CURRENT INTELLIGENCE BULLETIN

INTERIM GUIDANCE FOR THE MEDICAL SCREENING OF WORKERS POTENTIALLY EXPOSED TO ENGINEERED NANOPARTICLES

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

We are requesting the review of this document as part of our pre-dissemination review. Written comments on the document should be sent to NIOSH Docket Office, Robert A. Taft Laboratories, 4676 Columbia Parkway, MS C-34, Cincinnati, Ohio 45226 or by email at nioshdocket@cdc.gov. All electronic comments should be formatted as Microsoft Word and make reference to docket number NIOSH-115. A draft of the document can be found at the following web address: http://www.cdc.gov/niosh/review/public/115/

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SUMMARY

Concerns have been raised about whether workers exposed to engineered nanoparticles are at increased risk of adverse health effects. Therefore, the purpose of this document is to provide interim guidance from the National Institute for Occupational Safety and Health (NIOSH) concerning whether specific medical screening (that is, medical tests for asymptomatic workers) is appropriate for these workers.

Medical screening is only part of a complete safety and health management program that follows a hierarchy of controls and involves various occupational health surveillance measures. Since specific medical screening of workers exposed to engineered nanoparticles has not been extensively discussed in the scientific literature, this document is intended to fill the knowledge gap on an interim basis.

Although increasing evidence indicates that exposure to some engineered nanoparticles can cause adverse health effects in laboratory animals, no studies of workers exposed to the few engineered nanoparticles tested in animals have been published. The current body of evidence about the possible health risks of occupational exposure to engineered nanoparticles is quite small. **Insufficient scientific and medical evidence now exists to recommend the specific medical screening of workers potentially exposed to engineered nanoparticles.** Nonetheless, the lack of evidence on which to recommend specific medical screening does not preclude its consideration by employers interested in taking precautions beyond standard industrial hygiene measures. If nanoparticles are composed of a chemical or bulk material for which medical screening recommendations exist, they would apply to nanoparticles as well.

Ongoing research on the hazards of engineered nanoparticles is needed along with the continual

reassessment of available data to determine whether specific medical screening is warranted for workers who are producing or using nanoparticles. **In the meantime, the following recommendations are provided for workplaces where workers may be exposed to engineered nanoparticles in the course of their work:**

- **Take prudent measures to control workers' exposures to nanoparticles.**
- **Conduct hazard surveillance as the basis for implementing controls.**
- **Consider established medical surveillance approaches to help assess whether control measures are effective and identify new or unrecognized problems and health effects.**

NIOSH will continue to examine new research findings and update its recommendations about medical screening programs for workers exposed to nanoparticles. Additionally, NIOSH is seeking comments on the strengths and weaknesses of exposure registries for workers potentially exposed to engineered nanoparticles.

1.0 PURPOSE

Concerns have been raised about whether workers exposed to engineered nanoparticles are at increased risk of adverse health effects. Therefore, the purpose of this document is to provide interim guidance from the National Institute for Occupational Safety and Health (NIOSH) concerning specific medical screening for these workers—that is, medical tests for asymptomatic workers. Such screening would be beyond any medical surveillance already occurring as part of existing occupational health surveillance.

2.0 BACKGROUND

Nanotechnology is a system of innovative methods for controlling and manipulating matter at the near-atomic scale to produce engineered materials, structures, and devices. Engineered nanoparticles are generally considered to be a class or subset of nanomaterials with at least one dimension that is approximately 1 to 100 nanometers (www.nano.gov/html/facts/whatIsNano.html). At these scales, materials often exhibit unique properties that affect their physical, chemical, and biological behavior.

Potential occupational health risks associated with manufacturing and using nanomaterials are not yet clearly understood. Many engineered nanomaterials and devices are formed from nanometer-scale particles (nanoparticles) that are initially produced as aerosols or colloidal suspensions. Exposure to these materials during manufacturing and use may occur through inhalation, dermal contact, and ingestion; however, inhalation exposure is the main route of concern [ASCC 2006]. Minimal information is currently available about dominant exposure routes, potential exposure, and material toxicity. The existing information comes primarily from the study of ultrafine particles (typically defined as particles smaller than 100 nanometers) [Aitken et al. 2004; Donaldson et al. 2005, 2006; Maynard and Kuempel 2005; Oberdörster et al. 2005a,b; Kreyling et al. 2006; Gwinn and Vallyathan 2006; Borm et al. 2006; Helland et al. 2007]. The term “ultrafine” is frequently used in the context of particles with dimensions less than 100 nanometers that have not been intentionally produced but are the incidental products of processes involving combustion, welding, or diesel engines. It is currently unclear whether the use of source-based definitions of nanoparticles and ultrafine particles is justified from a safety and health perspective. However, if engineered nanoparticles have the same physicochemical characteristics that are associated with reported effects from ultrafine particles, they

may also pose the same health concerns.

Experimental animal studies have indicated that many types of poorly soluble nanoscale particles elicit a greater pulmonary inflammatory response than do larger particles of the same composition on a mass for mass basis [Oberdörster et al. 1994; Lison et al 1997; Zhang et al. 2000, 2003; Brown et al. 2001; Höhr et al. 2002; Duffin et al. 2007]. Other physicochemical properties such as surface reactivity, chemical composition, crystal structure, and shape have been shown to influence the toxicity of nanoparticles [Zang et al. 1998; Dick et al. 2003; Warheit et al. 2007a, b]. Some types of engineered nanoparticles have been shown in experimental animal studies to cause adverse lung effects (e.g., pulmonary inflammation and progressive fibrosis) [Lam et al. 2004, 2006; Shvedova et al. 2005] and cardiovascular effects (e.g., inflammation, blood platelet activation, plaque formation, and thrombosis) [Radomski et al. 2005; Donaldson et al. 2006; Li et al. 2007]. Elevated lung cancer has been reported in some studies of workers exposed to ultrafine particles (diesel exhaust and welding fume) [Steenland et al. 1998; Garshick et al. 2004; Antonini 2003]. Exposure to ultrafine particles have raised concerns about possible adverse effects in workers exposed to engineered nanoparticles [Royal Society and Academy of Engineering 2004; Maynard and Kuempel 2005; IRRST 2006; Nel et al. 2006; Schulte and Salmanca-Buentello 2007; Maynard 2007; Lam et al. 2006; Kuempel et al. 2007; Aitken et al. 2004; ASCC 2006].

3.0 OCCUPATIONAL HEALTH SURVEILLANCE

NIOSH has historically recommended implementing occupational health surveillance programs when workers are exposed to potentially hazardous materials. Occupational health surveillance involves the ongoing systematic collection, analysis, and dissemination of exposure and health data on groups of workers for the purpose of preventing illness and injury; this information is frequently used for

establishing and evaluating the hierarchy of preventive actions [Halperin 1996]. The general term *occupational health surveillance* includes medical and hazard surveillance. Occupational health surveillance is an essential component of an effective occupational safety and health program [Harber et al. 2003; NIOSH 2006b; Wagner and Fine 2008; Baker and Matte 2005]. This document supports that concept; however, the main focus of the document is whether additional medical screening is warranted for workers potentially exposed to engineered nanoparticles.

3.1 Medical Surveillance

NIOSH recommends the medical surveillance of workers when they are exposed to hazardous materials. The elements of a medical surveillance program generally include the following:

1. An initial medical examination and collection of medical and occupational histories;
2. Periodic medical examinations at regularly scheduled intervals, including specific medical screening tests when warranted;
3. More frequent and detailed medical examinations as indicated on the basis of findings from these examinations;
4. Post-incident examinations and medical screening following uncontrolled or non-routine increases in exposures such as spills;
5. Worker training to recognize symptoms of exposure to a given hazard;
6. A written report of medical findings, and;
7. Employer actions in response to identification of potential hazards.

3.1.1 Medical Screening

Medical screening (also referred to as medical monitoring) is one form of medical surveillance, and includes medical testing to detect preclinical changes in organ function or changes that occur in the very early stages of disease—before a person would normally seek medical care and when intervention is beneficial [Ashford et al. 1990; Baker and Matte 2005; Halperin et al. 1986; Harber et al. 2003; ILO 1998]. Medical screening complements a complete safety and health management program that follows the hierarchy of controls traditionally used by safety and health professionals (elimination, substitution, exposure controls, environmental monitoring, good work practices, and respiratory and other personal protection).

The feasibility and appropriateness of conducting medical screening can be judged according to established criteria [Halperin et al. 1986; Borak et al. 2006; Baker and Matte 2005; Harber 2003]. Inherent in all criteria for medical screening is that the specific disease endpoint(s) must be known to allow for test selection (see Appendix A).

3.1.2 Assessing Data from Medical Surveillance Programs

Results from medical surveillance may be assessed in several ways. Assessing data aggregated across groups of workers allows an occupational health professional to determine patterns and trends of potential health effects. In addition, medical surveillance data can be assessed on an individual basis for a sentinel event. A sentinel event represents an exposure or disease that signals the failure of controls to prevent occupational disease or injury [Rutstein et al. 1983; Mullan and Murphy 1991; ILO 1998]. For example, a case of lead poisoning signals that a worker has been exposed to lead at concentrations that would not have occurred if all aspects of the Occupational Safety and Health

Administration (OSHA) lead standards (29 CFR* 1910.1025 and 29 CFR 1926.62) had been followed. At this time, no health outcomes that have been determined to be sentinel events are related to engineered nanoparticle exposures.

3.2 Hazard Surveillance and Risk Management

Hazard surveillance involves identifying hazards in the workplace and assessing the extent to which they can be linked to workers, the effectiveness of controls, and the reliability of exposure measures [Sundin and Frazier 1989; Froines et al. 1989]. Hazard surveillance for engineered nanoparticles is a component of occupational health surveillance and is used for defining the elements of the risk management program. A risk management program involves taking action to minimize exposure to potential hazards. In the case of engineered nanoparticles (even in the absence of adequate health information) an understanding of potential worker exposures forms the basis for ongoing risk management. The elements of a risk management program include recognizing potential exposures and determining appropriate actions for minimizing them (e.g., implementing engineering controls, employing good work practices, and using personal protective equipment) [NIOSH 2006a]. Hazard surveillance can serve as the basis of a risk management program by identifying the jobs and processes that involve production and use of engineered nanoparticles and the work tasks associated with them.

**Code of Federal Regulations.* See CFR in References.

3.3 Frequent Uses for Medical Surveillance

3.3.1 Initial Medical Examinations

Medical examinations and/or tests are used in many workplaces to determine whether an employee is currently able to perform the essential functions of the job (with or without reasonable accommodation) without posing a direct and imminent threat to the safety or health of the worker or others. Workplace medical examinations must be conducted in compliance with the Americans with Disabilities Act of 1990 (ADA) [Public Law No. 101-336]. For example, this law prohibits making a job offer contingent upon the applicant's submission to a medical examination. Post-offer/pre-acceptance medical examinations and examinations conducted before placing a worker in a given job may provide useful baseline information. Such baseline information may not necessarily be gathered because of workplace exposure to engineered nanoparticles. However, it may benefit workers with such exposures if questions arise later about health effects related to nanoparticle exposures.

3.3.2 Ongoing Medical Examinations and Screening

Ongoing medical surveillance of workers occurs routinely in many workplaces. Such surveillance may be prescribed by law or may be completely voluntary. Although OSHA does not have a standard that specifically addresses occupational exposure to engineered nanoparticles, OSHA has a number of standards (Appendix B) that require medical surveillance of workers. Workplaces with engineered nanoparticles of materials addressed by current OSHA standards are subject to the requirements of those standards, including the requirements for medical surveillance. In addition, medical surveillance of workers handling engineered nanoparticles may also be triggered by the presence of other hazardous substances (with associated recommendations for medical surveillance) in nanoparticle operations.

In addition to substance-specific standards, OSHA standards with broader applicability may also be relevant. For example, employers must follow the medical evaluation requirements of OSHA's respiratory protection standard [29 CFR 1910.134] when respirators are necessary to protect worker health. This standard includes elements of medical surveillance. Likewise, the OSHA standard for occupational exposure to hazardous chemicals in laboratories [29 CFR 1910.1450] requires medical consultation following the accidental release of hazardous chemicals.

NIOSH has recommended medical surveillance (including screening) of workers exposed to certain occupational hazards (Appendix C). None of the hazards noted in Appendix C are identified as engineered nanoparticles; but medical surveillance would apply to workers exposed to nanoparticles made up of chemicals for which NIOSH has a recommendation. These workers may benefit in the future if questions arise about the health effects of their exposures to nanoparticles.

4.0 DISCUSSION and CONCLUSIONS

Assessing the potential toxicity of engineered nanoparticles is at an early stage. A body of scientific evidence has accrued from toxicology studies on selected engineered nanoparticles and from epidemiology studies of individuals exposed to incidental nanoparticles (e.g., from high-temperature combustion processes [Kuempel et al. 2007; Gwinn and Vallyathan 2006; Donaldson et al. 2006]. This evidence raises concerns and suggests that safety and health professionals should consider precautionary management approaches [Schulte and Salamanca-Buentello 2007; NIOSH 2006a; Royal Society and Royal Academy of Engineering 2004; Borm et al. 2006; IRSST 2006] such as the implementation of occupational risk management programs. Such approaches are described in the document *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH* [NIOSH

2006a].

The current body of evidence about the possible health risks of occupational exposures to engineered nanoparticles is not sufficient to support the determination of specific medical screening for identifying preclinical changes associated with exposure to engineered nanoparticles. No substantial link has been established between occupational exposure to engineered nanoparticles and adverse health effects. In addition, the toxicological research to date is insufficient to recommend such monitoring, the appropriate triggers for it, or components of it. As the volume of research on the potential health effects increases, continual reassessment will be needed to determine whether medical screening is warranted for workers who are producing or using engineered nanoparticles. NIOSH will continue to examine new research findings and update its recommendations on medical screening programs for workers exposed to nanoparticles. A further discussion about the lack of sufficient evidence to recommend specific medical screening for workers exposed to engineered nanoparticles is presented in Appendix D.

At this time, only a few types of engineered nanoparticles have been studied, and a clear and consistent picture of the relevant endpoints for workers has not yet emerged. Various physicochemical parameters of nanoparticles (e.g., composition, size, shape, surface characteristics, charge, functional groups, crystal structure, and solubility) appear to affect toxicity [Oberdörster et al. 2005a; Borm et al. 2006; Warheit et al. 2007b; IRSST 2006]. It is not known whether size is the overriding parameter, though it generally appears to be the major factor in enhancing the toxicity of engineered nanoparticles as compared to that of larger particles of the same composition. Results from a limited number of experimental animal studies with engineered nanoparticles indicate the potential for respiratory and circulatory effects [Aitken et al. 2004; Borm et al. 2006; ASCC 2006;

IRRST 2006]; however, it is not clear which effects are most critical, whether they are dose-dependent, and if these effects are relevant to human exposure. Additional studies are needed to determine the biological significance of different physicochemical parameters and whether these parameters can be used to predict the potential toxicity of other untested engineered nanoparticles.

When occupational health surveillance is being established, it is necessary to understand the relative, absolute, and population-attributable risks to workers who are handling engineered nanomaterials. This understanding includes understanding the hazard as well as the extent of exposure and ultimately the risk. Limited information is available on these topics, but exposures may be generally low relative to the airborne exposures of the same material in larger but respirable particle sizes. The level of risk resulting from lower exposures to nanomaterials is unknown. Ultimately, epidemiological studies of exposed workers will be needed to help assess exposure-response relationships. Although such studies are difficult to conduct, they are more likely than medical screening to clarify the relationship between exposure and adverse effects at this time.

Finally, there is not yet enough research to make categorical determinations of the hazards based on combinations of physicochemical factors [ASCC 2006; Aitken et al. 2004]. Although preliminary studies indicate that while specific medical screening may be warranted in the future, insufficient information is now available to make any recommendations beyond hazard surveillance. NIOSH will continue to assess the scientific evidence and periodically update the guidance on medical screening.

5.0 RECOMMENDATIONS

Continued *in vivo* and *in vitro* toxicological research is needed to identify potential health endpoints related to occupational exposure to engineered nanoparticles. Epidemiological studies of exposed workers will be needed to establish associations between exposures to engineered nanoparticles and adverse health effects and to assess for exposure-response relationships. Research is needed to assess various candidate biological markers that may ultimately be used in medical screening, including molecular markers [Schulte 2005]. This research is needed to assess sensitivity, specificity, and predictive value of biomarkers and clinical tests that could be used in the screening of workers' health.

The following recommendations are provided for workplaces where workers may be exposed to engineered nanoparticles during the course of their work.

5.1 Take prudent measures to control exposures to engineered nanoparticles.

A prudent approach to controlling exposures to engineered nanoparticles has been described in the NIOSH draft document *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH* [NIOSH 2006a].

5.2 Conduct hazard surveillance as the basis for implementing controls.

To establish prudent measures for controlling exposure to engineered nanoparticles, it is first important to identify which jobs or processes involve the production or use of engineered nanoparticles. Employers should identify and document the presence of engineered nanoparticles in their workplaces and the work tasks associated with them. This information will serve as the basis for applying various control measures [NIOSH 2006a].

5.3 Consider established medical surveillance approaches to help assess whether controls are effective and identify new or unrecognized problems and health effects.

Currently, there are many established uses for medical surveillance by employers and occupational health practitioners (see Section 3.3). These may pertain to workers exposed to engineered nanoparticles, but they are not specifically focused on them. Employers should consider using these established approaches to assess whether there is an increased frequency of adverse respiratory and cardiovascular effects. NIOSH continues to recommend occupational health surveillance as an important part of an effective occupational safety and health program. Lack of evidence for recommending medical screening for workers potentially exposed to engineered nanoparticles should not preclude its use by employers who want to take precautions in addition to industrial hygiene measures. However, nonspecific medical testing could have negative consequences including adverse effects of the tests such as radiation from chest radiographs, unnecessary anxiety from false positive screening tests, and the cost of additional diagnostic evaluations [Nasterlack et al. 2007; Schulte 2005; Marcus et al. 2006].

NIOSH is seeking comments on the strengths and weaknesses of exposure registries for various workers potentially exposed to engineered nanoparticles. As the understanding of occupational exposure to engineered nanoparticles increases, exposure registries may be needed to form the basis for epidemiologic research (Appendix E). Such registries probably need to cover workers from numerous companies to reflect the diversity of exposures, to account for the small number of workers exposed at a given site, and to assess chronic health effects.

NIOSH seeks comments on:

- Who would fund, staff, or use such registries; for how long and to what end?
- Are the issues associated with volunteer bias, litigation bias, and subsequent misclassification of registrants major limitations?
- Do exposure registries carry an implied promise of further action, and if so by whom?

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APPENDIX A

CRITICAL ASPECTS OF AN OCCUPATIONAL MEDICAL SCREENING PROGRAM

Assessment of workplace hazards

Identification of target organ toxicities for each hazard

Selection of test for each “screenable health effect”

Development of action criteria

Standardization of data collection process

Performance of testing

Interpretation of test results

Test confirmation

Determination of work status

Notification

Diagnostic evaluation

Evaluation and control of exposure

Recordkeeping

[Baker and Matte 2005].

APPENDIX B

OSHA STANDARDS THAT INCLUDE REQUIREMENTS FOR MEDICAL SURVEILLANCE

- 2-acetylaminofluorene
- acrylonitrile
- 4-aminodiphenyl
- inorganic arsenic
- asbestos
- benzene
- benzidine
- bis-chloromethyl ether
- 1,3–butadiene
- coke oven emissions
- cotton dust
- dibromochloropropane
- 3.3’-dichlorobenzidine
- 4-dimethylaminoazobenzene
- cadmium
- occupational exposure to hazardous chemicals in the laboratories
- ethylene oxide
- ethyleneimine
- formaldehyde
- hazardous waste
- lead
- methyl chloromethyl ether
- alpha-naphthylamine
- beta-naphthylamine
- methylene chloride
- 4-nitrobiphenyl
- n-nitrosodimethylamine
- beta-propriolactone
- vinyl chloride
- methylenedianiline
- bloodborne pathogens
- chromium (VI)

APPENDIX C

HAZARDS FOR WHICH NIOSH HAS RECOMMENDED THE USE OF MEDICAL SURVEILLANCE

NIOSH publication number	Title and date	NTIS stock number
76-195	Acetylene (1976)	PB 267068
77-112	Acrylamide (1976)	PB 273871
78-116	Acrylonitrile (1978)	PB 81-225617
77-151	Alkanes (C5-C8) (1977)	PB 273817
76-204	Allyl Chloride (1976)	PB 267071
74-136	Ammonia (1974)	PB 246699
78-216	Antimony (1978)	PB 81-226060
74-110	Arsenic, Inorganic (1974) (Revised 1975)	PB 228151
75-149	Arsenic, Inorganic (1975)	PB 246701
72-10267	Asbestos (1972)	PB 209510
77-169	Asbestos (Revised) (1976)	PB 273965
78-106	Asphalt Fumes (1977)	PB 277333
74-137	Benzene (1974)	PB 246700
*	Benzene (Revised) (1976)	PB 83-196196
77-166	Benzoyl Peroxide (1977)	PB 273819
78-182	Benzyl Chloride (1978)	PB 81-226698
72-10268	Beryllium (1972)	PB 210806
*	Beryllium (Revised) (1977)	PB 83-182378
	2-Butoxyethanol [See: Ethylene Glycol Monobutyl Ether]	
77-122	Boron Trifluoride (1976)	PB 274747
76-192	Cadmium (1976)	PB 274237
77-107	Carbaryl (1976)	PB 273801
78-204	Carbon Black (1978)	PB 81-225625
76-194	Carbon Dioxide (1976)	PB 266597
77-156	Carbon Disulfide (1977)	PB 274199
73-11000	Carbon Monoxide (1972)	PB 212629
76-133	Carbon Tetrachloride (1975)	PB 250424
*	Carbon Tetrachloride (Revised) (1979)	PB 83-196436
76-170	Chlorine (1976)	PB 266367
75-114	Chloroform (1974)	PB 246695
*	Chloroform (Revised 1979)	PB 83-195856
77-210	Chloroprene (1977)	PB 274777
73-11021	Chromic Acid (1973) [Revised; see Chromium VI]	PB 222221
76-129	Chromium VI (1975)	PB 248595
78-191	Coal Gasification Plants (1978)	PB 80-164874
95-106	Coal Mine Dust	PB 96-191713
78-107	Coal Tar Products (1977)	PB 276917
82-107	Cobalt (1981)	PB 82-182031

NIOSH publication number	Title and date	NTIS stock number
73-11016	Coke Oven Emissions (1973)	PB 216167
80-106	Confined Spaces, Working in Construction [See: Excavations] (1979)	PB 80-183015
75-118	Cotton Dust (1974)	PB 246696
78-133	Cresol (1978)	PB 86-121092
77-108	Cyanide, Hydrogen and Cyanide Salts (1976)	PB 266230
78-115	Dibromochloropropane (1978) 1,2-Dichloroethane [See: Ethylene Dichloride]	PB 81-228728
96-104	2-Diethylaminoethanol (1996)	PB 96-197371
78-215	Diisocyanates (1978)	PB 81-226615
78-131	Dinitro-ortho-Cresol (1978)	PB 80-175870
77-226	Dioxane (1977)	PB 274810
76-128	Elevated Work Stations, Emergency Egress from (1975)	PB 248594
76-206	Epichlorohydrin (1976)	PB 81-227019
77-221	Ethylene Dibromide (1977)	PB 276621
76-139	Ethylene Dichloride (1976)	PB 85-178275
78-211	Ethylene Dichloride (1,2-Dichloroethane)(Revised) (1978)	PB 80-176092
90-118	Ethylene Glycol Monobutyl Ether and Ethylene Glycol Monobutyl Ether Acetate (1991)	PB 91-173369
91-119	Ethylene Glycol Monomethyl Ether, Ethylene Glycol Monoethyl Ether, and Their Acetates	PB 92-167147
83-103	Excavations, Development of Draft Construction Safety Standards for, Volume 1 (1983)	PB 84-100569
*	Excavations, Development of Draft Construction Safety Standards for, Volume 2 (1983)	PB 83-233353
77-152	Fibrous Glass (1977)	PB 274195
76-103	Fluorides, Inorganic (1975)	PB 246692
77-193	Fluorocarbon Polymers, Decomposition Products of (1977)	PB 274727
77-126	Formaldehyde (1976)	PB 273805
85-116	Foundries (1985)	PB 86-213477
79-133	Furfuryl Alcohol (1979)	PB 80-176050
78-166	Glycidyl Ethers (1978)	PB 81-229700
83-126	Grain Elevators and Feed Mills (1983)	PB 83-138537
89-106	Hand-Arm Vibration (1989)	PB 90-168048
83-125	Guidelines for Controlling Hazardous Energy During Maintenance and Servicing (1983)	PB 84-199934
72-10269	Hot Environments (1972)	PB 210794
86-113	Hot Environments (Revised 1986)	PB 86-219508
78-172	Hydrazines (1978)	PB 81-225690
	Hydrogen Cyanide [See: Cyanide, Hydrogen and Cyanide Salts]	

NIOSH publication number	Title and date	NTIS stock number
76-143	Hydrogen Fluoride (1976)	PB 81-226516
77-158	Hydrogen Sulfide (1977)	PB 274196
78-155	Hydroquinone (1978)	PB 81-226508
75-126	Identification System for Occupationally Hazardous Materials (1974)	PB 246698
76-142	Isopropyl Alcohol (1976)	PB 273873
*	Kepone (1976)	PB 83-196170
78-173	Ketones (1978) Labeling [See: Identification System for Occupationally Hazardous Materials]	PB 80-176076
73-11010	Lead, Inorganic (1972)	PB 214265
78-158	Lead, Inorganic (Revised) (1978)	PB 81-225278
	Lockout/Tagout [See: Hazardous Energy]	
76-188	Logging from Felling to First Haul (1976)	PB 266411
76-205	Malathion (1976)	PB 267070
73-11024	Mercury, Inorganic (1973)	PB 222223
76-148	Methyl Alcohol (1976) Methyl Chloroform [See: 1,1,1-Trichloroethane]	PB 273806
77-106	Methyl Parathion (1976)	PB 274191
76-138	Methylene Chloride (1976)	PB 81-227027
98-102	Metalworking Fluids (1998)	PB 99-133910
77-164	Nickel, Inorganic (1977)	PB 274201
76-141	Nitric Acid (1976)	PB 81-227217
78-212	Nitriles (1978)	PB 81-225534
76-149	Nitrogen, Oxides of (1976)	PB 81-226995
78-167	Nitroglycerin and Ethylene Glycol Dinitrate (1978)	PB 81-225526
73-11001	Noise (1972)	PB 213463
2006-123	Occupational Exposure to Refractory Ceramic Fibers	
98-126	Occupational Noise Exposure	PB 98-173-735
83-127	Oil and Gas Well Drilling (1983)	PB 84-242528
77-115	Organotin Compounds (1976)	PB 274766
84-115	Paint and Allied Coating Products (1984)	PB 85-178978
76-190	Parathion (1976)	PB 274192
	Perchloroethylene [See: Tetrachloroethylene]	
78-174	Pesticides, Manufacture and Formulation	PB 81-227001
76-196	Phenol (1976)	PB 266495
76-137	Phosgene (1976)	PB 267514
77-225	Polychlorinated Biphenyls (1977)	PB 276849
84-103	Precast Concrete Products Industry (1984)	PB 85-220051
88-101	Radon Progeny in Underground Mines (1988)	PB 88-173455
77-192	Refined Petroleum Solvents (1977)	PB 85-178267

NIOSH publication number	Title and date	NTIS stock number
2006-123	Refractory Ceramic Fibers (2006)	PB 2006-112303
75-120	Silica, Crystalline (1974)	PB 246697
76-105	Sodium Hydroxide (1975)	PB 246694
83-119	Styrene (1983)	PB 84-148295
74-111	Sulfur Dioxide (1974)	PB 228152
*	Sulfur Dioxide (Revised) (1977)	PB 83-182485
74-128	Sulfuric Acid (1974)	PB 233098
77-121	1,1,2,2-Tetrachloroethane (1976)	PB 273802
76-185	Tetrachloroethylene (Perchloroethylene) (1976)	PB 266583
78-213	Thiols: N-Alkane Mono, Cyclohexane, and Benzene (1978)	PB 81-225609
78-179	o-Tolidine (1978)	PB 81-227084
73-11023	Toluene (1973)	PB 222219
73-11022	Toluene Diisocyanate (1973) [Revised; See: Diisocyanates]	PB 222220
76-184	1,1,1-Trichloroethane (Methyl Chloroform) (1976)	PB 267069
73-11025	Trichloroethylene (1973)	PB 222222
77-127	Tungsten and Cemented Tungsten Carbide (1977)	PB 275594
73-11009	Ultraviolet Radiation (1972)	PB 214268
77-222	Vanadium (1977)	PB 81-225658
78-205	Vinyl Acetate (1978)	PB 80-176993
*	Vinyl Chloride (1974)	PB 246691
*	Vinyl Halides (1979)	PB 84-125699
77-140	Waste Anesthetic Gases and Vapors (1977)	PB 274238
88-110	Welding, Brazing, and Thermal Cutting (1988)	PB 88-231774
75-168	Xylene (1975)	PB 246702
76-104	Zinc Oxide (1975)	PB 246693
*Denotes the absence of a publication number or that recommendations were provided in testimony by NIOSH to the U.S. Department of Labor.		

APPENDIX D

EXAMPLES OF LIMITATIONS IN THE EVIDENCE BASE FOR SPECIFIC MEDICAL SCREENING OF WORKERS EXPOSED TO ENGINEERED NANOPARTICLES

Key among the criteria for recommending specific medical screening include determining whether the substance in question is a hazard and whether the disease to be averted is sufficiently common in the worker population to justify routine screening [Nasterlack et al. 2007; Borak et al. 2006; Halperin et al. 1986]. For engineered nanoparticles, there is insufficient evidence for a definitive hazard determination. Only a small number of the myriad types of engineered nanoparticles have undergone experimental animal inhalation testing, and no broad categories of physicochemical risk factors have been identified to allow for projecting hazards across particle types. No chronic inhalation studies of engineered nanoparticles have been conducted to date. The existence of a few short-term inhalation studies on carbon nanotubes and nanoscale metal oxides is not adequate to identify what disease endpoints to assess in medical screening. Insufficient information exists regarding the absolute, relative or population-attributable risks associated with nanoparticle exposures [Nasterlack et al. 2007].

Examples of the issues in determining the rationale for recommending medical screening for workers potentially exposed to engineered nanoparticles are described as follows.

Single-Walled Carbon Nanotubes (SWCNTs)

Intratracheal (IT) exposure to SWCNTs has been associated with interstitial fibrosis in the rat (Lam et al. 2004]. Aspiration of purified SWCNTs caused rapid and progressive interstitial fibrosis in mice [Shvedova et al. 2005]. NIOSH has also shown that inhalation of SWCNTs cause interstitial fibrosis

[paper in preparation]. The problem is that purified SWCNTs are not redox reactive and the interstitial fibrosis is not driven by oxidant generation and inflammation. Therefore, measurement of markers of oxidant stress or inflammation in humans would not be predictive. If fibrosing interstitial lung disease was considered the health endpoint of concern, one could monitor carbon monoxide diffusion capacity of the lung noninvasively. Although capable of detecting pre-clinical disease, a significant decline in diffusion would suggest that a significant loss of alveolar-capillary gas exchange surface had already occurred. In addition, virtually no published data exist on occupational exposure concentrations for working in SWCNT operations. Hence, too little information exists at this time to verify disease endpoints, and/or too little information exists on exposure and ultimately risk to workers handling these materials.

Nanoscale Metal Oxides

Pulmonary exposure to nanoscale metal oxides such as titanium dioxide (TiO_2) have been shown in rat models to cause pulmonary inflammation [Oberdörster et al. 2005] and inhibit the ability of the systemic microvasculature to respond to dilators [Nurkiewicz et al.2006; Nurkiewicz et al. in press] after IT or inhalation exposures. Ultrafine (nanoscale) TiO_2 has been shown to be more potent in causing these effects than fine TiO_2 on an equivalent mass basis. These effects have been associated with oxidant stress and induction of inflammatory mediators. Therefore, markers of oxidant stress and inflammation could be considered as early indicators of human exposure/response. Oxidant stress markers have been suggested as markers of toxicity to metal oxide nanoparticles as a class [Nel et al. 2006]. Examples of such markers would be nitrous oxide or isoprostanes in exhaled breath or blood markers of oxidant stress. However, the utility of these markers for screening workers exposed to engineered nanoparticles has not been demonstrated. In addition, some research shows that nanoscale

TiO_2 is linked to cancer of the lung and the International Agency for Research on Cancer (IARC) has categorized titanium dioxide as a possible carcinogen to humans [IARC 2006]. Nonetheless, no evidence clearly demonstrates that medical screening of asymptomatic workers exposed to lung carcinogens decreases the chance of dying from cancer (NCI 2007; Marcus et al. 2006).

Nanoscale Cadmium

Cadmium is a substance that has medical screening recommendations to prevent or assess lung and kidney toxicity (see Appendices B and C). At a minimum, these recommendations should pertain to nanoscale cadmium (e.g., such as that used in the production of quantum dots). Medical screening is typically triggered by the airborne concentration of the substance in the workplace (e.g., the "action level" concentration). An action level is some fraction, usually 50%, of an occupational exposure limit (OEL). Whether the action level concentration recommended for nonnanoscale cadmium particles is adequate for nanoscale cadmium is unknown. Workplaces with engineered nanoparticles of materials addressed by current OSHA standards are subject to the requirements of those standards, including the requirements for medical surveillance.

APPENDIX E

EXPOSURE REGISTRIES

Exposure registries are useful tools for surveillance of new or perceived hazards. A registry provides a structured and orderly approach to handling the problem of identifying and maintaining communication with workers exposed to hazardous substances [Schulte and Kaye 1988]. An exposure registry is the enrollment of persons exposed or likely to have been exposed to occupational or environmental hazards; it may include managing these groups with regard to primary or secondary preventive efforts. In occupational situations, company employee rosters are de facto registries; however, they may not address employees who leave a company. Moreover, for a new technology such as nanotechnology, the registry could enroll persons from various companies. Generally, exposure registries are developed and maintained by government entities, but there are examples of private-sector registries related to exposure to commercial products.

The purposes and functions of exposure registries may be summarized as follows:

- Delineate a population at risk
- Follow cohort to ascertain exposure-disease associations
- Follow cohort to ensure the institution of appropriate primary and secondary prevention and medical surveillance
- Follow cohort to allow for appropriate social, legal, and economic support
- Demonstrate societal concern for the cohort and provide a base for political action relevant to the exposure
- Notify a cohort of an exposure, preventive measures, or therapeutic advances that were not understood or known at the time the registry was established

Various issues should be addressed when considering development of exposure registries. These

include the term of registry, needs of registrants, confidentially of information, cost of maintaining the registry, and potential impact of the registry on workers and companies.

Registries are essentially the collection of individual worker information over time with at least a preliminary plan for analysis. Data collected in registries may be subject to limitations. Exposure registries are not always useful in etiologic research. For diseases with low prevalence following low-level exposures, exposure registries are not very effective tools because (1) exposure classification is often difficult, (2) the statistical power of prospective studies is low, and (3) the time period of the study may be impractically long. Moreover, changes in exposures experienced by registry participants over time may complicate the ability to establish clear exposure-disease relationships.

Exposure registries may provide opportunities to determine the exposure-disease association and risk. Also, when practical prospective studies can be designed, registries can be used to establish hypotheses. Many questions arise when considering an exposure registry for etiologic research.

- How can exposed persons be adequately differentiated from nonexposed persons?
- What group could serve as a comparison group so that the disease experience of the exposed group can be evaluated?
- How long should the group be followed?

These questions can become quite technical, but often even the most basic questions are the hardest to resolve. At this time, society in general and companies in particular are faced with the dilemma of balancing a desire to expand a potentially bountiful technology against the potential hazards from it. The real risks from the technology are not known, and the perceived risks are undetermined. In this

regard, nanotechnology is no different from any other emerging technology. As one commentator noted: “Even if studies showed every commercially relevant nanoparticle to be harmless in every real world scenario, public skepticism about the safety of nanoparticles could still build and sharply limit their use in products” [Holman 2006]. One of the first areas where exposures to nanoparticles will occur is in the workplace. In the face of uncertainty about the hazards of nanoparticles, a corporate or societal response (such as implementing selected exposure registries in potentially high exposure sectors) may assure the public that appropriate efforts are being taken to identify and control potential hazards in a timely fashion.