers have observed from experiments that carbon nanotubes (especially single-walled or multi-walled carbon nanotubes) seem to be more toxic than other forms of carbon.<sup>33</sup> Others have debated that claim because the nanotubes used had trace impurities of iron or solvents. Indeed, some studies suggest that other forms of nanoscale carbon such as C<sub>60</sub> fullerenes might prevent toxicity by being antioxidants.<sup>34</sup>

Possibly at stake here, or in similar debates over other engineered nanomaterials, may be the *purity* of the engineered nanomaterials. At this stage, people don't have absolutely repeatable control on manufacturing processes; nanotech production is now roughly where the production of indium gallium arsenide phosphide (InGaAsP) semiconductor lasers were in the early to mid 1980s—relatively low yield of reliable production. Thus, buckyball products from one supplier are not necessarily identical to those from another, so toxicity may differ. The size of particles, their manufacture, experimental methods, whether the materials were characterized at the time the experiment was performed or were characterized earlier by the

**Figure 3. Biokinetics of Nanoscale Particles**

Nanoscale particles can end up in different parts of the body depending on size and other characteristics as well as routes of entry. Although many uptake and translocation routes have been demonstrated, others still are hypothetical and need to be investigated. Translocation rates are largely unknown, as are accumulation and retention in critical target sites and their underlying mechanisms. These, as well as potential adverse effects, largely depend on physicochemical characteristics of the surface and core of NSPs. Both qualitative and quantitative changes in NSP biokinetics in a diseased or compromised organism also need to be considered.

[Source: Günter Oberdörster et al., *Environmental Health Perspectives*, 2005]



supplier, and the comparison of their results with other studies all are relevant to understanding research results.

**Stay tuned.** With more research under way, there are more and new publications reporting on nanotoxicology.<sup>35</sup> Until more is certain, the National Institute for Occupational Safety and Health (NIOSH) has announced research needs and interim guidelines for protecting workers in nanotech industries in its report *Approaches to Safe Nanotechnology*.<sup>36</sup>

## VI. Cautions for reading reports

Be curious about what you read and look for signs of accuracy.

**Consider original sources** of popular stories and potential sources of error or exaggeration. For example, many figures are given for the number of consumer products containing engineered nanomaterials. If you check the source material, you might find that the list actually includes all marketing claims of “nano” and that no one has checked to see if nanomaterials are actually involved. This is important to the accuracy of those lists, because some marketing claims have been found to be misleading. The list of products will continue to grow each year, however, it can be misleading if lists purportedly reflecting actual nanotechnology end products also include support technology or products whose only nanotechnology is a marketing gimmick.

**Look for appropriate qualifiers.** Such words as “preliminary” or “this particular material,” as opposed to broad statements signal careful description—although there are no guarantees! At this early stage of manufacturing, samples from different suppliers are by no means standard, having different percentages of trace impurities, different distributions of sizes, etc. For example, the physical characteristics or toxicity of carbon nanotubes (CNTs) from one supplier are *not* necessarily representative of the behavior of all CNTs. Indeed, the lack of uniformity is a significant barrier to commercialization and medical use. Good R&D takes time. Until manufacturing technology becomes consistent, qualifiers are an essential part of any story. And when you read a story without qualifiers, you might want to wonder about what was likely left out.

**Look for issues of scale.** In 2005, popular articles reported on a study that asserted that alumina (aluminum oxide) nanoparticles in soils appeared to slow the growth of plants<sup>38</sup>—possibly important for environmental disposal. What the scientific report failed to state, however, is that alumina *dissolved in solution* is highly toxic to plants.<sup>39</sup> So the observed toxicity may have been irrelevant to engineered nanomaterials. In other words, even though journalists had accurately reported the paper’s findings, the scientific paper itself was faulty in ascribing cause and effect—and those deficiencies were magnified in the popular press. So question a paper’s conclusions. Ask: “Is this substance also toxic in different forms or in solution? Are the effect(s) reported unique to its nanostructure? What do skeptics say about these conclusions?” See if other researchers have commented on the paper.

**Check to see whether reported exposures were actually to nanomaterials rather than micrometer-sized particles—and indeed, to individual nanomaterials.** In solution or in air, it’s quite difficult to keep nanomaterials separate, as they tend to clump in larger aggregates or agglomerates. Not only do those larger particles have different physical and biological properties than individual nanomaterials, they may also have properties different from the original materials from which the nanomaterials were manufactured. Furthermore, not all aggregates are alike, even when composed of identical nanoparticles! For example, when C<sub>60</sub> fullerenes are mixed with water, they can crystallize into aggregates that can be circular, rectangular, or triangular, depending on how fast water is added<sup>40</sup>—and the properties of different-shaped aggregates may differ enough to be significant to environmental disposal.

**Be cautious about generalizing results from one study to another.** For example, some researchers hypothesize that nanoparticles may be easily absorbed trans-dermally (through the skin) because some quantum dots are. Quantum dots are used for such experiments because they fluoresce, so their passage through skin is easily tracked. Although quantum dots are indeed nanoparticles, their behavior may differ from nanoparticles of other shapes, sizes, or compositions (which are harder to track). Some cosmetic manufacturers may differ with these conclusions based on unpublished proprietary research, but do due diligence in tracing assertions back to primary sources.<sup>41</sup>

**Don’t assume that experimental results can be extended to actual biological systems or the environment.** Many toxicology experiments have been done *in vitro*—in Petri dishes or otherwise outside a biological system. This is often the first step in trying to determine whether a material should be studied for potential adverse effects *in vivo* or, in a living system. *In vivo* studies are conducted in animal models that can give some insight into potential responses in a human system. But extrapolating research findings from animal models to humans is difficult at best, as the animal models point to possible, but not certain, reactions. Sometimes such extrapolation is highly misleading. Recent research, for instance, has shown that human skin is much less penetrable to at least some nanoscale materials than animal skin—even though that animal skin has been used successfully to test for adverse effects at larger scales. Moreover, some *in vivo* experiments have introduced engineered nanoparticles into experimental animals by a route to which humans would never be exposed—such as injection directly into the bloodstream or lungs.

Thus, laboratory results may not be duplicated in real-life systems. In environmental studies, it is important to know whether real world conditions or laboratory conditions that do not reflect natural environments were involved. Uncontrolled real world factors such as weathering from exposure to air or ultraviolet light may complicate reactions, either increasing or decreasing risks to environmental or human health.

***Probe possible other reasons for toxicity.*** For example, one possible explanation for the toxicity of fullerenes is that they may cause oxidative stress, a mechanism that leads to cell damage or cell death.<sup>42</sup> On the other hand, some investigators have also run experiments with directly contradictory results, suggesting that fullerenes may act as antioxidants, actually protecting against oxidative stress.<sup>43</sup> Mechanisms for toxicity may differ from nanomaterial to nanomaterial.

***Don't assume common-sense macroscopic physics holds at the nanoscale.*** Some current occupational safety and health protective measures may be completely adequate to protect nanoworkers—sometimes contradicting ordinary logic. For example, current HEPA filters are designed to capture as many airborne particles of different sizes as possible. At this time, HEPA filters trap 300-nm particles with a capturing efficiency better than 99.97%. But measurements demonstrate they also trap NSPs down to 3 nm—100 times smaller—with even greater efficiency. Tests reveal that airborne NSPs behave enough like gases that their random (Brownian) motion gives a surprisingly high chance of their hitting and sticking to the filter.<sup>44</sup>

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## Endnotes

- <sup>1</sup>For the promise seen by the electronics industry in nanotech, see the chapter Emerging Research Devices <http://www.itrs.net/Common/2005ITRS/ERD2005.pdf> International Technology Roadmap for Semiconductors. <http://www.itrs.net/Common/2005ITRS/Home2005.htm> (2005).
- <sup>2</sup>For just one example report of new frontiers, see *Technology Review's* review of nanotech developments in 2005 [http://www.technologyreview.com/NanoTech-Materials/wtr\\_16096.318.p1.html](http://www.technologyreview.com/NanoTech-Materials/wtr_16096.318.p1.html) (2005).
- <sup>3</sup>Feynman's lecture "Plenty of Room at the Bottom" appears in full at <http://www.its.caltech.edu/~feynman/plenty.html>.
- <sup>4</sup>See, for example, the National Cancer Institute's National Alliance for Nanotechnology in Cancer at <http://nano.cancer.gov/index.asp>.
- <sup>5</sup>The term "engineered nanomaterials" includes both individual engineered nanoparticles, and also materials made of engineered nanoparticles bound together.
- <sup>6</sup>See, for example, the Environmental Protection Agency's (EPA) white paper <http://es.epa.gov/ncei/nano/>.
- <sup>7</sup>See, for example, A. Nel, T. Xia, L. Mädler, and N. Li, Toxic Potential of Materials at the Nanoscale, *Science*, **311**, 622–627 (February 3, 2006). See also J. Kuzma, Editor, *The Nanotechnology-Biology Interface: Exploring Models for Oversight* report of a workshop on September 15, 2005, University of Minnesota: Center for Science, Technology, and Public Policy, <http://www.hhh.umn.edu/centers/stpp/nanotechnology.html>. (2006).
- <sup>8</sup>For questions regarding occupational health, see the regularly updated nanotechnology page of the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC) at <http://www.cdc.gov/niosh/topics/nanotech/>.
- <sup>9</sup>For questions of environmental risk, see, for example, EPA, Science Policy Council, *Nanotechnology White Paper* external review draft, <http://www.epa.gov/osa/nanotech.htm> (December 2, 2005). See also R. Denison, Getting Nanotechnology Right the First Time, *Environmental Defense*, [http://www.environmentaldefense.org/documents/4446\\_EnvironmentalDefenseStatementNRCNanopanel25Mar05.pdf](http://www.environmentaldefense.org/documents/4446_EnvironmentalDefenseStatementNRCNanopanel25Mar05.pdf) (March 2005).
- <sup>10</sup>See, for example, P. Montague, 2005 in Review—Dark Clouds on the Technology Horizon: Nanotech problems pile up and the industry asks to be regulated, *Rachel's Democracy & Health News* (December 22, 2005). Reprinted at <http://www.pej.org/html/modules.php?op=modload&name=News&file=article&sid=4008>.
- <sup>11</sup>European Environment Agency, Late Lessons from Early Warnings: the Precautionary Principle 1896–2000, *Environmental Issue Report* No. 22, [http://reports.eea.eu.int/environmental\\_issue\\_report\\_2001\\_22/en](http://reports.eea.eu.int/environmental_issue_report_2001_22/en) (November 22, 2001). See also P. Montague, Nanotechnology and the Precautionary Principle, *Rachel's Democracy & Health News* **816** [http://www.rachel.org/bulletin/bulletin.cfm?Issue\\_ID=2498](http://www.rachel.org/bulletin/bulletin.cfm?Issue_ID=2498) (April 28, 2005).
- <sup>12</sup>See, for example, "How the Public Makes Sense of Nanotechnology" at the National Cancer Institute's web site (December 12, 2005) at [http://nano.cancer.gov/news\\_center/nanotech\\_news\\_2005-12-12d.asp](http://nano.cancer.gov/news_center/nanotech_news_2005-12-12d.asp).
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- <sup>14</sup>See, for example, A. Maynard and E. Kuempel, Airborne Nanostructured Particles and Occupational Health, *Journal of Nanoparticle Research* (December 2005).
- <sup>15</sup>L. Goldman and C. Coussens, Editors, *Implications of Nanotechnology for Environmental Health Research*. Roundtable on Environmental Health Sciences, Research and Medicine, The National Academies Press (2005). Available at <http://www.nap.edu/catalog/11248.html>.
- <sup>16</sup>EPA, Science Policy Council, *Nanotechnology White Paper*, December 2, 2005 external review draft <http://www.epa.gov/osa/nanotech.htm>.
- <sup>17</sup>One attempt to start standardizing definitions is the British Standards Institution's *Vocabulary—Nanoparticles*, Publicly Available Specification 71:2005. Available at <http://www.bsi-global.com/Manufacturing/Nano/index.xalter>.
- <sup>18</sup>See, for example, NIOSH Current Intelligence Bulletin: Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide, <http://www.cdc.gov/niosh/docs/preprint/tio2/pdfs/TIO2Draft.pdf> (November 22, 2005).
- <sup>19</sup>See, for example, [http://www.ansi.org/news\\_publications/news\\_story.aspx?menuid=7&articleid=1084](http://www.ansi.org/news_publications/news_story.aspx?menuid=7&articleid=1084).
- <sup>20</sup>Example sizes appear at [http://www.nano.gov/html/facts/The\\_scale\\_of\\_things.html](http://www.nano.gov/html/facts/The_scale_of_things.html).
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- <sup>22</sup>P. Jain and T. Pradeep, Potential of silver nanoparticle-coated polyurethane foam as an antibacterial water filter, *Biotechnology and Bioengineering* **90**(1), 59–63 (Published online February 18, 2005); see also S. Chen, J. Liu, and H. Zeng, Structure and antibacterial activity of silver-supporting activated carbon fibers, *Journal of Materials Science*, **40**(23), 6223–6231 (December 2005). Abstract at <http://www.springerlink.com/3hbvfyma34lyckd55sn2aeqnn/app/home/contribution.asp?referrer=parent&backto=issue,26,44;journal,8,634;linkingpublicationresults,1:100181.1>.
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- <sup>24</sup>See <http://nobelprize.org/chemistry/laureates/1996/presentation-speech.html>.
- <sup>25</sup>See [http://home.att.net/~cat6a/allot\\_carbon-I.htm](http://home.att.net/~cat6a/allot_carbon-I.htm).
- <sup>26</sup>D. Warheit, <http://pubs.acs.org/cen/nanofocus/top/83/8351sci1.html>.
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- <sup>28</sup>G. Oberdörster, E. Oberdörster, and J. Oberdörster, Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles, *Environmental Health Perspectives* **113**(7), 823–839 (July 2005). Available at <http://www.pubmedcentral.gov/articlerender.fcgi?tool=pubmed&pubmedid=16002369>. Supplemental web sections by the same authors appears at <http://chp.niehs.nih.gov/members/2005/7339/supplemental.pdf>.
- <sup>29</sup>See, for example, R. Singh *et al.*, Tissue biodistribution and blood clearance rates of intravenously administered carbon nanotube radiotracers, *Proceedings of the National Academy of Sciences* (February 21, 2006), abstract at <http://www.pnas.org/cgi/content/abstract/0509009103v1>.
- <sup>30</sup>Toxic Substances Control Act (TSCA) <http://www.epa.gov/region5/defs/html/tsca.htm>.
- <sup>31</sup>EPA has many options under TSCA by which it can regulate new chemicals. If a new substance is given a new name by the Chemical Abstract Service then it immediately falls under TSCA regulation. The Chemical Abstract Service gives a new substance a CAS # once it has been described in the scientific literature enough that the Service decides that a new chemical name is justified. EPA can also decide that a chemical – e.g., carbon is being made available as a "new use" (carbon nanotubes) and declare that TSCA regulation will be applied. The same is true for other engineered nanomaterials; macroscopic CdSe vs quantum dot sized CdSe. EPA is examining and will, following their voluntary program, make a decision about the nanosized TiO<sub>2</sub>. The FDA monograph states that from the human health standpoint there is (or was not at the time of the decision) no data indicating any difference between the micro and the nano-sized TiO<sub>2</sub>. If data become available showing otherwise, they will surely reexamine this decision.
- <sup>32</sup>D. Warheit; see bottom story "Questioning Common Perceptions About Nanoparticle Toxicity" at <http://pubs.acs.org/cen/nanofocus/top/83/8351sci1.html>. It should be noted that the samples used were of different origin (synthesized vs. natural) and most likely the observed singularity may be due to the difference in surface structure between different quartz samples.
- <sup>33</sup>Cited in Thomas and Sayre, *op. cit.*
- <sup>34</sup>N. Gharbi, *et al.*, [60]fullerene is a powerful antioxidant in vivo with no acute or subacute toxicity, *Nano Letters* **5**(12), 2578–2585 (Dec. 2005). Abstract at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=16351219&query=hl=5&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16351219&query=hl=5&itool=pubmed_docsum); written up in Buckyballs Can be Nontoxic...Maybe, National Cancer Institute, [http://nano.cancer.gov/news\\_center/nanotech\\_news\\_2006-01-09c.asp](http://nano.cancer.gov/news_center/nanotech_news_2006-01-09c.asp) (Jan. 9, 2006). Yet, a report by A. Shvedova *et al.*, Unusual inflammatory and fibrogenic pulmonary responses to single-walled carbon nanotubes in mice, *American Journal of Physiology—Lung* **289**, 698–393 (November 2005), clearly demonstrates progressive diffuse interstitial pulmonary fibrosis in response to aspiration of dispersed single walled carbon nanotubes, which were purified to remove contaminating iron.
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- <sup>36</sup>National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC), *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH*. [http://www.cdc.gov/niosh/topics/nanotech/nano\\_exchange.html](http://www.cdc.gov/niosh/topics/nanotech/nano_exchange.html) (October 1, 2005).
- <sup>37</sup>See, for example, R. Weiss, Nanotechnology Regulation Needed, Critics Say, *Washington Post*, <http://www.washingtonpost.com/wp-dyn/content/article/2005/12/04/AR2005120400729.html> (December 5, 2005), although the number was later corrected. See also K. Bullis, Can EPA Regulate Nano? *Technology Review*, <http://www.washingtonpost.com/wp-dyn/content/article/2005/12/04/AR2005120400729.html> (December 20, 2005).
- <sup>38</sup>See press release "NJIT Study Shows Nanoparticles Could Damage Plant life," at [http://www.njit.edu/publicinfo/press\\_releases/release\\_797.php](http://www.njit.edu/publicinfo/press_releases/release_797.php), reporting on the work of D. Watts of New Jersey Institute of Technology. See also L. Wang and D. Watts, Particle surface characteristics may play an important role in phytotoxicity of alumina nanoparticles, *Toxicology Letters* **158**, 122–132 (2005).
- <sup>39</sup>V. Murashov, Comments on "Particle surface characteristics may play an important role in phytotoxicity of alumina nanoparticles ...", and the affirmative response by D. Watts, accepted for publication in *Toxicology Letters* (March 2006).
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- <sup>41</sup>A primer on quantum dots is R. Hardman, A Toxicologic Review of Quantum Dots: Toxicity Depends on Physicochemical and Environmental Factors, *Environmental Health Perspectives*, **114**(2), 165 (February 2006); available at <http://www.ehponline.org/members/2005/8284/8284.html>.
- <sup>42</sup>Goldman and Coussens, *op. cit.*, p. 27.
- <sup>43</sup>Gharbi *et al.*, *op. cit.*
- <sup>44</sup>Two mechanisms are at play here. Particles generally larger than 300 nm are collected by impaction due to particle inertia and particles smaller than 300 nm tend to be collected by diffusion, behaving more like a gas. The 300-nm "valley" is the minima between these two different particle collection mechanisms and is often quoted as the most penetrating particle size for filter media.