

Massachusetts Chemical & Materials Fact Sheet

Engineered Nanomaterials

(revised December 2017)

This fact sheet is part of a series of chemical and material fact sheets developed by TURI to help Massachusetts companies, community organizations and residents understand the use of hazardous substances and their effects on human health and the environment. This fact sheet also includes information on safer alternatives and safer use options.

Engineered Nanomaterials: What are They?

Engineered nanomaterials are a diverse set of very smallscale substances. They are commonly defined as engineered objects that have at least one dimension between 1 to 100 nanometers (nm), or roughly 100,000 times smaller than the diameter of a human hair.¹ While some types of nanomaterials occur naturally or are formed incidentally, this fact sheet focuses on nanomaterials that are intentionally designed, engineered and manufactured for use in commercial materials, devices and structures.

There is tremendous variation among engineered nanomaterials. They can vary not only in chemical composition, but also in size, shape, and surface coatings. They can exist as films or sheets, as fibers, horns, rings, tubes, spheres, or irregularly shaped particles. They can be engineered from nearly any chemical substance or mineral.

The physical, chemical and biological characteristics of nano-scale materials can be substantially different from the characteristics of the same substance of a larger size. Material strength, optical properties, conductivity and reactivity of nanomaterials often far exceed that of their larger bulk counterparts. These novel properties have spurred tremendous interest in nanotechnology across many industrial, commercial and medical sectors.

While nanomaterial research and development is still relatively young, these materials are now being used in thousands of industrial and consumer products, including paints and coatings, sensors, photovoltaics, electronics, tires, textiles, sporting goods, and personal care products. They are also being used in medical diagnostic and drug delivery devices, and in environmental remediation.²

Broad categories of nanomaterials		
Category	Examples	
Metals	Silver, gold, copper	
Metal oxides	Titanium dioxide, zinc oxide, iron oxide	
Carbon-based	Multi- and single-walled carbon nanotubes, fullerenes	
Dendrimers	Hyperbranched polymers, dendrigraft polymers, dendrons	
Composites	Nano clays, polymer beads	
Crystalline semiconductors	Quantum dots	

Human Health and Environmental Concerns

Many of the chemical, biological and physical properties of engineered nanomaterials that make them technologically and commercially desirable are the same properties that may make engineered nanomaterials more toxic than the same substance of a larger size. Unbound nanoparticles and nanofibers are of particular concern for human health and the environment because of the potential for exposure. These are engineered nanomaterials that are in loose powder form or suspended in liquids and therefore dispersible, rather than being confined within a matrix or bound to surfaces.

The environmental fate and transport of nanoparticles is complicated by the fact that in air and water they can exist as individual particles or agglomerates, or they can adhere to larger particles. Because nanoparticles have a slow rate of settling, some engineered nanomaterials can remain suspended in air and water for longer periods of times and become more broadly dispersed over wider geographic areas than larger particles of the same size.³ Individual nanoparticles or small agglomerates are so small that they can readily enter the human body through inhalation, ingestion and through the skin. In workplaces, inhalation is a widely recognized route of human exposure.

Decades of particle toxicology research have established that particle size influences hazard. As particles become smaller, several key characteristics of the material change compared to their bulk counterpart. At the same exposure dose, compared to micrometer scale particles, nanoscale materials:

- are greater in sheer number;
- have greater surface area;
- have enhanced ability to redistribute from their site of deposition and to travel by new pathways, including the

The Toxics Use Reduction Institute is a research, education, and policy center established by the Massachusetts Toxics Use Reduction Act of 1989. University of Massachusetts Lowell • 600 Suffolk Street, Suite 501 • Lowell, Massachusetts 01854-2866 Ph: (978) 934-3275 • Fax: (978) 934-3050 • Web: <u>www.turi.org</u> lymphatic and nervous systems, to many tissues and organs; and

• have the potential to deliver a higher dose of complex materials attached to their surface.⁴⁻⁶

Substances that are hazardous in bulk form (e.g., cadmium) can generally be expected to be hazardous at the nanoscale. Substances that are not hazardous in bulk form may, however, be hazardous at the nanoscale because of the above nanoscale properties.

Examples of Engineered Nanomaterials

The following provides a brief overview of four engineered nanomaterials in which there is strong industrial or commercial interest and/or use, and on which evidence is emerging about effects on human health and the environment: carbon nanotubes, quantum dots, nano titanium dioxide and nanosilver. The highly reactive nature of nanomaterials suggests that their physical-chemical characteristics may change over time. Physical-chemical characteristics at specific lifecycle stages are important considerations when addressing toxicity.

Carbon nanotubes

Carbon nanotubes (CNTs) are hexagonal sheets of carbon (graphite) assembled into tubes – they resemble miniscule rolls of chicken wire. CNTs are divided into two broad categories:

- Single-walled carbon nanotubes (SWCNTs), which may have diameters of approximately 1 nm;
- Multi-walled carbon nanotubes (MWCNTs), which consist of single-walled tubes stacked one inside the other, with diameters ranging from 5 nm to 200 nm.

Over the last two decades many different types of CNTs have been produced at the industrial scale. CNTs are now used commercially in a number of applications, including sporting goods, anti-static paints, and sensors. Some applications, such as use as medical devices for drug delivery, are still under investigation.

Carbon nanotubes – properties and uses*		
Types	Single-walled carbon nanotubes (SWCNTs), Multi-walled carbon nanotubes (MWCNTs)	
Properties	Excellent tensile strength, thermal and electrical conductivity	
Size	SWCNTs: approx. 1 nm (diameter) MWCNTs: 5 to 200 nm (diameter) Lengths vary, from nanometers to millimeters	
Uses	Sporting goods equipment, coatings (e.g., anti-static paints), batteries, supercapacitors, sensors, water filtration equipment, photovoltaics, biomedical devices, digital memory devices, other uses	
*Note: some uses are still in the R&D stage.		

CNTs can vary dramatically in size, shape and chemical composition, either by design or as a result of contamination during production. They may be straight, bent or curly, rigid or partly flexible. They can exist as single entities or bundled together in ropes or compact tangles that look and act like particles rather than tubes. In addition, they may be functionalized with a wide variety of chemicals on their surface to enhance desired chemical, biochemical, electrical, or physical properties. They may also contain a variety of contaminants bound to the surface, often as a result of using metal catalysts in manufacturing the nanomaterial. These physical-chemical characteristics determine the inherent functional properties and hazards of a specific carbon nanotube.

Health effects. Over the past decade, toxicological studies have revealed human health impacts primarily due to inhalation exposure hazards:

- Lung inflammation and fibrosis. In 2013, the National Institute for Occupational Safety and Health (NIOSH) issued a report based on a comprehensive review of the science and concluded that both SWCNTs and MWCNTs can cause pulmonary inflammation and progressive pulmonary fibrosis (scarring of the lung).⁷ Physical-chemical characteristics such as metal content and structural defects enhance these toxic effects. Recent studies of manufacturing workers have documented biomarkers of both pulmonary inflammation and fibrosis associated with CNT exposure.⁸
- **Carcinogenicity.** In 2014, the International Agency for Research on Cancer (IARC) classified one type of MWCNTs that have high aspect ratios (long, straight and rigid in their physical characteristics) as a **potential human carcinogen.**⁹ This is based on rodent evidence that this type of MWCNT can cause mesothelioma, a type of cancer that affects the outer lining of the lung or abdomen.
- **Tumor development.** Studies conducted by NIOSH researchers have shown that MWCNTs have the capacity to **promote the development and growth of lung tumors** when test animals are first exposed to a chemical that is known to initiate lung cancer.¹⁰

Adsorption. One important feature of CNTs is their tremendous ability to adsorb other chemicals. This property is being commercialized in the use of CNTs in drinking water filtration devices. However, the presence of CNTs in the environment could increase the bioavailability of other environmental contaminants, such as heavy metals or organic pollutants. Chemical contaminants adsorbed onto CNTs become accessible to organisms for uptake, including soil, terrestrial and aquatic organisms.

Ecotoxicity. CNTs are highly stable and biopersistent – they can reside in an organism for long periods of time. Pure CNTs do not disperse well in water because they are poorly soluble, and also because they often entangle or aggregate/agglomerate. However, the solubility of CNTs can be enhanced if the surface of the CNT is oxidized or if functional groups are added. When CNTs are engineered to be soluble, studies have identified ecotoxicity concerns. SWCNTs and MWCNTs of various lengths and surface treatments can inhibit the growth of both freshwater and marine algae.¹¹ Studies of aquatic invertebrates document that ingested CNTs (both MWCNTs and SWNCTs) may interfere with food intake and movement at low concentrations,^{12,13} and appear to be more toxic after longer exposures.^{14,15} Studies examining effects on juvenile rainbow trout demonstrate that exposure to SWCNTs dispersed in water caused systemic toxicity, with effects starting at extremely low concentrations (0.1 mg/L). This is considered by the Globally Harmonized System of Classification and Labeling of Chemicals as "extremely toxic to aquatic life."¹⁶

Quantum dots

Quantum dots (QDs) are nanocrystals. A typical QD is composed of a crystalline semiconductor core encased within another kind of semiconductor material as a shell. The semiconductor core can be comprised of metal complexes, noble metals, and/or magnetic transition metals. QDs containing cores of cadmium (cadmium selenide [CdSe] or cadmium telluride [CdTe]) and shells of zinc sulfide (ZnS) have been used most frequently.¹⁷ QDs can significantly vary in chemical composition, size, charge and surface coatings (i.e., chemical functional groups on the particle surface), depending on the application.

Due to their extremely small size (1–100 nm), QDs have unique electronic and optical properties that create a bright and intense fluorescence as long as the QD is stable. Since their discovery in the 1980s, QDs have been incorporated into medical imaging devices, and are currently under investigation for use in traceable drug delivery, biological probes, and drug carriers. They are also being incorporated into solar cells and electronic devices such as LEDs that make use of their optical and electronic properties.

Quantum dots – properties and uses*		
Types	Can be made from cadmium selenide (CdSe), cadmium telluride (CdTe) and zinc selenide (ZnSe)	
Properties	Reactive core influences the material's optical properties	
Size	1 to 100 nm	
Uses	Medical imaging, photovoltaics, light emitting diodes (LEDs), telecommunications, sensors, drug delivery	
*Note: some uses	are still in the R&D stage	

Health effects. QDs containing cadmium cores raise concern for human health, as this compound is highly reactive and toxic.

- Chronic health effects including carcinogenicity. Bulk level cadmium (Cd) is a known human lung carcinogen and may also cause kidney and prostate cancer.¹⁸ Chronic low-level exposures have also been linked to kidney, bone and lung disease.¹⁹ Despite cancer concerns due to the Cd core in QDs, no carcinogenicity study of Cd-containing QDs has been conducted to date.
- Health effects related to physiochemical properties. Research suggests that the toxicity of Cd-containing QDs varies depending on size, chemical surface coatings, and charge, among other characteristics.²⁰ For example, cellular studies indicate that Cd-containing QDs with smaller diameters had greater toxicity compared to larger QDs.²¹ When uncoated, CdSe quantum dots were toxic to liver cells. This toxicity was related to the release of Cd²⁺ ions from the QD core.²² Additional studies have shown Cd ions to be released from QDs with and without a shell layer.²³
- **Respiratory effects.** Studies to date have primarily focused on acute outcomes and how the Cd from QDs distributes throughout the body once exposed. For example, the few respiratory toxicology studies conducted to date have observed dose-dependent lung injury and inflammation with CdSe QDs that were functionalized with carboxyl or amine groups. Researchers suggest that the toxicity findings appear dependent on the dissolution of the QD structure and the subsequent bioavailability of free Cd.²⁴ After pulmonary exposure, the kidneys appear to be the main organ from which Cd from the QDs is distributed to other organs. This is also true of bulk Cd.^{24,25}

Ecotoxicity. Current evidence indicates that cadmiumcontaining QDs can accumulate and exert toxic effects on micro-organisms, invertebrates and fish species in both freshwater and seawater.²⁶ UV radiation appears to increase the toxicity of QDs.²⁶ Ecotoxicity in organisms at the different trophic levels is dependent on physical-chemical properties, among other factors such as environmental conditions. Examples of toxicity effects include reduction in algal photosynthetic activity and growth inhibition,^{27,28} DNA damage in invertebrates,^{29,30} and decreased cell viability and DNA damage in various fish species.^{30,31}

Nano titanium dioxide

Nano titanium dioxide (TiO₂) is derived from three crystalline forms of titanium dioxide: rutile, anatase and brookite. For decades, TiO₂ at the nanoscale has been used as a whitening agent in paints and pigments and as an anticaking agent. In addition to these industrial uses, nano TiO₂ is widely used in cosmetics and sunscreens and in some food products such as chewing gum.

 TiO_2 is generally thought to be a low toxicity substance. However, its toxicity changes at the nanoscale. Studies demonstrate that nano TiO_2 particles (about 20-30 nm) are considerably more toxic than micrometer-sized TiO_2 (>100nm).^{32,33}

Nano titanium dioxide – properties and uses		
Types	Crystalline nano forms: rutile, anatase and brookite	
Properties	Whitening agent, anti-caking agent	
Size	10 to 200 nm	
Uses	Paints, coatings, printer ink, plastics, household products, cosmetics, sunscreens, food products	

Health effects. NIOSH issued a report based on a comprehensive review of health effect studies. The report reviewed impacts associated with different sizes of TiO_2 , including the nanoscale. For nano TiO_2 , the report documented toxicological evidence of:³⁴

- **Pulmonary inflammation**. Nano TiO₂ can both cause pulmonary inflammation and exacerbate pre-existing symptoms.
- **Genotoxicity.** Under certain conditions, nano TiO₂ can damage DNA (e.g., nano TiO₂ particles exposed to UV light; specific TiO₂ particle types).
- **Carcinogenicity.** NIOSH determined that occupational exposure (by inhalation) to nano TiO₂ particles should be considered a potential occupational carcinogen.
- **Organ effects.** Nano TiO₂ accumulates particularly in the liver even at low exposure levels. Toxicological effects have been observed on the liver, but at generally very high doses.³⁵

Although studies suggest that intact skin does appear to block nano TiO_2 from entering the body, the European Union's Scientific Committee on Consumer Safety recommended that cosmetics and sunscreens containing nano TiO_2 not contain particles with high photocatalytic activity, which enhances toxicity.³⁶

Ecotoxicity. Because of widespread industrial and consumer use, there is concern about releases of nano TiO_2 into the environment. Studies have observed effects on some aquatic fish species,³⁷⁻³⁹ yet the greatest impact may be the ability of TiO_2 to adsorb and enhance the bioavailability of other toxic contaminants in the aquatic environment, including lead, arsenic and cadmium.⁴⁰⁻⁴² As with other nanomaterials, the aquatic toxicity of TiO_2 is dependent on factors such as solubility, pH of the aquatic system, and state of agglomeration.

Nanosilver

Unlike most engineered nanomaterials, nanosilver (nano Ag) is not a recent innovation. Colloidal silver is a form of silver that is based on extremely small particles and has been used for medical applications for over 100 years. In recent years, however, the use of nano Ag has increased dramatically.

Silver in all forms has antimicrobial properties. However, the nonspecific antimicrobial function of nano Ag has resulted in its broad use in commercial and consumer products, including food preparation equipment, personal care products, textiles, paints and pigments, and wound dressings, among others.⁴³

Nanosilver – properties and uses		
Types	Colloidal silver, spun silver, nanosilver powder and polymeric silver	
Properties	High surface reactivity, strong antimicrobial properties	
Size	10 to 200 nm	
Uses	Medical devices and wound dressings, paints and pigments, water purification, insecticides, and antimicrobial uses in a wide variety of consumer products (e.g., children's toys, textiles and shoes, cosmetics and personal care products, food preparation tools and appliances)	

Ecotoxicity. Studies demonstrate that nano Ag, like bulk silver, is **toxic to aquatic species**, including various invertebrate, algae and fish species.⁴⁴⁻⁴⁷ Studies suggest that the toxicity of nano Ag is largely due to silver ions – similar to the toxicity of bulk silver. One analysis evaluated the existing ecotoxicity data, using the Globally Harmonized System of Classification and Labeling of Chemicals, and classified nano Ag as "acutely very toxic" and "potentially chronically very toxic."⁴⁸ These findings are concerning because nano Ag is often released from the material on which it is used (e.g., textiles, food preparation surfaces) and contaminate rivers, lakes and ocean water bodies.⁴⁹

As with all antimicrobial agents, there is a general concern about their impact on wastewater treatment systems that are dependent on microbial activity. The formation of silver sulfide nanoparticles has been repeatedly observed in studies assessing effects of nano Ag on wastewater treatment systems.^{51,52} This nano Ag sulfidation reduces the antimicrobial impact on wastewater treatment systems.⁵¹⁻⁵³ The extent of sulfidation appears to be size dependent – affecting smaller particles more than larger particles (e.g., 10 nm versus 100 nm).⁵¹ Ecotoxicity assessments of nano Ag in sludge from wastewater treatment facilities are lacking. Preliminary studies reveal that, if incinerated, a proportion of incinerated nano Ag could transform into the metallic form (depending on incineration time and temperature) – an important consideration for the disposal of incinerated biosolids.^{52,54}

Health effects. Based on a comprehensive review of available published studies, a draft NIOSH report concludes that there are risks of lung and liver effects associated with exposure to Ag nanoparticles in the range of 15-20 nm.⁵⁵ Findings are based on oral and inhalation toxicological studies (90 day studies in rats) that observed:⁵⁶⁻⁶⁰

- **Lung effects.** Exposure was associated with compromised lung function and lung inflammation.
- **Organ effects.** Once deposited in the lung, nano Ag can be transported in the blood to cause cellular changes in the kidneys and liver. Signs of liver necrosis have been observed.
- **Deposition in spleen, olfactory bulb and brain.** Beyond the lungs, liver and kidneys, significant increases in the amount of silver after exposure have been observed in the spleen, olfactory bulb, and brain.

Additional health concerns. In vitro cellular studies summarized in the NIOSH report show that once nano Ag is present in organs and tissues, it can cause DNA damage, genotoxicity, oxidative stress and cell death. Scientists have also noted that **antimicrobial resistance** is a growing concern and a recent European Commission panel concluded that more research on the topic is needed.^{61,62}

Safer Alternatives

As with most emerging technologies, there remains significant uncertainty regarding the health and environmental effects of engineered nanomaterials. Commercialization of products and processes based on new technologies, including engineered nanomaterials, should not proceed until their hazards are well understood.

When making decisions about product design, it is important to consider whether the function proposed for a nanoparticle is necessary or if it can instead be achieved using a bulk material. For numerous functions in a given application, such as material strength or optical properties, existing bulk materials may satisfactorily achieve the desired function and should be used instead of nanomaterials, given significant data gaps regarding the health and safety of nanomaterials.

Considerations for the Safer Development and Safer Use of Engineered Nanomaterials

There is growing interest in "green" nanotechnology – reducing hazard through appropriate design and applications of engineered nanomaterials. Green nanotechnology straddles two disciplines: green chemistry and green engineering. Both of these disciplines consider hazard across the life cycle as an inherent property of chemicals and materials. Hazard is seen as a design attribute – more specifically a design flaw – and considered part of the feasibility equation, on equal footing with technical and economic feasibility considerations.

Researchers at TURI have started such a blueprint for design rules for safer nanotechnology. The design rules include five principles, which together follow the acronym SAFER, as shown in the table below.⁶³ These principles focus on aspects such as modifying physical-chemical characteristics of the material to diminish the hazard, considering alternative materials, and enclosing the material within another, less hazardous, material. Other researchers have proposed other more specific design rules, which include avoiding chemical compositions of engineered nanomaterials that contain known toxic elements such as cadmium, and avoiding nanomaterials with dimensions that are known to possess hazardous properties (such as CNTs that resemble asbestos fibers).⁶⁴

Design Principles for SAFER Nanotechnology⁶³

1. Size, surface and structure: Diminish or eliminate the hazard by changing the size, surface, or structure of the nanoparticle while preserving the functionality of the nanomaterial for the specific application 2. Alternative materials: Identify either nano or bulk safer alternatives that can be used to replace a hazardous nanoparticle 3. Functionalization: Add additional molecules (or atoms) to the nanomaterial to diminish or eliminate the hazard while preserving desired properties for a specific application 4. Encapsulation: Enclose a nanoparticle within another less hazardous material 5. Reduce the quantity: In situations where the above design principles cannot be used to reduce or eliminate the hazard of a nanomaterial, and continued use is necessary, investigate opportunities to use smaller quantities while still maintaining product functionality

In addition to **eliminating** nanomaterials or **reducing** their toxicity whenever possible, **safer workplace practices** are essential. Facilities using engineered nanomaterials, including research labs as well as industrial and commercial enterprises, must follow strict procedures to ensure the protection of workers, consumers, communities and the environment. At a minimum, entities using engineered nanomaterials or nanoenabled products should implement a risk management program that includes:^{65,66}

- Evaluating available hazard information for the nanomaterials used on site (e.g., physical-chemical properties, toxicology, health effects data);
- Assessing employees' job tasks to determine the potential for exposure;
- Educating and training all employees regarding the proper handling of engineered nanomaterials;
- Prohibiting cleaning with dry methods, such as sweeping or blowing air;

- Containing all potential release points of engineered nanomaterials by installing and evaluating engineering controls (e.g., exhaust ventilation) and environmental control technologies to prevent environmental releases;
- Selecting proper personal protective equipment; and
- Systematically and continuously evaluating exposures to ensure that occupational and environmental control measures are working properly.

Sophisticated risk management programs such as this can only be developed and implemented by health and safety professionals trained in the unique challenges of engineered nanomaterials. Small start-up companies and others without such capabilities on staff should seek outside expertise, such as consultants or state health departments.

Regulatory Context

There are currently no Massachusetts regulations specifically governing the use or release of nanomaterials. Other states, however, have pursued regulations focused primarily on understanding use characteristics, analytical testing methods and environmental health and safety data if known. For example, in 2010-11, California invoked its authority to request information from companies manufacturing or using specific nanomaterials of concern in California, including carbon nanotubes, quantum dots, nanosilver and nano titanium dioxide, among others.⁶⁷ In 2006, Berkeley, California, was the first city to issue an ordinance requiring facilities that manufacture or use nanomaterials to report and disclose to city officials the current toxicology and occupational and environmental risk management controls that are in place to mitigate impacts.⁶⁸

At the federal level, nanomaterials are primarily regulated by the Environmental Protection Agency (EPA) under the Toxics Substances Control Act (TSCA). Chemical substances under TSCA are regulated on the basis of their Chemical Abstract Service (CAS) identification number - a system that differentiates based on molecular structure, not size. For the majority of nanomaterials, including nanosilver and nano TiO₂, TSCA does not differentiate between the nano form and the bulk form. These nanomaterials are regulated as "existing chemicals" under TSCA. However, some nanomaterials, including QDs and CNTs, are subject to "new chemical" provisions under TSCA. For nanomaterials considered a "new chemical," manufacturers must submit a PreManufacturing Notice (PMN). In many cases, EPA has subsequently issued Significant New Use Rules (SNURs) for these materials. As of 2017, companies using or manufacturing nanomaterials that have not been subject to PMNs or SNURs will be subject to a one-time reporting and recordkeeping rule (see table).⁶⁹

Other EPA statutes also apply to nanomaterials. If a pesticidal claim is made about a nanomaterial product, it is subject to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Although the EPA National Ambient Air Quality Standards (NAAQS) regulate particulate matter in air that is smaller than 2.5 μ m (PM_{2.5}), these regulations currently do not specifically address nanosized particles as distinct from particles in the micrometer size range. If engineered nanomaterials enter drinking water, they may be regulated under the Safe Drinking Water Act, although no maximum contaminant level goals (MCLGs) and maximum contaminant levels (MCLs) have been established for nanomaterials based on their nano-size properties.

The Occupational Safety and Health Administration (OSHA) has issued no permissible exposure limits (PELs) for engineered nanomaterials. NIOSH has published recommended exposure limits (RELs) for CNTs⁷ and nano TiO₂,³⁴ as shown in the table below.

Regulatory Considerations	
Occupational Exposure Limits*	 CNTs: NIOSH REL⁷: 1 µg/m³, as elemental carbon Nano TiO₂: NIOSH REL³⁴: 0.3 mg/m³ Nano Ag: NIOSH's draft (2015) report stated that there is not enough available data to develop a REL for nano Ag and recommends that worker exposures to nano Ag not exceed the current REL for silver of 10µg/m^{3,55}
	Federal Insecticide, Fungicide and Rodenticide Act
	 Companies making pesticidal claims about a nanomaterial product must comply with FIFRA and register the pesticide with EPA. Conditional registrations have been issued for some nano Ag anti-microbial products. However, in June 2017, the U.S. Court of Appeals for the Ninth Circuit revoked the conditional approval for the product "Nanosilva."⁷⁰
	Toxics Substances Control Act
EPA	 EPA requires manufacturers and importers of nanomaterials that are considered "new chemicals" to submit a premanufacture notice (PMN) to EPA at least 90 days in advance of a new chemical's commercialization. EPA approval is based on consent orders between EPA and the particular firm, which outline the terms of use, including environmental and health protections and toxicity testing requirements. Significant New Use Rules (SNURs) have been issued for dozens of nanomaterials that were
	 previously the focus of PMNs. Companies that manufacture (including import) or process certain chemical substances already in commerce as nanoscale materials must comply with a one-time reporting and recordkeeping rule and notify the agency of specific information, including specific chemical identity; production volume; methods of manufacture; processing, use, exposure and release information; and available health and
	safety data. Some exceptions apply. The rule went into effect on August 14, 2017 and reporting is required by August 14, 2018. nended Exposure Limit, based on an 8-hour time

*REL: Recommended Exposure Limit, based on an 8-hour time weighted average.

References

- International Standards Organization. ISO-80004-1:2015 Nanotechnologies -- Vocabulary -- Part 1: Core terms. Retrieved 1/5/2017 at: <u>http://www.iso.org/obp/ui/.</u>
- National Institute for Environmental Health Sciences. Nanomaterials. Retrieved 1/5/2017 at: https://www.niehs.nih.gov/health/topics/agents/sya-nano/.
- Environmental Protection Agency, Senior Policy Council. Nanotechnology White Paper. 2007. Retrieved 1/5/2017 at: <u>http://www.epa.gov/osa/pdfs/nanotech/eap-nanotechnology-whitepaper-0207.pdf.</u>
- 4. Fubini B, et al. Physico-chemical features of engineered nanoparticles relevant to their toxicity. Nanotoxicology. 2010;4:347-63.
- Donaldson K, et, al. Nanotoxicity: challenging the myth of nano-specific toxicity. Curr Opin Biotechnol. 2013;24(4):724-34.
- European Commission. Examination and Assessment of the Consequences for Industry, Consumers, Human Health and the Environment of Possible Options for Changing REACH Requirements for Nanomaterials (Annex 3 to final report). Ispra, Italy: Joint Research Centre, Institute for Health and Consumer Protection, 2013. Retrieved 1/5/2017 at: <u>http://ec.europa.eu/environment/chemicals/nanotech/reachclp/pdf/Annex_3_Options%20Applied%20to%20Case%20St</u> <u>udies_20130109.pdf</u>.
- National Institute for Occupational Safety and Health. Current Intelligence Bulletin No.65: Occupational Exposure to Carbon Nanotubes and Nanofibers. 2013. Retrieved 12/1/2016 at: <u>https://www.cdc.gov/niosh/docs/2013-145/pdfs/2013-145.pdf</u>.
- Fatkhutdinova LM, et al. Fibrosis biomarkers in workers exposed to MWCNTs. Toxicol Appl Pharmacol. 2016;299:125-31.
- 9. Grosse Y, et al. Carcinogenicity of fluoro-edenite, silicon carbide fibres and whiskers, and carbon nanotubes. Lancet Oncol. 2014;15(13):1427-8.
- 10. Sargent LM, et al. Promotion of lung adenocarcinoma following inhalation exposure to multi-walled carbon nanotubes. Part Fibre Toxicol. 2014;11:3.
- 11. Jackson P, et al. Bioaccumulation and ecotoxicity of carbon nanotubes. Chem Cent J. 2013;7(1):154.
- 12. Kim KT, et, al. Acute toxicity of a mixture of copper and single-walled carbon nanotubes to Daphnia magna. Environ Toxicol Chem. 2010;29(1):122-6.
- Zhu X, et, al. Acute toxicities of six manufactured nanomaterial suspensions to Daphnia magna. J Nanopart Res. 2009;11:67-75.
- Kim KT, et, al. Influence of multiwalled carbon nanotubes dispersed in natural organic matter on speciation and bioavailability of copper. Environ Sci Technol. 2009;43(23):8979-84.
- 15. Edgington AJ, et al. The influence of natural organic matter on the toxicity of multiwalled carbon nanotubes. Environ Toxicol Chem. 2010;29(11):2511-8.
- Smith CJ, et al. Toxicity of single walled carbon nanotubes to rainbow trout, (Oncorhynchus mykiss): respiratory toxicity, organ pathologies, and other physiological effects. Aquat Toxicol. 2007;82(2):94-109.

- Stone, V. Environmental and Human Health Impacts of Nanotechnology. In: Lead JR, Smith E, editors. Environmental and human health impacts of nanotechnology. Chichester, West Sussex, U.K.; Hoboken, N.J.: Wiley; 2009.
- 18. Cogliano VJ, et al. Preventable exposures associated with human cancers. J Natl Cancer Inst. 2011;103(24):1827-39.
- Agency for Toxics Substances Disease Registry. Toxicological Profile for Cadmium. September 2012. Retrieved 1/5/2016 at: https://www.atsdr.cdc.gov/toxprofiles/tp5.pdf.
- 20. Hardman R. A toxicologic review of quantum dots: toxicity depends on physicochemical and environmental factors. Environ Health Perspect. 2006;114(2):165-72.
- 21. Lovrić J, et al. Differences in subcellular distribution and toxicity of green and red emitting CdTe quantum dots. J Mol Med (Berl). 2005;83(5):377-85.
- 22. Derfus AM, et al. Probing the cytotoxicity of semiconductor quantum dots. Nano Letters. 2004;1:11-8.
- Kloepfer JA, et al. Quantum dots as strain- and metabolismspecific microbiological labels. Appl Environ Microbiol. 2003;69(7):4205-13.
- 24. Roberts JR, et al. Lung toxicity and biodistribution of Cd/Se-ZnS quantum dots with different surface functional groups after pulmonary exposure in rats. Part Fibre Toxicol. 2013;10:5.
- 25. Ma-Hock L, et al. Short term inhalation toxicity of a liquid aerosol of CdS/Cd(OH)₂ core shell quantum dots in male Wistar rats. Toxicol Lett. 2012;208(2):115-24.
- 26. Rocha TL, et al. Environmental behaviour and ecotoxicity of quantum dots at various trophic levels: A review. Environ Int. 2017;98:1-17.
- 27. Lin S, et al. Effects of quantum dots adsorption on algal photosynthesis. J Phys Chem C. 2009;113:10962-6.
- Wang J, et al. Toxicity assessment of manufactured nanomaterials using the unicellular green alga Chlamydomonas reinhardtii. Chemosphere. 2008;73(7):1121-8.
- 29. Rocha TL, et al. Immunocytotoxicity, cytogenotoxicity and genotoxicity of cadmium-based quantum dots in the marine mussel Mytilus galloprovincialis. Mar Environ Res. 2014;101:29-37.
- Gagné F, et al. Ecotoxicity of CdTe quantum dots to freshwater mussels: impacts on immune system, oxidative stress and genotoxicity. Aquat Toxicol. 2008;86(3):333-40.
- Tang S, et al. Cadmium sulfate and CdTe-quantum dots alter DNA repair in zebrafish (Danio rerio) liver cells. Toxicol Appl Pharmacol. 2013;272(2):443-52.
- Ferin J, et al. Pulmonary retention of ultrafine and fine particles in rats. Am J Respir Cell Mol Biol. 1992;6(5):535-42.
- 33. Renwick LC, et al. Increased inflammation and altered macrophage chemotactic responses caused by two ultrafine particle types. Occup Environ Med. 2004;61(5):442-7.
- National Institute for Occupational Safety and Health.. Current Intelligence Bulletin No 63: Occupational Exposure to Titanium Dioxide. 2011. Retrieved 1/5/2017 at: https://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf.
- 35. Shi H, et al. Titanium dioxide nanoparticles: a review of current toxicological data. Part Fibre Toxicol. 2013;10:15.

- European Commission, Scientific Committee on Consumer Safety. Opinion on Titanium Dioxide (nanoform) COLIPA no. 75. April 2014.
- Yeo MK, Kang M. Effects of CuxTiOy nanometer particles on biological toxicity during zebrfish embryogenesis. Korean J Chem Eng. 2009;26:711-8.
- Ma H, et al. Phototoxicity of TiO2 nanoparticles under solar radiation to two aquatic species: Daphnia magna and Japanese medaka. Environ Toxicol Chem. 2012;31(7):1621-9.
- Zhu X, et al. Toxicity and bioaccumulation of TiO2 nanoparticle aggregates in Daphnia magna. Chemosphere. 2010;78(3):209-15.
- 40. Miao W, et al. Effects of titanium dioxide nanoparticles on lead bioconcentration and toxicity on thyroid endocrine system and neuronal development in zebrafish larvae. Aquat Toxicol. 2015;161:117-26.
- Sun H, et al. Influence of titanium dioxide nanoparticles on speciation and bioavailability of arsenite. Environ Pollut. 2009;157(4):1165-70.
- 42. Zhang X, et al. Enhanced bioaccumulation of cadmium in carp in the presence of titanium dioxide nanoparticles. Chemosphere. 2007;67(1):160-6.
- 43. Varner KE, et al. State-of-the-Science Review: Everything Nanosilver and More. Washington DC: Environmental Protection Agency, 2010.
- 44. Gaiser BK, et al. Effects of silver and cerium dioxide microand nano-sized particles on Daphnia magna. J Environ Monit. 2011;13(5):1227-35.
- 45. Asghari S, et al. Toxicity of various silver nanoparticles compared to silver ions in Daphnia magna. J Nanobiotechnology. 2012;10:14.
- 46. Kim J, et al. Differentiation of the toxicities of silver nanoparticles and silver ions to the Japanese medaka (Oryzias latipes) and the cladoceran Daphnia magna. Nanotoxicology. 2011;5(2):208-14.
- Laban G, et al. The effects of silver nanoparticles on fathead minnow (Pimephales promelas) embryos. Ecotoxicology. 2010;19:185-95.
- Juganson K, et al. NanoE-Tox: New and in-depth database concerning ecotoxicity of nanomaterials. Beilstein J Nanotechnol. 2015;6:1788-804.
- 49. Geranio L, et al. The behavior of silver nanotextiles during washing. Environ Sci Technol. 2009;43(21):8113-8.
- OECD. Nanomaterials in Waste Streams: Current Knowledge on Risks and Impacts. Paris: 2016. Retrieved 1/5/2017 at: <u>http://www.keepeek.com/Digital-Asset-</u> <u>Management/oecd/environment/nanomaterials-in-waste-</u> <u>streams 9789264249752-en#page14.</u>
- 51. Kaegi R, et al. Fate and transformation of silver nanoparticles in urban wastewater systems. Water Res. 2013;47:3866-3877.
- 52. Impellitteri CA, et al. Transformation of silver nanoparticles in aged biosolids. Water Res. 2013; 47:3878-3886.
- Levard C, et al. Sulfidation of silver nanoparticles: An antidote to their toxicity. Environ Sci Technol. 2013;47:13440-13448.
- Meier C, et al. Transformation of silver nanoparticles in sewage sludge during incineration. Environ Sci Technol. 2016;50:3503-3510.
- 55. National Institute for Occupational Safety and Health. External Review Draft - Current Intelligence Bulletin: Health Effects of Occupational Exposure to Nanosilver. December 2015.

- 56. Sung JH, et al. Subchronic inhalation toxicity of silver nanoparticles. Toxicol Sci. 2009;108(2):452-61.
- Song KS, et al. Recovery from silver-nanoparticle-exposureinduced lung inflammation and lung function changes in Sprague Dawley rats. Nanotoxicology. 2013;7(2):169-80.
- 58. Kim YS, et al. Subchronic oral toxicity of silver nanoparticles. Part Fibre Toxicol. 2010;7:20.
- Ji JH, et al. Twenty-eight-day inhalation toxicity study of silver nanoparticles in Sprague-Dawley rats. Inhal Toxicol. 2007;19(10):857-71.
- Lankveld DP, et al. The kinetics of the tissue distribution of silver nanoparticles of different sizes. Biomaterials. 2010;31(32):8350-61.
- 61. European Commission, Scientific Committee on Emerging and Newly Identified Health Risks. Opinion on: Nanosilver: safety, health and environmental effects and role in antimicrobial resistance. 2014.
- 62. Ma Y, et al. Shift in antibiotic resistance gene profiles associated with nanosilver during wastewater treatment. FEMS Microbiol Ecol. 2016;92(3).
- 63. Morose G. The five principles of design for safer nanotechnology. J Clean Prod. 2010;18:285–9.
- 64. Hutchison JE. Greener nanoscience: a proactive approach to advancing applications and reducing implications of nanotechnology. ACS Nano. 2008;2(3):395-402.
- 65. National Institute for Occupational Safety and Health. Managing the Health and Safety Concerns Associated with Engineered Nanomaterials. March 2009. Retrieved 1/5/2017 at: <u>https://www.cdc.gov/niosh/docs/2009-125/pdfs/2009-125.pdf</u>
- 66. Office of Technical Assistance and Technology. OTA Technology Guidance Document: Nanotechnology – Considerations for Safe Development. Retrieved 1/5/207 at: <u>http://www.mass.gov/lwd/docs/dos/nano/ota-nanotech-guidance-doc.pdf.</u>
- 67. California Department of Toxic Substances. Chemical Information Call-In Overview. Retrieved 1/5/2017 at: <u>http://www.dtsc.ca.gov/PollutionPrevention/Chemical Call I</u> <u>n.cfm</u>.
- 68. City of Berkeley. Planning and Development Department Toxics Management Division. Manufactured Nanoscale Materials Health & Safety Disclosure. August 2007. Retrieved 1/5/2017 at: <u>https://www.cityofberkeley.info/uploadedFiles/Planning (ne</u>

w site map walk-through)/Level 3 -General/Manuffactured Nanoscale Materials.pdf.

- 69. Environmental Protection Agency. Control of Nanoscale Materials under the Toxic Substances Control Act. Retrieved 7/15/2017 at: <u>https://www.epa.gov/reviewing-new-chemicals-</u><u>under-toxic-substances-control-act-tsca/control-nanoscale-</u><u>materials-under</u>
- 70. Natural Resources Defense Council v. Environmental Protection Agency. United States Court of Appeals for the Ninth Circuit. Filed May 17, 2017. Retrieved 7/15/2017 at: <u>http://cdn.ca9.uscourts.gov/datastore/opinions/2017/05/30/15-72308.pdf.</u>