Nanotechnology in Organic Production, Processing and Packaging

INTRODUCTION

Nanomaterials and nanoproducts are being increasingly manufactured and applied in many aspects of human life, such as medical applications, cosmetic sectors, microelectronic industries, and agricultural sectors. Nanomaterials are generally considered as substances which are very small in size, with at least one dimension of 100 nm or less. Nanotechnology is a wide range of technologies with great potentials and uncertainties. While some nanoproducts are commercially available already, some "nanoproducts" are still imagined products at this point of time, and some products are conventional products but claimed to be "nanoproducts". Research results related to nanomaterials are not always consistent. It was found that some research was conducted following the methodologies which were designed for conventional materials but are improper for nanomaterials. Presented below is an evaluation of some of the factors related to the application of nanotechnology in organic production, processing and packaging.

NANOTECHNOLOGY

Nanotechnology, as defined in "Approaches to Safe Nanotechnology - Managing the Health and Safety Concerns Associated with Engineered Nanomaterials" by the National Institute for Occupational Safety and Health (NIOSH), U.S. Department of Health and Human Services (DHHS), is "the manipulation of matter on a near-atomic scale to produce new structures, materials, and devices" (NIOSH, 2009). NIOSH (2009) specifies that:

> The U.S. National Nanotechnology Initiative[1] defines a technology as nanotechnology only if it involves all of the following:
>
> Research and technology development involving structures with at least one dimension in the range of 1–100 nanometers (nm), frequently with atomic/molecular precision
>
> Creating and using structures, devices, and systems that have unique properties and functions because of their nanoscale dimensions
>
> The ability to control or manipulate on the atomic scale.

NANOMATERIALS

Size Approach

Nanomaterials, nanoparticles, and other terms are used to describe nano-scale substances. "The International Organization for Standardization Technical Committee 229 (Nanotechnologies) is developing globally recognized nomenclature and terminology for nanomaterials" (NIOSH, 2009). The following is quoted from NIOSH (2009) with slight editorial change:

> According to ISO/TS 27687:2008, a *nano-object* is defined as material with one, two, or three external dimensions in the size range from approximately 1–100 nm.
>
> Sub-categories of nano-objects are
>
> (*1*) *nanoplate*, a nano-object with one external dimension at the nanoscale;
> (*2*) *nanofiber*, a nano-object with two external dimensions at the nano-scale with a nanotube defined as a hollow nanofiber and a nanorod as a solid nanofiber; and
> (*3*) *nanoparticle*, a nano-object with all three external dimensions at the nanoscale.

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[1] All internet materials cited in this document were accessed as on May 19, 2010.

> Nano-objects are commonly incorporated in a larger matrix or substrate referred to as a *nanomaterial*.
>
> Nano-objects may be suspended in a gas (as a nanoaerosol), suspended in a liquid (as a colloid or nanohydrosol), or embedded in a matrix (as a nanocomposite).

This size requirement seems decisive, universal, and simple, but actually it is complicated and open to further debate. The first question is how nanoparticles are measured. "The precise definition of particle diameter depends on particle shape as well as how the diameter is measured. Particle morphologies may vary widely at the nanoscale" (NIOSH, 2009). Nanoparticles could be spherical, rod-shaped, or plate-shaped. Furthermore, nanoparticles may not necessarily exist as discrete particles. "The particles may be present as discrete nano-objects, or as aggregates or agglomerates of nano-objects. These agglomerates may have diameters larger than 100 nm. In the case of an aerosol consisting of micrometer-diameter particles formed as agglomerates of nano-objects, the definition of nanoaerosol is open to interpretation" (NIOSH, 2009).

The most important property of nanoparticles is the ratio of surface area to mass, as given below. Nanoparticles can be different in shapes and in sizes, but the activities, especially chemical activities, of these nanoparticles could be about the same, when the ratios of surface area to mass are close to each other.

The size selection of 1-100 nm may also be arbitrary. Particles with sizes less than 10-30 nm might be environmentally relevant, since properties of these particles change dramatically (Madden et al., 2006). Auffan et al. (2009) suggested that "particles larger than about 30 nm do not in general show properties that would require regulatory scrutiny beyond that required for their bulk counterparts." Sizes of several commercially available nanoparticles are less than 30 nm.

Property Approach

Alternatively, nanoparticles are defined as whether target substances possess properties which are different from the properties when the same substance exists as "bulk material." An EU definition described a nanomaterial as a "material with one or more external dimensions, or an internal structure, which could exhibit novel characteristics compared to the same material without nanoscale features" (Heselhaus, 2010). It seems that "novel characteristics" override physical dimensions. Lead (2010) elaborated that "how do we treat nanostructured surfaces or aggregates of nanoparticles whose total size is not in the nano range? Although size is a useful guide, a better conceptual definition of 'nano' is that size at which novel properties and processes manifest themselves. This definition is difficult to use by regulators and standards organizations, but is scientifically extremely useful in allowing a greater freedom to pursue relevant and interesting questions."

In fact, discussions about aggregates and agglomerates of nano-objects, NIOSH (2009) stated that:

> It is generally accepted that if the nanostructure associated with the nano-object is accessible (through physical, chemical, or biological interactions), then the aerosol may be considered a nanoaerosol. However, if the nanostructure within individual micrometer-diameter particles does not directly influence particle behavior (for instance, if the nanoparticles were inaccessibly embedded in a solid matrix), the aerosol would not be described as a nanoaerosol.

"Here we argue that evidence for novel size-dependent properties alone, rather than particle size, should be the primary criterion in any definition of nanoparticles when making decisions about their regulation for environmental, health and safety reasons" (Auffan et al., 2009).

Source Approach

Nanomaterials are primarily generated from three sources: nanoparticles generated in natural processes, unintentionally produced nanoparticles by human activities (or frequently termed as anthropogenic activities), and intentionally manufactured (or engineered) nanoparticles (Oberdörster et al., 2005; Nowack and Bucheli, 2007; Farre et al., 2009).

Natural nanoparticles: Nanotechnology might be a new technology in the human mind, but nature is working in this way already (Oberdörster et al., 2005; Farre et al., 2009). Nanoparticles are produced in natural activities: volcanic eruptions, dust storms, wild fire disasters, waterfalls, ocean-wave breakout, rock/soil weathering, freshwater and seawater mixing, etc. For example, carbon nanotubes and fullerenes were found in 10,000-year-old ice cores from Greenland (Murr et al., 2004).

Incidental nanoparticles: Anthropogenic activities generate nanomaterials which are not produced on purpose. Particles of welding fumes, exhausts of auto engines and airplanes, dust produced in grain milling, industrial emission (such as coal burning), mining operations, metal smelting, road dust, smoking, etc, are good examples of these traditionally and unintentionally produced nanoparticles. Kittelson (1998) reviewed about engines and nanoparticles. Most of the particles released by engines were in the nanoparticle range (diameter < 50 nm). From the point of view of occupational safety regulations, NIOSH (2009) discussed the sources and differences between "ultrafine particles" and "nanoparticles." Combining NIOSH (2009) and the discussions in Lead (2010), "ultrafine particles" are incidental nanoparticles which are airborne particles smaller than 100 nm in diameter, not intentionally produced, but are incidental products of processes involving combustion, welding, diesel engines, and/or transportation. In terms of property, incidental nanoparticles are generated in a relatively uncontrolled manner, and usually are physically and chemically heterogeneous.

Engineered nanoparticles: Engineered nanoparticles, or manufactured nanoparticles, are frequently referred simply as "nanoparticles" (NPs) that are manufactured (or engineered, or synthesized) nanoparticles (MNPs) which are deliberately designed and produced by human activity with very specific properties or compositions (e.g., shape, size, surface properties, and chemistry) for specific purposes (Klaine et al., 2008; Lead, 2010).

"At present, the amounts of NPs originating from dedicated industrial production are marginal relative to those produced and released unintentionally, through combustion, for instance" (Farre et al., 2009).

Application Approach

Some commercial nanoproducts are simply nanoparticles preserved as discrete particles with specially formulated surfactants. Some commercial nanoproducts are manufactured from nanoparticles, and might keep the properties of nanoparticles (e.g. TiO_2 nanoparticles in paint). Some commercial nanoproducts are manufactured from nanoparticles but are converted to "bulk" materials. TiO_2 nanoparticles in paint could be an example of this kind of "bulk" material, depending on how the human health consequences and environmental effects are assessed.

Based on property approach as given above, products made from nanomaterials may be termed as "nanoproducts" if the nanomaterials' properties are the product's main features. However, if nanomaterials are converted to bulk products and lose the nanomaterial's unique properties, the products and the nanomaterials might not be considered as nanoproducts or nanomaterials anymore, in terms of human health and environmental impacts, since these products do not possess high surface area to mass ratios, are too big to pass certain physical barriers, and behave like conventional "bulk" materials.

PRODUCTION OF NANOMATERIALS

Nanofibers by Electrospinning

Biodegradable fibers such as cotton scrap or waste (cellulose) were dissolved in a solvent (ethylene diamine). The solution was pushed out through a tiny pinhole while a high voltage was applied to the pinhole. Nanofibers with less than 100 nm in diameter were produced (Frey, 2003). By using electrospinning (Yarin and Zussman, 2004), nanofibers are made out from polymers, composites, ceramic, and metal (Teo and Ramakrishna, 2006).

Top-down Nanoparticles

Nanoparticles are mainly produced in two ways: top-down (i.e. breaking small particles to nanosizes) and bottom-up (i.e. making nanomaterials from solutions and gases, or from ions, atoms, and molecules to nanoparticles). Dust storms, road dust, milling dust, etc, are good top-down examples. Dust storms are natural. Road dust and milling dust are anthropogenic but are not produced on purpose. Some nanoparticles are manufactured on purpose, by reducing big chunks of materials into smaller particles of desired shapes and sizes, such as by cutting, breaking, grinding, milling, ion implantation, laser ablation, etc (Oberdörster et al., 2005). In laser ablation, a high energy laser beam is shot onto a target and nanoparticles are generated.

The production of silver nanoparticles was reviewed by Tolaymat et al. (2010). Silver metal in its bulk form was made to nanoscale by using specialized methodologies such as lithography and laser ablation, but these top-down methods accounted for less than 4% of all methods presented in about 200 papers (Tolaymat et al., 2010). Commercially available ZnO powders (~500 nm) were sealed in a steel cylinder (volume 8 cm^3) with one steel ball (diameter 12 mm), and were milled to nanoparticles with grain size less than 20 nm (Damonte et al., 2004).

These manufacturing methods are primarily physical processes in nature. The chemical compositions and properties of nanoparticles are mostly the same as the bulk starting material. Mass production of nanoparticles via top-down approaches might be fairly limited, relative to the mass production of nanoparticles via bottom-up approaches, as it is given below.

Bottom-up Nanoparticles

Flocculation, taking place naturally in the mixing zone of freshwater and seawater, is a good bottom-up example. Volcanic eruptions and wild fire disasters are other good examples of bottom-up processes.

Carbon nanotubes and nanofibers: Carbon nanomaterials were manufactured by using arc discharge, laser ablation and chemical vapor deposition. In chemical vapor deposition, methane, ethylene, acetylene, hexane, alcohol and carbon monoxide were used as carbon feeding gases (Khodakovskaya et al., 2009). Mass production of carbon nanotubes and carbon nanofibers with relatively high length and aspect ratio was claimed by Toubestani et al. (2010). In that chemical vapor deposition method (Toubestani et al., 2010), methane was the feeding gas.

Silver nanomaterials (Ag): Based on the review of 200 papers (Tolaymat, et al., 2010), silver nanoparticles (silver metal) were found mainly synthesized via reduction of $AgNO_3$ (83% of all types of silver salts) by $NaBH_4$ (23% of reducing reagents) or citrate (10% of reducing reagents) in water (80% of all types of inorganic and organic solvents). The reducing reagents also worked as capping and stabilizing agents for the control of particle size to ensure a relatively stable suspension. Silver particles were mostly spherical with less than 20 nm diameter.

Titanium dioxide (TiO_2): Nano TiO_2 particles were manufactured by using different methods (Chai et al., 2007). $TiCl_4$, $Ti(SO_4)_2$, $TiOSO_4$ and $Ti\{OCH(CH_3)_2\}_4$ (titanium isopropoxide) were used for making nano titanium particles via the bottom-up approach. Surfactants were used to keep nanoparticles from agglomeration (Chai et al., 2007; Senthilnathan and Philip, 2009).

Copper nanoparticles (Cu): Copper nanoparticles could be manufactured by vapor deposition, electrochemical reduction, radiolytic reduction, thermal decomposition, and chemical reduction. From $CuCl_2$, copper ions (Cu^{2+}) were reduced in water/acetone aqueous system, and copper nanoparticles (copper metal, 20 nm) were produced and capped with oleic acid (Wang et al., 2005; Khanna et al., 2008).

Bottom-up processes are frequently chemical changes in nature. The chemical compositions and properties of nanomaterials are different from those of starting materials (e.g. C vs. CH_4, Ag vs. $AgNO_3$, TiO_2 vs. $TiCl_4$, and Cu vs. $CuCl_2$). The end nanoparticles are mixed with other chemicals which could be the starting materials (e.g. $AgNO_3$ in Ag nanoparticles) and other chemicals used during the manufacturing processes (e.g. reducing reagents and capping reagents).

"Particles in the nanometer size range do occur both in nature and as a result of existing industrial processes. Nevertheless, new engineered nanomaterials and nanostructures are different because they are being fabricated from the 'bottom up'. Nanomaterial properties differ compared with those of the parent compounds because about 40–50% of the atoms in nanoparticles (NPs) are on the surface, resulting in greater reactivity than bulk materials. Therefore, it is expected that NPs will have different biological effects than parent compounds" (Farre et al., 2009).

Different from the top-down approach where sophisticated equipments are used, the bottom-up approach does not need special or sophisticated equipments. In fact, nanomaterials can be "manufactured" in a beaker by adding several widely available chemicals together. Mass production is also significantly easy.

Capping Reagents

Nanoparticles may agglomerate and aggregate to bigger particles, due to the nanoparticle's high surface area and thermodynamic instability. Capping reagents are used to control the size of nanoparticles and to stabilize nanoparticles. Capping reagents may also play roles in protecting nanoparticles from being oxidized. Therefore, capping reagents are important factors in making nanoparticles in bottom-up processes. It is interesting to note that nanoparticles are manufactured on purpose because nanoparticles possess unique surface properties, then the surface is protected with capping reagents on purpose to make the surface less active.

From the point of view of human health, environmental effects and agricultural applications, nanoparticles are not pure substances but rather a mixture of several substances, including capping reagents. It might be the capping reagents and not the nanoparticles which actually cause toxicological effects (Farre et al., 2009).

PROPERTY OF NANOMATERIALS

Nanoparticles are not mysterious substances but are just small, or smaller than small, particles. A one-nm sphere to a basketball is one golf ball to the earth. Nanomaterials possess properties which are absent when the same material exits as bulk form. These properties may include altered color, other optical properties, magnetism, strength, flexibility, electrical conductivity, reactivity, etc.

The ratio of surface area to mass of one gram silver ball is 1 $cm^2\ g^{-1}$. After that silver ball is made into 10^{15} spheres with 60-nm diameter, the ratio is 100,000 $cm^2\ g^{-1}$ (10 $m^2\ g^{-1}$). In heterogeneous phase reactions (gas-liquid, gas-solid, liquid-solid, or solid-solid), it is the surface where actual reactions take place and the magnitude of surface area decides how fast a reaction can be. In this silver ball case, the reaction speed of 1-g silver as 60-nm nanoparticles is 100,000 times faster than that of 1-g silver as silver ball, other conditions excluded.

A sphere is the geometric shape which keeps the minimum surface area at a given mass. Surface areas of any other shapes are greater than the surface area of spheres at an equal mass. This is why shapes of nanoparticles are also an important property of nanoparticles, one-dimension size alone is an insufficient definition of nanoparticles, and the ratio of surface area to mass would be a better definition. In bottom-up approach where nanoparticles grow up from ions, atoms, and molecules, nanoparticles will rarely be spheres, as demonstrated by relevant crystallography.

The extraordinary surface area to mass ratio is probably the most significant feature of nanoparticles, at least in terms of human health, environmental effects, and agriculture applications. Other features are also important. For example, nanoparticles can pass physical barriers (such as blood-brain barriers) freely where conventional bulk materials are simply blocked out and rejected from any chances of potential reactions (Oberdörster et al., 2005).

ENVIRONMENTAL EFFECTS

Environmental Fate of Nanomaterials

At present, the amounts of manufactured nanomaterials in environment are marginal relative to those produced by natural processes and by unintentional human activities (Farre et al., 2009). Environmental effects of nanomaterials could be important issues in localized areas where nanomaterials are manufactured, transported, and applied. These occupational safety issues relevant to nanomaterials are well discussed in NIOSH (2009).

Manufactured nanomaterials are preserved with special stabilizers so that these materials are stable (e.g. NanoBioSilver). Due to nanoparticle's high ratio of surface area to mass, nanoparticles tend to form aggregates that can be trapped or eliminated through sedimentation. The environmental fate and effect of nanoparticles are substantially reviewed (Colvin, 2003; Oberdorster et al., 2005; Nowack and Bucheli, 2007; Klaine et al., 2008; Farre et al., 2009). However, direct evidences and results are still scarce. "As yet, no peer-reviewed literature is available on concentrations (or speciation) of NPs in natural waters or sediments" (Klaine et al., 2008).

"It can be concluded that analytical approaches to NPs in the aquatic environment are still in an initial phase of development. Their optimisation is a key point in order to allow field experiments and monitoring programmes, the latter forming the basis of a realistic risk assessment" (Farre et al., 2009).

Physicochemical Characterization

NanoImpactNet is European network on the health and environmental impact of nanomaterials. Based on its workshop in September, 2008, the physicochemical characterization information was identified. The following is quoted from Stone et al. (2010):

> The physicochemical characterisation information identified as important for environmental studies included measures of aggregation/agglomeration/dispersability, size, dissolution (solubility), surface area, surface charge, surface chemistry/composition, with the assumption that chemical composition would already be known.
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> There is a need to have test materials for ecotoxicology, and several substances are potentially useful, including TiO_2 nanoparticles, polystyrene beads labelled with fluorescent dyes, and silver nanoparticles. Some of these test materials could then be developed into certified reference materials over time. No clear consensus was reached regarding the classification of nanomaterials into categories to aid environmental studies, except that a chemistry-based classification system was a reasonable starting point, with some modifications. It was suggested, that additional work may be required to derive

criteria that can be used to generate such categories that would also include aspects of the material structure and physical behaviour.

TOXICITY

Bacteria-nanoparticle Interactions

Engineered nanomaterials would sooner or later be released to the environment. Aruguete and Hochella (2010), based on 82 papers, reviewed the bacteria-nanoparticle interactions and their environmental implications. The topic is complicated. As discussed by Aruguete and Hochella (2010), nanomaterials themselves could be different by compositions (elemental: Ag or C; oxide: ZnO or TiO_2), sizes, shapes (spherical, rod, or triangular plane), coatings, and agglomeration states; bacterial species were different, at least by gram-positive and gram-negative species; and finally, not only nanoparticles would exert effects on bacteria, but bacteria would also affect nanoparticles. A case by case analysis was necessary.

In addition to those variations, experimental results obtained in laboratories need to be carefully extrapolated to environmental conditions. An example cited by Aruguete and Hochella (2010) was that *Eschericia coli* cells were treated with 50 ppm ($\mu g\ mL^{-1}$) of silver nanoparticles in liquid Luria broth medium for one hour. This high level of silver nanoparticles might not be found in the environment in general. A general conclusion was that "the field of bacteria– nanomaterial interactions is in its infancy and is wide open for further investigation" (Hochella, 2010).

Li et al. (2008), based on 136 papers, reviewed about antimicrobial nanomaterials for water disinfection and microbial control. Different antibacterial nanoparticles discussed in the paper fell into three general categories: naturally occurring antibacterial substances, metals and metal oxides, and novel engineered nanomaterials. These materials included peptides and chitosan, nano silver particles, nano titanium dioxide, nano zinc oxide, fullerenes, and carbon nanotubes. "These nanoparticles interact with microbial cells through a variety of mechanisms. he nanoparticles can either directly interact with the microbial cells, e.g. interrupting transmembrane electron transfer, disrupting/penetrating the cell envelope, or oxidizing cell components, or produce secondary products (e.g. reactive oxygen species (ROS) or dissolved heavy metal ions) that cause damage" Li et al. (2008).

Silver Metal (Ag)

"It is estimated that of all the nanomaterials in medical and healthcare sector, nanosilver application has the highest degree of commercialization" (Chen and Schluesener 2008). "Silver nanoparticles are widely used in medical devices and supplies such as wound dressings, scaffold, skin donation, recipient sites, sterilized materials in hospitals, medical catheters, contraceptive devices, surgical instruments, bone prostheses, artificial teeth, and bone coating. One can also observe their wide use in consumer products such as cosmetics, lotions, creams, toothpastes, laundry detergents, soaps, surface cleaners, room sprays, toys, antimicrobial paints, home appliances (e.g., washing machines, air and water filters), automotive upholstery, shoe insoles, brooms, food storage containers, and textiles" (Tolaymat, et al., 2010). A search of "silver" in "Project on emerging nanotechnologies" yielded 300 items of nanomaterials and/or nanoproducts.

Silver nanoparticles (average particle size 10 nm) were claimed to be used for treating large volumes of liquid. As it was instructed (Nano Silver Technology), "Need to treat large volumes of liquid (swimming pools, spas, water purification stations)? No problem! Just 1.0 L of our 3% dispersion added to 10,000L of liquid results in a concentration of silver of ~3ppm, which still provides good antimicrobial activity." The maximum concentration of (dissolved) silver is 0.1 mg L^{-1} (0.1 ppm) in drinking water, as set by U.S. EPA (40 CFR 143), and is 0.1 mg L^{-1} in beverages including bottled water, as set by U.S. FDA (21 CFR 165). That amount of silver (3 ppm) in swimming pool is not regulated either by EPA or FDA since that silver is elemental form but not dissolved. It is understood that water in a swimming pool is for swimming but not for drinking. However, even if people were able to keep their mouths tightly shut while swimming, the absorption of water through skin would be unavoidable. Then there is the question of whether nanoparticles will pass through the skin barrier.

The toxic impact of silver nanoparticles on *Japanese* medaka fish (*Oryzias latipes*) was evaluated by Chae et al. (2009), based on the measurement of six "stress-related" genes which were claimed to be reliable and representative fish biomarkers. Equivalent amounts of silver nanoparticles and dissolved silver were used at two concentration levels (silver nanoparticles, particle size 50 nm: 1 μg L^{-1} and 25μg L^{-1}, and silver nitrate: 1.58 μg L^{-1} and 39.46μg L^{-1}, respectively) (Note: 1.58 μg of $AgNO_3$ L^{-1} is equivalent to 1 μg Ag L^{-1}). "The results suggest that these two silver forms have distinguishable toxic fingerprints between them. While the Ag-NPs led to cellular and DNA damage, as well as carcinogenic and oxidative stresses, genes related with metal detoxification/metabolism regulation and radical scavenging action were also induced. In contrast, the ionic silver led to an induction of inflammatory response and metallic detoxification processes in the liver of the exposed fish, but resulted in a lower overall stress response when compared with the Ag-NPs" (Chae et al., 2009).

The effects of silver and gold nanoparticles on rainbow trout (*Oncorhynchus mykiss*) hepatocytes were investigated by Farkas et al. (2010). Silver nanoparticles and gold nanoparticles were made in-house by reducing $AgNO_3$ and $HAuCl_4$ respectively with citrate and sodium borohydride in Milli-Q water. The sizes of these nanoparticles were less than 10 nm in the respective stock solutions. These nanoparticles agglomerated to bigger sizes (up to 80 nm) in contact with cell growth media or dissolved organic carbon (DOC). Liver cells (hepatocytes) were collected from the trout fish, isolated, and treated with silver nanoparticles, silver ions, and mixture of silver nanoparticles and DOC, respectively. The concentrations were from 1.9 mg L^{-1} to 19 mg L^{-1} with the control containing about 0.06 mg L^{-1} of silver. Similarly, the liver cells were treated with gold nanoparticles, gold ions, and mixture of gold nanoparticles and DOC. The concentrations were from 1.7 mg L^{-1} to 17 mg L^{-1} with the control containing about 0.06 mg L^{-1} of gold. It was found that silver nanoparticles and silver ions caused a significant reduction in membrane integrity and cellular metabolic activity. Silver nanoparticles could also be slightly more toxic than silver ions in a concentration-dependent manner. The presence of DOC did not significantly change the toxicity of silver nanoparticles. Gold nanoparticles induced different toxic effects but were less toxic than silver nanoparticles in membrane integrity and cellular metabolic activity.

When bovine serum albumin (BSA, μmol L^{-1} concentration range) was treated with 40-50 nm silver nanoparticles (mg L^{-1} concentration range) which were made in-house from the reduction of $AgNO_3$ with citrate, "nanoAg had obvious toxic effects on BSA: nanoAg could increase the amount of helix and decrease the beta sheet structure, leading to a loosening of the protein skeleton. In the loose structure, internal hydrophobic amino acids are exposed and the characteristic fluorescence of BSA is obviously quenched" (Liu et al., 2009).

About 133 papers were reviewed about "Nanosilver: A nanoproduct in medical application" by Chen and Schluesener (2008). The traditional belief was that bulk silver products were relatively non-toxic to mammalian cells, except for argyria (a condition caused by improper exposure to elemental silver or silver compounds. The most dramatic symptom of argyria is that the skin becomes blue or bluish-grey colored) and some minor problems. "When it comes back to silver nanoparticles, in sharp contrast to the attention paid to their applications, only a few studies have provided very limited insights into such aspects as their entry portals into human body, biodistribution, organ accumulation as well as their potential interactions with tissues, cells and molecules and their relevant toxicological implications: Taking into account their unique physicochemical properties, it is unlikely that nanoparticles do not possess unique toxicity mechanisms. It remains to be determined whether silver nanoparticles as well as other nanomaterials will introduce new mechanisms of injury from which new pathologies may result" (Chen and Schluesener, 2008).

Depending on how they were produced, nano silver products were not only just silver nanoparticles but also mixed with other chemicals as reducing agents and stabilizing agents (Tolaymat et al., 2010). These different factors need to be included in evaluating environmental impacts of manufactured silver nanoparticles.

Cerium Oxide (CeO_2)

Nano cerium oxide is used as an additive to diesel fuels where it improves the combustion efficiency of engine carbon deposits. Cerium oxide nanopowder (10-20 nm and surface area of 80 $m^2 g^{-1}$) and micron size powder (< 5 µm) are available commercially (e.g. from Sigma-Aldrich). The toxicity of cerium oxide to freshwater alga *Pseudokirchneriella subcapitata* was investigated (Rogers et al., 2010). The inhibitory concentration values, giving 50% reduction in algal growth rate after 72 h (IC_{50}), were 10.3±1.7 and 66±22 mg L^{-1} for the nanoparticles and bulk materials respectively. These IC_{50} values were in the mg L^{-1} concentration range, and were several orders of magnitude above CeO_2 concentrations currently predicted in the environment from its use as a diesel additive. To the question of whether nanoparticles would be more toxic than micron size powders, the research result was not very conclusive, although the two IC_{50} values were different.

Titanium Dioxide (TiO_2)

Different formulations of titanium dioxide were used commercially as white pigments in plastics, interior and exterior house paints, and automobile paints. These particles were about 300 nm in size with 6-28 $m^2 g^{-1}$ of surface areas and were refereed as “fine particles” (Warheit et al., 2005). Titanium dioxide particles were also used in sunscreens to block UV light and in toothpaste as white pigments.

By using nano-TiO_2 particles (average particle size 21 nm) as representative of nanomaterials and lysozyme as representative of enzymes, the effect of “nanomaterials” on “enzymes” was investigated by Xu et al. (2010). It was found that lysozyme was adsorbed to TiO_2 particles following Langmuir isothermal adsorption. Adsorbed lysozyme bridged TiO_2 particles together to aggregates. Meanwhile, lysozyme was warped and deformed, resulting from the adsorption, from β-helix spatial structure into β-sheet. The β-sheet can induce the formation of amyloid fibrils, a process which plays a major role in pathology. Deformed lysozyme lost some of its bacteriolysis capability. Xu et al. (2010) concluded that nano-TiO_2 might have some toxic impacts on biomolecules.

Fine TiO_2 particles (average size 300 nm with 6-28 $m^2 g^{-1}$ of surface areas), either base TiO_2 or coated TiO_2 (with alumina, amorphous silica, or triethanolamine), were used in pulmonary toxicity inhalation and instillation studies on rats (Warheit et al., 2005). It was found that lung exposure in rats to exceedingly high concentrations of titanium dioxide particles produced low pulmonary toxicity. Titanium particles with the largest surface area (28 $m^2 g^{-1}$) produced adverse lung effects compared to other particles with 6-12 $m^2 g^{-1}$ of surface area, but even these impacts were viewed as minor when compared to other dust. Similar experiments were conducted with “nanoscale rods” (92-233 nm long and 20-35 nm wide, 26.5 $m^2 g^{-1}$) and “nanoscale dots” (5.8-6.1 nm spherical, 169.4 $m^2 g^{-1}$) of titanium dioxide by the same Warheit research group (Warheit et al., 2006). The basic conclusion was that nanosize particles were not more cytotoxic or inflammogenic to the lung compared to larger sized particles of similar composition, i.e. those fine particles as given above. Warheit et al. (2006) pointed out that “these findings run counter to the postulation that surface area is a major factor associated with the pulmonary toxicity of nanoscale particle types.” However, this might be a good example whether substantially different properties should be expected from these “fine” particles and “nano” particles. In other words, this might be a good example whether nanoparticles should be clearly defined as particles with dimensions of less than 100 nm. The surface areas of these two groups of materials are different but are not substantially different. If these surface areas are contrasted with the surface areas of “bulk” particles (e.g. particle size at micrometer or sub-millimeter range), the surface areas of “fine” and “nano” particles could well be considered as “similar.”

The toxicity of nano copper oxide, zinc oxide and titanium oxide to freshwater alga *Pseudokirchneriella subcapitata* was investigated by Aruoja et al. (2009). The 72 h EC_{50} (half maximal effective concentration) values were 5.83 mg L^{-1} for nano TiO_2, and 35.9 mg L^{-1} for bulk TiO_2, respectively. Therefore, nanoparticles of TiO_2 were more toxic than their bulk materials.

Copper Oxide (CuO)

Copper oxide may be used to replace noble metal catalysts for carbon monoxide oxidation. The toxicity of nano copper oxide, zinc oxide and titanium oxide to freshwater alga *Pseudokirchneriella subcapitata* was investigated by Aruoja et al. (2009). The 72 h EC_{50} values were 0.71mg L^{-1} for nano CuO, and 11.6 mg L^{-1} for bulk CuO, respectively. "At 72 h EC_{50} values of nano CuO and CuO, 25% of copper from nano CuO was bioavailable and only 0.18% of copper from bulk CuO. Thus, according to recombinant bacterial and yeast Cu-sensors, copper from nano CuO was 141-fold more bioavailable than from bulk CuO. Also, toxic effects of Cu oxides to algae were due to bioavailable copper ions" (Aruoja et al., 2009).

Zinc Oxide (ZnO)

Nano zinc oxide is used in personal care products (e.g. sunscreens), coatings and paints. The toxicity of nano zinc oxide, as well as the toxicity of bulk zinc oxide and zinc ions, to freshwater alga *Pseudokirchneriella subcapitata* was investigated (Franklin et al., 2007). One of the major purposes was to investigate whether nano zinc oxide would be more toxic than bulk zinc oxide or zinc ions. Contrary to a general assumption that nanoparticles might be more toxic than bulk materials since nanoparticles might be more available to organisms, the toxicity of nano zinc oxide (ca. 30 nm), bulk zinc oxide (size not specified) and zinc ions (as $ZnCl_2$) was about the same, with a 72 h IC_{50} value near 60 μg Zn L^{-1}, attributable solely to dissolved zinc. One reason was that particle aggregation was significant, resulting in flocs ranging from several hundred nanometers to several microns. The major reason was the rapid dissolution of nano zinc oxide in a freshwater medium, with a saturation solubility in the milligram per liter range, similar to that of bulk zinc oxide.

The toxicity of nano copper oxide, zinc oxide and titanium oxide to freshwater alga *Pseudokirchneriella subcapitata* was investigated by Aruoja et al. (2009). "ZnO nanoparticles were most toxic followed by nano CuO and TiO_2. The toxicities of bulk and nano ZnO particles were both similar to that of $ZnSO_4$ (72 h EC_{50} ~ 0.04 mg Zn L^{-1})" (Aruoja et al., 2009).

Toxicity

These limited examples given above are not meant to cover the complex topic of toxicity, but some observations might be made. With respect to dissolved metal ions, nanoparticles not only provided sources of dissolved metal ions, but also worked as physical factors such as causing deformation of proteins (e.g. TiO_2 nanoparticles). In other words, nanoparticles might exert more toxic effects on organisms than sole dissolved forms of the same material.

The chemical and toxic properties of bulk materials extended to nanomaterials. The toxicity of silver nanoparticles was higher than that of gold nanoparticles, and the toxicity of ZnO was still significantly higher than those of CuO, TiO_2, or CeO_2. The solubility of ZnO nanoparticles was significantly higher than those of CuO, TiO_2, or CeO_2 nanoparticles. When the solubility of nanoparticles was sufficiently high (e.g. ZnO), the toxicities of nanoparticles and the dissolved forms of the same metal (e.g. Zn) were about the same.

There might be substantial (physical, chemical, and toxicological) changes associated with the change of particle size from "bulk" to "fine." These changes might not be substantial when particles change from "fine" to "nano." In other words, "fine" particles and "nano" particles might not be totally different, and the nature would not go as what human call it. "Fine" particles and "nano" particles are generated in natural processes and anthropogenic activities. Nanoparticles were referred as ultrafine particles in air, and colloids in soil and water, with slightly different size ranges. The toxicities of "nano" materials increased from those of "fine" materials, but the changes were not substantially different, or at least not catastrophically different, as demonstrated in the examples of fine and nano TiO_2 particles. Nanoparticles might be "new" and the knowledge of toxic effects of nanoparticles might be limited, but the toxic effects of fine particles and colloidal materials, natural origin or industrial origin, were relatively well investigated (Oberdörster et al., 2005; Nel 2005; Klaine et al., 2008; Stern and McNeil, 2008; Farre et al., 2009; Manchikanti and Bandopadhyay, 2010). The toxicities of nanomaterials might not be dramatically and mysteriously different from the toxicities of those relevant "fine" materials.

Carbon nanotubes were found to penetrate the coat of plant seeds which were cultured in medium containing 10-40 μg mL^{-1} of carbon nanotubes (Khodakovskaya et al., 2009). Toxicities of nanoparticles were confirmed, as given in the above examples and other works (Colvin, 2003; Oberdörster et al., 2005; Elder et al., 2007; NIOSH, 2009). However, toxic effects of a substance depend on the *in situ* dose, duration and dimension (shape, size-distribution, surface reactivity, surface area, etc). Nanoparticles, while being well preserved and stable in manufactured forms (i.e. remaining as discrete nanoparticles), could quickly aggregate or be coated by other materials in natural environment and loose the unique "nano" properties (Warheit et al., 2007; Murdock et al., 2008). In fact, effective techniques were urgently needed to keep nanoparticles "active" when nanoparticles were used in water treatment applications (Li et al., 2008). The existence and magnitude of purposely engineered nanoparticles in natural environment, relative to the existence and magnitude of natural nanoparticles and incidental nanoparticles, are important but probably still scarcely known (Murr et al., 2004; Farre et al., 2009). Further, nanomaterials need to be well characterized in evaluating the toxicities of nanomaterials, and traditional approaches used in evaluating the toxicities of bulk materials may not apply well in "nano" situations (Boverhof and David, 2010). Conclusions about toxicities of nanoparticles induced from laboratory simulations might need substantially extra work to be extrapolated to natural environments.

APPLICATION EXAMPLES

Nanomaterials possess novel characteristics. "Research on the potential applications of nanotechnology continues to expand rapidly worldwide. New nanotechnology consumer products emerge at a rate of three to four per week. Over the course of the next decade, nanotechnology could have a $1 trillion impact on the global economy and employ two million workers—half of them residing in the U.S." (NIOSH, 2009).

Industry makes great efforts in designing, developing, manufacturing, and promoting nanomaterials and related products. In order to expand to potential markets, some products are claimed to be "nanomaterials" or "nanoproducts," or "produced by using nanotechnologies," but actually may just be conventional products in miniature scale. Realized applications, anticipated applications and imaginary products in agriculture and food industry were discussed by National Science Foundation Workshop (NSF, 2001), Shannon et al. (2008), USDA Workshop Scott and Chen, 2003, Kuzma and VerHage (2006), Joseph and Morrison (2006), Taylor (2008), AZ nanotechnology, AZ Materials, Nano Werk, Project on emerging nanotechnologies, and Warad and Dutta. The Nanomaterial Database Search provided a quick link to various nanomaterials.

Milk Homogenization

"Milk is an oil-in-water *emulsion*, with the fat globules dispersed in a continuous skim milk phase. If raw milk were left to stand, however, the fat would rise and form a cream layer. Homogenization is a mechanical treatment of the fat globules in milk brought about by passing milk under high pressure through a tiny orifice, which results in a decrease in the average diameter and an increase in number and surface area, of the fat globules. The net result, from a practical view, is a much reduced tendency for creaming of fat globules. Three factors contribute to this enhanced stability of homogenized milk: a decrease in the mean diameter of the fat globules (a factor in Stokes Law), a decrease in the size distribution of the fat globules (causing the speed of rise to be similar for the majority of globules such that they don't tend to cluster during creaming), and an increase in density of the globules (bringing them closer to the continuous phase) owing to the adsorption of a protein membrane" (University of Guelph). "As Kathryn explained, when milk is left on its own, fat globules collect together and rise to the surface of the liquid to form that delicious layer of cream. Homogenization prevents the fat globules from clumping and keeps the fat dispersed in a kind of emulsion throughout the milk. To do this, hot milk is pumped through small screens at very high pressure. This breaks the fat into smaller and smaller globules and also strips away their protective membrane. Casein, an emulsifying agent naturally present in milk, adheres to the bare surface of the fat. The case in both weighs the fat down (preventing it from rising to the surface) and keeps the fat molecules from collecting together. Homogenization makes for creamier milk since the smaller and more numerous fat globules coat the tongue more evenly. On the downside, homogenized milk usually tastes bland when compared to non-homogenized milk because the process also disrupts flavor molecules in the milk. While homogenization and pasteurization usually go hand-in-hand, this isn't strictly necessary and likely has more to do with consumer demand" (Kathryn).

Homogenized milk, on one hand, might be considered as a product of nanotechnology via the top-down approach: big fat globules are reduced in size on purpose so that the increased surface keeps fat in emulsion. On the other hand, the practice of milk homogenization started in 1899 (University of Guelph), much earlier than the passage of the Organic Foods Production Act of 1990. After homogenization, the average sizes of fat globules are 0.4 µm (400 nm), significantly greater than the conventional nanosizes of 1 to 100 nm. The process is virtually physical in nature. The chemical compositions and the nutrient values of homogenized milk are not changed from raw milk. The taste and flavor are changed but are more or less personal preferences. Emulsion is a very common practice in food industry.

Grain Milling

Wheat, corn, etc, are broken to powders in grain milling. Like road dust, it is very likely that nanoparticles are produced during grain milling and it is a good top-down example. From the point of view of occupational safety, people should be protected from these nanoparticles during grain milling (NIOSH, 2009). On the other hand, these nanoparticles are not "engineered on purpose." The process is virtually physical in nature, the chemical compositions of these nanoparticles are not expected to be changed from the bulk starting materials, and the nutrient values would remain the same as the bulk materials. The practice of grain milling apparently started much earlier than the passage of the Organic Foods Production Act of 1990.

Smoking

Probably no manufacture claimed to use nanotechnology to produce nanoparticles during smoking. Like wild fire disaster and coal burning, nanoparticles could be generated during smoking. Smoking might be the biggest effect of nanoparticles on human health up to date.

Silver Ion Generating Wash Machines

A type of washing machine with a device to generate silver ions were claimed to be using nanotechnology to inhibit bacteria in clothing. U.S. EPA issued a "Federal Register Notice" on September 21, 2007 to regulate these wash machines as pesticides. In "Pesticide Registration: Clarification for Ion Generating Equipment," U.S. EPA indicated that "the Agency has now determined that these machines will be regulated as pesticides if the machines contain silver or other substances, and if they generate ions of those substances for express pesticidal purposes" and "while recent press articles have referred to the silver ion generating washing machine as a product of nanotechnology, EPA has not yet received any information that suggests that this product uses nanotechnology" (http://www.epa.gov/oppad001/ion_gen_equip.htm).

Silver Nanotextiles

Silver nanoparticles were incorporated into and onto fibers for expected antiviral properties. Geranio et al. (2009) investigated the release of silver (silver ion and silver particle) from nine silver nanotextiles during washing. Depending on how nano silver particles were incorporated to fibers, the amount and form (ion or particle) of silver greatly varied between different silver nanotextiles. "The percentage of the total silver emitted during one washing of the textiles varied considerably among products (from less than 1 to 45%). In the washing machine the majority of the Ag (at least 50% but mostly >75%) was released in the size fraction >450 nm, indicating the dominant role of mechanical stress. A conventional silver textile did not show any significant difference in the size distribution of the released silver compared to many of the textiles containing nano-Ag" (Geranio et al., 2009).

Packing Materials

Bayer Polymers claimed to incorporate nanoparticles (miniature silicate platelets) into plastic films and make the films better material for food packing (Bayer Polymers). However, not much technical detail was available. Similarly, one research group (Li et al., 2009; Yang et al., 2010) incorporated particles (300-500 nm, Ag, kaolin, anatase TiO_2, rutile TiO_2, etc) into low-density polyethylene (LDPE) and made to 40 μm (40,000 nm) thick plastic films. The films were made into packing bags. Compared to the packing bags made from 40 μm thick-LDPE only film, the bags enforced with particles provided "better" preserving effect for two tested fruits (strawberries and Chinese jujube). The "better" preserving effect was judged from less water loss (and correspondingly low sugar concentrations) in the fruits preserved with enforced LDPE bags, compared to the fruits preserved with LDPE only bags.

The densities are 0.91-0.94 g cm^{-3} for LDPE, 10.5 g cm^{-3} for silver, 4.23 g cm^{-3} for titanium dioxide, and 2.2-2.6 g cm^{-3} for kaolin, respectively. Analog to cement-only cement and sand-pebble-enforced cement, enforced LDPE bags would reasonably be expected to provide better "preserving" capacity, in terms of physical strength, water and air permeability, and light blocking. Whether the particles were nano-size or not might be relatively irrelevant, as long as the film thickness (40,000 nm) was substantially greater than the particle sizes (300-500 nm) so that particles could be well made into films. Of course, the particle sizes and the ratios of particles to LDPE should be in correct ranges to make usable bags, just like in a case of making usable sand-pebble-cement mixture.

Adding pigments and other materials to plastic is a common practice. Bayer Polymers hypothesized that the oxygen penetrating route from one side of plastic film to the other side was increased due the presence of nano-particles embedded in the plastic film, but no technical details were provided. An important and unique feature of nanoparticles is the extraordinary high ratio of surface area to mass. After particles were made into plastics, the surfaces were covered and not "active" anymore. In this sense, it is fairly debatable whether the product (the bags) could still be claimed to possess "nano-features," although the particles themselves might be nano-products (Strictly speaking, those particles used in the research, 300-500 nm in sizes, are not commonly considered as nanoparticles). It might just be a choice of name selection whether a product was indeed a nano-product. According to NIOSH (2009), as given above in "Property Approach" of section NANOMATERIALS, "if the nanostructure within individual micrometer-diameter particles does not directly influence particle behavior (for instance, if the nanoparticles were inaccessibly embedded in a solid matrix), the aerosol would not be described as a nanoaerosol."

Those "nano-packing" materials might not be so miracle, as claimed by producers, but might not be a fact for panic either for consumers. These particles might not likely be transferred to fruits during food-storage since the particles were made into plastics (and not nanoparticles anyway). Particles at the very surface of plastic film could be scratched and transferred to fruits. Apparently this is very likely and should be investigated and confirmed. Are the particles transferred as discrete particles, or as chunks of materials consisting of plastics and particles? The second question, like in many other cases, is the amount of transfer. Not just to these so called "nano" products, pigments and other materials were also added to other plastic products, and the transfer might be in human life already. Nanoparticles are "nano" sizes and invisible to unassisted eyes. Visible marks on silverware are indications that materials have been transferred from point A to point B. A scratch of stainless steel spoon on a ceramic plate might transfer more materials, sizes probably from "nano" to "giant," than those "nano" particles to our human body, whether a scratch mark is visible or not. It does not mean that new "nano" products should be accepted without scrutiny. The point to make is that things should be analyzed based on what they are supported by in terms of valid research and testing, rather than what they are claimed to be.

From the point of view of general human health and environmental effects, these "nano" packing products could be a problem since particles would eventually be returned back to the environment, potential heavy metal sources with respect to pure LDPE only bags. LDPE is category 4 recyclable plastic.

Nanoproducts

An intuitive impression of "nano" is its size. In the applications where size counts (computers, airplanes, rockets, etc), products with or without nanotechnology might be fairly claimed to be nanoproducts, as long as the "size-saving" feature, as well as other features, are realized.

In terms of human health, environmental effects, and agriculture applications, the indirect impression of "nano" is its high ratio of surface area to mass, the corresponding high surface activity, and the potential to pass physical barriers (such as blood-brain barriers) freely. Because of these physical and chemical changes from bulk materials to nanomaterials, the toxicity effects are substantially different. Whether products are nanoproducts or not could be greatly evaluated based on whether the products possess the nano features-high surface activity and consequences.

SUMMARY

The definitions of nanoparticles and nanomaterials could be approached from comprehensive considerations of size, property, source and application. Nanomaterials made from bottom-up approaches may require more research and investigation than materials made from top-down approaches, at least in terms of human health and environment effects. The bottom-up materials not only provide the target materials but also frequently provide other materials such as capping reagents and stabilizing reagents which could be more toxic than the target materials.

The most important and unique property of nanoparticles is the extraordinary high ratio of surface to mass. Being small, nanoparticles could also directly pass physical barriers. Nanoparticles, in terms of toxicity and human health, not only provide ion sources (such as heavy metal sources), but also cause physical effects (such as causing deformation of enzymes). Nanoparticles could cause more toxic effects than the dissolved forms of equivalent materials.

The toxicity of nanoparticles and nanomaterials still requires substantial research and investigation, but is confirmed in various experiments. This should not be unexpected, considering the substantial research on the toxicities of heavy metals in the past. However, substantial work might be needed to extrapolate the conclusions obtained in laboratory settings to the natural environment.

Nanoparticles and nanotechnology are new but are not totally strange. Past knowledge and research still provide good reference, gold nanoparticles are still gold but not zinc, and things are not totally unexpected. It is important to delineate the scope of potential problems when facing multi-dimensional challenges. A case by case analysis is greatly needed in the situation mingled with inadequate scientific knowledge and commercial profits.

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