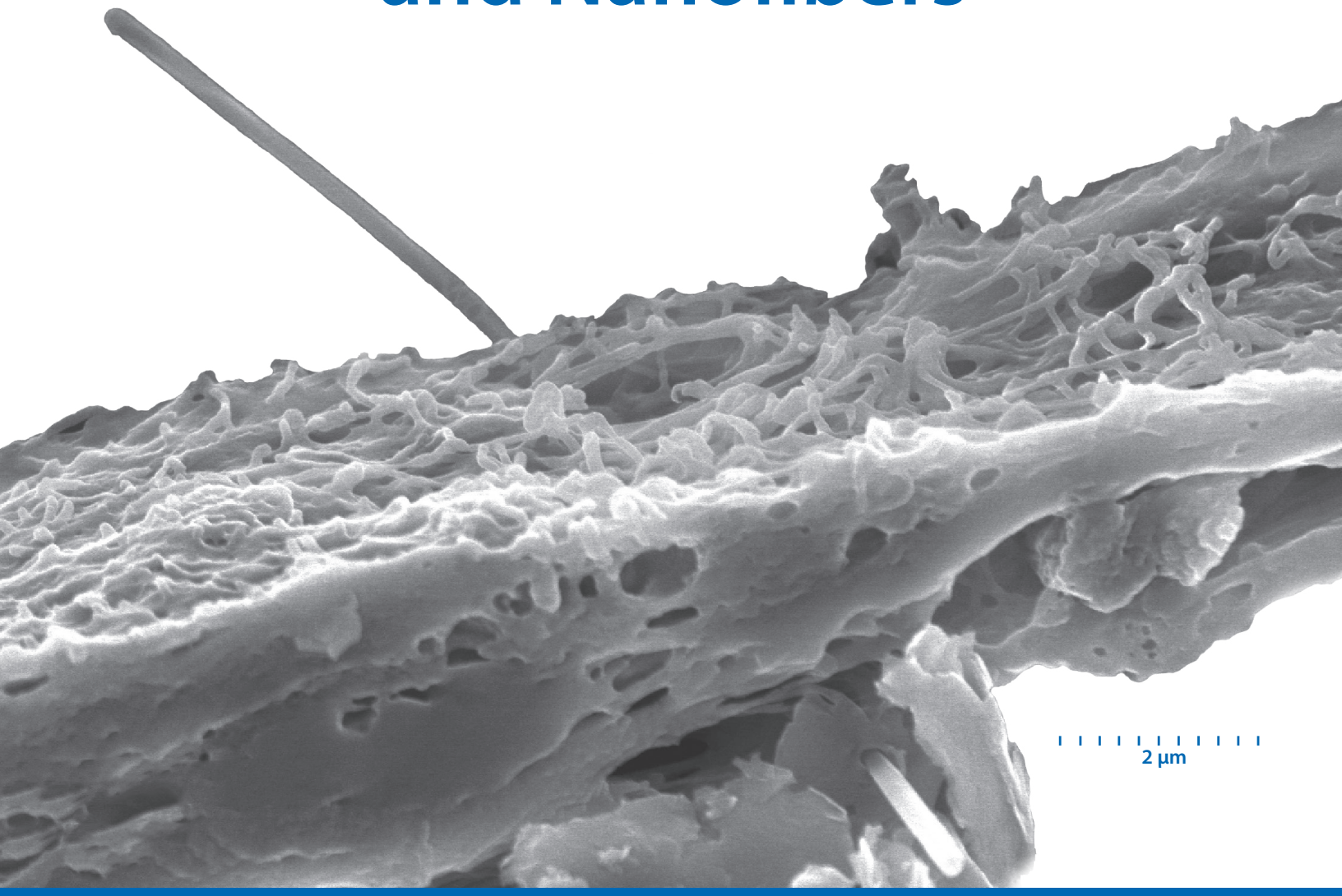
CURRENT INTELLIGENCE BULLETIN 65

Occupational Exposure to Carbon Nanotubes and Nanofibers



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

On the cover: High-resolution electron microscope image of a single multi-walled carbon nanotube (MWCNT) penetrating out of the lung surface into the pleural space. Figure 7D from Mercer et al. Particle and Fibre Toxicology 2010, 7:28

Article can be found at: http://www.particleandfibretoxicology.com/content/7/1/28

Image courtesy of Robert Mercer and Diane Schwegler-Berry, NIOSH.

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Foreword

The Occupational Safety and Health Act of 1970 (Public Law 91-596) was passed to assure safe and healthful working conditions for every working person and to preserve our human resources. This Act charges the National Institute for Occupational Safety and Health (NIOSH) with recommending occupational safety and health standards and describing exposures that are safe for various periods of employment, including (but not limited to) the exposures at which no worker will suffer diminished health, functional capacity, or life expectancy because of his or her work experience.

NIOSH issues Current Intelligence Bulletins (CIBs) to disseminate new scientific information about occupational hazards. A CIB may draw attention to a formerly unrecognized hazard, report new data on a known hazard, or disseminate information about hazard control. CIBs are distributed to representatives of academia, industry, organized labor, public health agencies, and public interest groups, as well as to federal agencies responsible for ensuring the safety and health of workers.

NIOSH is the leading federal agency conducting research and providing guidance on the occupational safety and health implications and applications of nanotechnology. As nanotechnology continues to expand into every industrial sector, workers will be at an increased risk of exposure to new nanomaterials. Today, nanomaterials are found in hundreds of products, ranging from cosmetics, to clothing, to industrial and biomedical applications. These nanoscale-based products are typically called "first generation" products of nanotechnology. Many of these nanoscale-based products are composed of engineered nanoparticles, such as metal oxides, nanotubes, nanowires, quantum dots, and carbon fullerenes (buckyballs), among others. Early scientific studies have indicated that some of these nanoscale particles may pose a greater health risk than the larger bulk form of these materials.

Results from recent animal studies indicate that carbon nanotubes (CNT) and carbon nanofibers (CNF) may pose a respiratory hazard. CNTs and CNFs are tiny, cylindrical, large aspect ratio, manufactured forms of carbon. There is no single type of carbon nanotube or nanofiber; one type can differ from another in shape, size, chemical composition (from residual metal catalysts or functionalization of the CNT and CNF) and other physical and chemical characteristics. Such variations in composition and size have added to the complexity of understanding their hazard potential. Occupational exposure to CNTs and CNFs can occur not only in the process of manufacturing them, but also at the point of incorporating these materials into other products and applications. A number of research studies with rodents have shown adverse lung effects at relatively low-mass doses of CNT and CNF, including pulmonary inflammation and rapidly developing, persistent fibrosis. Although it is not known whether similar adverse health effects occur in humans after exposure to CNT and CNF, the results from animal research studies indicate the need to minimize worker exposure.

This NIOSH CIB, (1) reviews the animal and other toxicological data relevant to assessing the potential non-malignant adverse respiratory effects of CNT and CNF, (2) provides a

quantitative risk assessment based on animal dose-response data, (3) proposes a recommended exposure limit (REL) of 1 μg/m^3 elemental carbon as a respirable mass 8-hour time-weighted average (TWA) concentration, and (4) describes strategies for controlling workplace exposures and implementing a medical surveillance program. The NIOSH REL is expected to reduce the risk for pulmonary inflammation and fibrosis. However, because of some residual risk at the REL and uncertainty concerning chronic health effects, including whether some types of CNTs may be carcinogenic, continued efforts should be made to reduce exposures as much as possible.

Just prior to the release of this CIB NIOSH reported at the annual meeting of the Society of Toxicology [03/11/2013] preliminary findings from a new laboratory study in which mice were exposed by inhalation to multi-walled carbon nanotubes (MWCNT) [see http://blogs.cdc.gov/niosh-science-blog/2013/03/mwcnt/]. The study was designed to investigate whether MWCNT have the potential to initiate or promote cancer. Mice receiving both an initiator chemical plus inhalation exposure to MWCNT were significantly more likely to develop tumors (90% incidence) and have more tumors than mice receiving the initiator chemical alone. These results indicate that MWCNT can increase the risk of cancer in mice exposed to a known carcinogen. The study did not indicate that MWCNTs alone cause cancer in mice. This research is an important step in our understanding of the hazards associated with MWCNT, but before we can determine whether MWCNT pose an occupational cancer risk, we need more information about workplace exposures, the types and nature of MWCNT being used in the workplace, and how that compares to the material used in this study. Research is underway at NIOSH to learn more about worker exposures and the potential occupational health risks associated with exposure to MWCNT and other types of CNTs and CNFs. As results from ongoing research become available, NIOSH will reassess its recommendations for CNT and CNF and make appropriate revisions as needed.

NIOSH urges employers to share this information with workers and customers. NIOSH also requests that professional and trade associations and labor organizations inform their members about the potential hazards of CNT and CNF.

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Executive Summary

Overview

Carbon nanotubes (CNTs) and nanofibers (CNFs) are some of the most promising materials to result from nanotechnology. The introduction of these materials and products using them into commerce has increased greatly in the last decade [Thostenson et al. 2001; Invernizzi 2011]. The development of CNT-based applications in a wide range of products is expected to provide great societal benefit and it is important that they be developed responsibly to achieve that benefit [Sanchez et al. 2009; Schulte et al 2012]. Worker safety and health is a cornerstone of responsible development of an emergent technology because workers are the first people in society to be exposed to the products of the technology and the workplace is the first opportunity to develop and implement responsible practices.

In this Current Intelligence Bulletin, NIOSH continues its long-standing history of using the best available scientific information to assess potential hazards and risks and to provide guidance for protecting workers. Since it is early in the development of these materials and their applications, there is limited information on which to make protective recommendations. To date, NIOSH is not aware of any reports of adverse health effects in workers using or producing CNT or CNF. However, there are studies of animals exposed to CNT and CNF that are informative in predicting potential human health effects consistent with ways in which scientists traditionally have used such data in recommending risk management strategies. NIOSH systematically reviewed 54 laboratory animal studies, many of which indicated that CNT/CNF could cause adverse pulmonary effects including inflammation (44/54), granulomas (27/54), and pulmonary fibrosis (25/54) (Tables 3–1 through 3–8). NIOSH considers these animal study findings to be relevant to human health risks because similar lung effects have been observed in workers exposed to respirable particulates of other materials in dusty jobs [Rom and Markowitz 2006; Hubbs et al. 2011]. There are well established correlations between results of animal studies and adverse effects in workers exposed to particulates and other air contaminants [NIOSH 2002, 2006, 2011a, b]. Moreover, in animal studies where CNTs were compared with other known fibrogenic materials (e.g., silica, asbestos, ultrafine carbon black), the CNTs were of similar or greater potency [Lam et al. 2004; Muller et al. 2005; Shvedova et al. 2005; Murray et al. 2012], and the effects, including fibrosis, developed soon after exposure and persisted [Shvedova et al. 2005, 2008; Porter et al. 2010; Mercer et al. 2011]. These are significant findings that warrant protective action. NIOSH conducted a quantitative assessment of risk using the animal studies with sufficient dose-response data, which included two subchronic (90-day) inhalation studies [Ma-Hock et al. 2009; Pauluhn 2010a] and five additional studies [Lam et al. 2004; Muller et al. 2005; Shvedova et al. 2005,2008; Mercer et al. 2011] conducted by other routes or durations. The estimated risk of developing early-stage (slight or mild) lung effects over a working lifetime if exposed to CNT at the analytical limit of quantification (NIOSH Method 5040) of 1 $\mu g/m^3$ (8-hr time-weighted average [TWA] as respirable elemental carbon) is approximately 0.5%

to 16% (upper confidence limit estimates) (Table A–8). In addition, the working lifetime equivalent estimates of the animal no observed adverse effect level (NOAEL) of CNT or CNF were also near 1 μg/m^3 (8-hr TWA) (Sections A.6.3.3 and A.7.6). Therefore, NIOSH recommends that exposures to CNT and CNF be kept below the recommended exposure limit (REL) of 1 μg/m^3 of respirable elemental carbon as an 8-hr TWA. Because there may be other sources of elemental carbon in the workplace that could interfere in the determination of CNT and CNF exposures, other analytical techniques such as transmission electron microscopy are described that could assist in characterizing exposures. Studies have shown that airborne background (environmental and in non-process areas in the workplace) concentrations to elemental carbon are typically less than 1 μg/m^3 and that an elevated exposure to elemental carbon in the workplace is a reasonable indicator of CNT or CNF exposure [Evans et al. 2010; Birch 2011a, b; Dahm et al. 2011]. Studies have also shown in some manufacturing operations that exposures can be controlled below the REL when engineering controls are used [Dahm et al. 2011]. However, NIOSH has not assessed the extent to which exposures can be controlled during the life cycle of CNT/CNF product use, but since airborne CNT/CNF behave as classical aerosols, the control of worker exposures appears feasible with standard exposure control techniques (e.g., source enclosure, local-exhaust ventilation) [NIOSH 2009a]. Previously in a 2010 draft of this CIB for public comment, NIOSH indicated that the risks could occur with exposures less than 1 μg/m^3 but that the analytic limit of quantification was 7 μg/m^3. Based on subsequent improvements in sampling and analytic methods, NIOSH is now recommending an exposure limit at the current analytical limit of quantification of 1 μg/m^3.

More research is needed to fully characterize the health risks of CNT/CNF. Long-term animal studies and epidemiologic studies in workers would be especially informative. However, the toxicity seen in the short-term animal studies indicates that protective action is warranted. The recommended exposure limit is in units of mass/unit volume of air, which is how the exposures in the animal studies were quantified and it is the exposure metric that generally is used in the practice of industrial hygiene. In the future, as more data are obtained, a recommended exposure limit might be based on a different exposure metric better correlated with toxicological effects, such as CNT/CNF number concentration [Schulte et al. 2012].

There are many uncertainties in assessing risks to workers exposed to CNT/CNF. These uncertainties, as described and evaluated in this document, do not lessen the concern or diminish the recommendations. Other investigators and organizations have been concerned about the same effects and have recommended occupational exposure limits (OELs) for CNT within the range of 1–50 μg/m^3 [Nanocyl 2009; Aschberger et al. 2010; Pauluhn 2010b; Nakanishi (ed) 2011a,b]. The relative consistency in these proposed OELs demonstrates the need to manage CNT/CNF as a new and more active form of carbon. To put this in perspective, since there is no Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for CNT/CNF, the PEL for graphite (5,000 μg/m^3) or carbon black (3,500 μg/m^3) [NIOSH 2007] might inappropriately be applied as a guide to control worker exposures to CNT/CNF. Based on the information presented in this document, the PELs for graphite or carbon black would not protect workers exposed to CNT/CNF.

The analysis conducted by NIOSH was focused on the types of CNT and CNF included in published research studies. Pulmonary responses were qualitatively similar across the various types of CNT and CNF, purified or unpurified with various metal content, and different dimensions [Lam et al. 2004; Shvedova et al. 2005, 2008; Muller et al. 2005; Ma-Hock et al.

2009; Pauluhn 2010a; Porter et al. 2010; Mercer et al. 2011; Murray et al. 2012; DeLorme et al. 2012]. The fibrotic lung effects in the animal studies developed early (within a few weeks) after exposure to CNT or CNF, at relatively low-mass lung doses, and persisted or progressed during the post-exposure follow-up (~1–6 months) [Shvedova et al. 2005, 2008; Mercer et al. 2008; Porter et al. 2010; Pauluhn 2010a; Murray et al. 2012]. However, the studied CNT and CNF only represent a fraction of the types of CNT and CNF that are, or will be, in commerce and it is anticipated that materials with different physical and chemical parameters could have different toxicities. At this time, however, given the findings in the published literature, NIOSH recommends that exposures to all CNT and CNF be controlled to less than 1 μg/m^3 of respirable elemental carbon as an 8-hr TWA, and that the risk management guidance described in this document be followed. Until results from research can fully explain the physical-chemical properties of CNT and CNF that define their inhalation toxicity, all types of CNT and CNF should be considered a respiratory hazard and exposure should be controlled below the REL.

In addition to controlling exposures below the REL, it is prudent for employers to institute medical surveillance and screening programs for workers who are exposed to CNT and CNF for the purpose of possibly detecting early signs of adverse pulmonary effects including fibrosis. Such an assessment can provide a secondary level of prevention should there be inadequacies in controlling workplace exposures. In 2009, NIOSH concluded that there was insufficient evidence to recommend specific medical tests for workers exposed to the broad category of engineered nanoparticles but when relevant toxicological information became available, specific medical screening recommendations would be forthcoming [NIOSH 2009b]. As described in this document, the toxicologic evidence on CNT/CNF has advanced to make specific recommendations for the medical surveillance and screening of exposed workers. That is, the strong evidence for pulmonary fibrosis from animal studies and the fact that this effect can be detected by medical tests is the basis for NIOSH specific medical screening recommendations. NIOSH also recommends other risk management practices in addition to controlling exposure and medical surveillance. These include education and training of workers and the use of personal protective equipment (e.g., respirators, clothing, and gloves).

In summary, the findings and recommendations in this Current Intelligence Bulletin are intended to minimize the potential health risks associated with occupational exposure to CNT and CNF by recommending a working lifetime exposure limit (1 μg/m^3, 8-hr TWA, 45 years), a sampling and analytical method to detect CNT and CNF, medical surveillance and screening and other guidelines. The expanding use of CNT/CNF products in commerce and research warrants these protective actions.

Background

The goal of this occupational safety and health guidance for carbon nanotubes (CNT) and carbon nanofibers (CNT) is to prevent the development of adverse respiratory health effects in workers. To date, NIOSH is not aware of any reports of adverse health effects in workers producing or using CNT or CNF. The concern about worker exposure to CNT or CNF arises from the results of recent laboratory animal studies with CNT and CNF. Short-term and subchronic studies in rats and mice have shown qualitatively consistent noncancerous adverse lung effects including pulmonary inflammation, granulomas, and fibrosis with inhalation, intratracheal instillation, or pharyngeal aspiration of several types of CNT

(single or multiwall; purified or unpurified). These early-stage, noncancerous adverse lung effects in animals include: (1) the early onset and persistence of pulmonary fibrosis in CNT-exposed mice [Shvedova et al. 2005, 2008; Porter et al. 2010; Mercer et al. 2011], (2) an equal or greater potency of CNT compared with other inhaled particles known to be hazardous (e.g., crystalline silica, asbestos) in causing pulmonary inflammation and fibrosis [Lam et al. 2004; Shvedova et al. 2005; Muller et al. 2005], and (3) reduced lung clearance in mice or rats exposed to relatively low-mass concentrations of CNT [Mercer et al. 2009; Pauluhn 2010a]. Findings of acute pulmonary inflammation and interstitial fibrosis have also been observed in mice exposed to CNF [Murray et al. 2012]. The extent to which these animal data may predict clinically significant lung effects in workers is not known. However, NIOSH considers these animal study findings of pulmonary inflammation, granulomas, and fibrosis associated with exposure to CNT and CNF to be relevant to human health risk assessment because similar lung effects have been observed in workers in dusty jobs [Rom and Markowitz 2006; Hubbs et al. 2011].

Some studies also indicate that CNT containing certain metals (nickel, 26%) [Lam et al. 2004] or higher metal content (17.7% vs. 0.2% iron) are more cytotoxic in vitro and in vivo [Shvedova et al. 2003, 2008]. However, in experimental animal studies, both unpurified and purified (low metal content) CNT are associated with early onset and persistent pulmonary fibrosis and other adverse lung effects [Lam et al. 2004; Shvedova et al. 2005; 2008]. Other studies indicate that differences in physical-chemical properties, including functionalization or bio-modification, may alter the lung retention and biological responses [Kagan et al. 2010; Osmond-McLeod et al. 2011; Pauluhn 2010a; Oyabu et al. 2011]. Although a number of different types of CNT and CNF have been evaluated, uncertainty exists on the generalizability of the current animal findings to new CNT and CNF.

In addition to the early-stage non-cancer lung effects in animals, some studies in cells or animals have shown genotoxic or carcinogenic effects. In vitro studies with human lung cells have shown that single-walled carbon nanotubes (SWCNT) can cause genotoxicity and abnormal chromosome number by interfering with mitosis (cell division) [Muller et al. 2008b; Sargent et al. 2009, 2011; Kisin et al. 2011]. Other in vitro studies did not show evidence of genotoxicity of some MWCNT [Wirnitzer et al. 2009; Kim et al. 2011].

Studies in mice exposed to multi-walled carbon nanotubes (MWCNT) have shown the migration of MWCNT from the pulmonary alveoli to the intrapleural space [Hubbs et al. 2009; Porter et al. 2010; Mercer et al. 2010]. The intrapleural space is the same site in which malignant mesothelioma can develop due to asbestos exposure. Intraperitoneal injection of CNT in mice has resulted in inflammation from long MWCNT (> 5 μm in length), but not short MWCNT (< 1 μm in length) or tangled CNT [Poland et al. 2008; Takagi et al. 2008; Muller et al. 2009; Murphy et al. 2011]. In rats administered CNT by peritoneal injection, the pleural inflammation and mesothelioma were related to the thin diameter and rigid structure of MWCNT [Nagai et al. 2011]. In a study of rats administered MWCNT or crocidolite by intrapulmonary spraying, exposure to either material produced inflammation in the lungs and pleural cavity in addition to mesothelial proliferative lesions [Xu et al. 2012].

Pulmonary exposure to CNT has also produced systemic responses including an increase in inflammatory mediators in the blood, as well as oxidant stress in aortic tissue and increase plaque formation in an atherosclerotic mouse model [Li et al. 2007; Erdely et al. 2009]. Pulmonary exposure to MWCNT also depresses the ability of coronary arterioles to respond to dilators [Stapleton et al. 2011]. These cardiovascular effects may be due to

neurogenic signals from sensory irritant receptors in the lung. Mechanisms, such as inflammatory signals or neurogenic pathways causing these systemic responses, are under investigation.

Additional research is needed to fully explain the mechanisms of biological responses to CNT and CNF, and the influence of physical-chemical properties. The findings of adverse respiratory effects and systemic effects reported in several animal studies indicate the need for protective measures to limit worker exposure to CNT and CNF.

CNT and CNF are currently used in many industrial and biomedical applications, including electronics, lithium-ion batteries, solar cells, super capacitors, thermoplastics, polymer composites, coatings, adhesives, biosensors, enhanced electron-scanning microscopy imaging techniques, inks, and in pharmaceutical/biomedical devices. CNT and CNF can be encountered in facilities ranging from research laboratories and production plants to operations where CNT and CNF are processed, used, disposed, or recycled. The data on worker personal exposures to CNT and CNF are extremely limited, but reported workplace airborne concentrations for CNT [Maynard et al. 2004; Han et al. 2008a; Bello et al. 2009, 2010; Tsai et al. 2009; Lee et al. 2010; Cena and Peters 2011; Dahm et al. 2011] and CNF [Methner et al. 2007; Evans et al. 2010; Birch 2011a; Birch et al. 2011b] indicate the potential for worker exposures in many tasks or processes and the reduction or elimination of exposures when measures to control exposure are used.

Assessment of the Health Risk and Recommended Exposure Limit

NIOSH has determined that the best data to use for a quantitative risk assessment and as basis for a recommended exposure limit (REL) are the nonmalignant pulmonary data from the CNT animal studies. At present, data on cancer and cardiovascular effects are not adequate for a quantitative risk assessment of inhalation exposure. NIOSH considers the pulmonary responses of inflammation and fibrosis observed in short-term and subchronic studies in animals to be relevant to humans, as inflammatory and fibrotic effects are also observed in occupational lung diseases associated with workplace exposures to other inhaled particles and fibers. Uncertainties include the extent to which these lung effects in animals are associated with functional deficits and whether similar effects would be clinically significant among workers. However, these fibrotic lung effects observed in some of the animal studies developed early (e.g., 28 days after exposure) in response to relatively low-mass lung doses, and also persisted or progressed after the end of exposure [Shvedova et al. 2005, 2008; Ma-Hock et al. 2009; Pauluhn 2010a; Porter et al. 2010; Mercer et al. 2011; DeLorme et al. 2012; Murray et al. 2012]. Given the relevance of these types of lung effects to humans, the REL was derived using the published subchronic and short-term animal studies with dose-response data of early stage fibrotic and inflammatory lung responses to CNT exposure (Section 5 and Appendix A).

Critical effect levels for the noncancerous lung effects estimated from the animal dose-response data (e.g., BMD, benchmark dose and BMDL, the 95% lower confidence limit estimates of the BMD) have been extrapolated to humans by accounting for the factors influencing the lung dose in each animal species. The no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) estimates reported in the subchronic inhalation studies were also evaluated as the critical effect levels. Working-lifetime exposure

concentrations were calculated based on estimates of either the deposited or retained alveolar lung dose of CNT assuming an 8-hour time-weighted average (TWA) exposure during a 40-hour workweek, 50 weeks per year, for 45 years. Based on BMD modeling of the subchronic animal inhalation studies with MWCNT [Ma-Hock et al. 2009; Pauluhn 2010a], a working lifetime exposure of 0.2–2 μg/m^3 (8-hour TWA concentration) was estimated to be associated with a 10% excess risk of early-stage adverse lung effects (95% lower confidence limit estimates) (Tables 5–1 and A–5). Risk estimates derived from short-term animal studies (Tables A–3 and A–4) were consistent with these estimates.

In addition to the BMD-based risk estimates, NOAEL or LOAEL values were used as the critical effect level in animals. As with the BMD(L) estimates, the human-equivalent working lifetime concentrations were estimated, although using dosimetric adjustment and uncertainty factors (Section A.6.3). The estimated human-equivalent working lifetime concentrations based on this approach were approximately 4–18 μg/m^3 (8-hr TWA), depending on the subchronic study and the interspecies dose retention and normalization factors used. Dividing these estimates by data-suitable uncertainty factors (e.g., UFs of 20–60), and assuming a threshold model, the estimated zero risk levels were <1 μg/m^3 as working lifetime 8-hr TWA concentrations. A recent subchronic inhalation (13-wk exposure plus 3 months follow-up) study of CNF in rats [DeLorme et al. 2012] showed qualitatively similar lung response as in a shorter-term (28-day) study of CNF administered by pharyngeal aspiration in mice [Murray et al. 2012] (Sections 3.5 and A.7). Using the NOAEL-based approach, the human-equivalent working lifetime concentration estimates were 1–4 μg/m^3 (8-hr TWA), depending on the data and assumptions used to estimate the human-equivalent dose (Section A.7).

In the 2010 draft Current Intelligence Bulletin (CIB) *Occupational Exposure to Carbon Nanotubes and Nanofibers*, NIOSH proposed a REL of 7 μg/m^3 elemental carbon (EC) 8-hr TWA, which was set at the upper limit of quantitation (LOQ) for NIOSH Method 5040 [NIOSH 2010a]. In the draft CIB, NIOSH acknowledged that workers may still have an excess risk of developing early-stage pulmonary effects including fibrosis if exposed over a full working lifetime at the proposed REL. In view of these health risks, and ongoing improvements in sampling and analytical methodologies, NIOSH is recommending a REL of 1 μg/m^3 EC as an 8-hr TWA respirable mass concentration using NIOSH Method 5040 (Section 6.1, Appendix C). The 45-yr working lifetime excess risk estimates of minimal level (grade 1 or greater) lung effects in rats observed by histopathology at 1 μg/m^3 (8-hr TWA concentration) range from 2.4% to 33% (maximum likelihood estimates, MLE) and 5.3% to 54% (95% upper confidence limit, UCL) estimates (Table A–7). The 45-yr working lifetime excess risk estimates of slight/mild (grade 2) lung effects at 1 μg/m^3 (8-hr TWA) range from 0.23% to 10% MLE and 0.53% to 16% (95% UCL) (Tables 5–2 and A–8). These estimates are based on a risk assessment using dose-response data from the rat subchronic inhalation studies of two types of MWCNT. The range in these risk estimates reflects differences across studies and/or types of MWCNT and the uncertainty in the estimation of working lifetime CNT lung burden. The lung burden estimates are based on either the retained lung dose (normal clearance) or deposited lung dose (no clearance). Although data from animal studies with CNF are more limited [Murray et al. 2012; DeLorme et al. 2012], physical-chemical similarities between CNT and CNF and findings of acute pulmonary inflammation and interstitial fibrosis in animals exposed to CNF [Murray et al. 2012] indicate the need to also control occupational exposure to CNF at the REL of 1 μg/m^3 EC. Because of uncertainties in the risk estimates some residual risk for adverse lung effects may exist at the REL; therefore, efforts should be made to reduce airborne concentrations to CNT and CNF as low as

possible. Until the results from animal research studies can fully explain the mechanisms (e.g., shape, size, chemistry, functionalized) that potentially increase or decrease their toxicity all types of CNT and CNF should be considered a respiratory hazard and occupational exposures controlled at the REL of 1 μg/m^3.

Exposure Measurement and Controls

Occupational exposure to all types of CNT and CNF can be quantified using NIOSH Method 5040. A multi-tiered exposure measurement strategy is recommended for determining worker exposure to CNT and CNF [Section 6.1]. When exposure to other types of EC (e.g., diesel soot, carbon black) are absent or negligible, environmental background EC concentrations are typically < 1 μg/m^3 including in facilities where CNT and CNF are produced and used [Evans et al. 2010; Birch 2011a, b; Dahm et al. 2011]. Thus, an elevated airborne EC concentration relative to background (environmental and in non-process areas in the workplace) is a reasonable indicator of CNT or CNF exposure. When exposure to other types of EC is possible, additional analytical techniques may be required to better characterize exposures. For example, analysis of airborne samples by transmission electron microscopy (TEM) equipped with energy dispersive x-ray spectroscopy (EDS) can help to verify the presence of CNT and CNF (Section 6.1.2).

Published reports of worker exposure to CNT and CNF using NIOSH Method 5040 (EC determination) are limited but in the study by Dahm et al. [2011] worker personal breathing zone (PBZ) samples collected at CNT manufacturers frequently found low to non-detectable mass concentrations of EC when engineering controls were present. In a study by Birch et al. [2011a], the outdoor air concentrations over four survey days, two months apart, were nearly identical, averaging about 0.5 μg/m^3. Respirable EC area concentrations inside the facility were about 6–68 times higher than outdoors, while personal breathing zone samples were up to 170 times higher. In studies where airborne particle concentrations were used as a surrogate for measuring the potential release of CNT and CNF, the use of engineering controls (e.g., local exhaust ventilation, wet cutting of composites, fume hood/enclosures) appeared to be effective in reducing worker exposure [Han et al. 2008; Bello et al. 2009; Tsai et al. 2009; Methner et al. 2010a; Cena and Peters 2011] (Section 2.1). However, direct reading instruments used in these studies are non-selective tools and often subject to interferences due to other particle sources, especially at low concentrations [Evans et al. 2010; Birch et al. 2011]. Control strategies and technologies developed by several industrial trade associations have proven successful in managing micrometer-sized fine powder processes, and should have direct application to controlling worker exposures from CNT and CNF processes. Examples include guidance issued for containing dry powder during manufacturing of detergents by the Association Internationale de la Savonnerie, de la Détergence et des Produits d'Entretien (AISE) [AISE 2001]. Following these guidelines makes it possible, at a minimum, to control enzyme-containing dust exposures below 60 ng/m^3 for enzymes. Additional guidance on a broader process and facility approach is available from the International Society for Pharmaceutical Engineering (ISPE). This organization offers guidance on the design, containment, and testing of various processes that handle finely divided dry powder formulations. One guide in particular, Baseline Guide Volume 1, 2nd Edition: Active Pharmaceutical Ingredients Revision to Bulk Pharmaceutical Chemicals, has broad applicability to CNT and CNF processes and is available from ISPE [ISPE 2007]. Finally, the Institute for Polyacrylate Absorbents (IPA) has developed guidelines for

its member companies to assist them in controlling worker exposures to fine polyacrylate polymer dust in the micrometer-size range through a combination of engineering controls and work practices [IPA 2013]. The extent to which worker exposure to CNT and CNF can be controlled below 1 μg/m^3 respirable mass concentration as an 8-hr TWA is unknown, but should be achievable in most manufacturing and end-use job tasks if engineering controls are used and workers are instructed in the safe handling of CNT/CNF materials.

Until results from research studies can fully explain the physical-chemical properties of CNT and CNF that define their inhalation toxicity, all types of CNT and CNF should be considered a respiratory hazard, and exposures should be controlled as low as possible below the REL. The REL is based on the respirable airborne mass concentration of CNT and CNF because the adverse lung effects in animals were observed in the alveolar (gas-exchange) region. "Respirable" is defined as the aerodynamic size of particles that, when inhaled, are capable of depositing in the alveolar region of the lungs [ICRP 1994]. Sampling methods have been developed to estimate the airborne mass concentration of respirable particles [ACGIH 1984; CEN 1993; ISO 1995; NIOSH 1998]. Reliance on a respirable EC mass-based REL will provide a means to identify job tasks with potential exposures to CNT and CNF so that appropriate measures can be taken to limit worker exposure.

Recommendations

In light of current scientific evidence from experimental animal studies concerning the hazard potential of CNT and CNF, steps should be taken to implement an occupational health surveillance program that includes elements of hazard and medical surveillance. NIOSH recommends that employers and workers take the following steps to minimize potential health risks associated with exposure to CNT and CNF.

1. Recommendations for Employers

- Use available information to continually assess current hazard potential related to CNT and CNF exposures in the workplace and make appropriate changes (e.g., sampling and analysis, exposure control) to protect worker health. At a minimum, follow requirements of the OSHA Hazard Communication Standard [CFR 1910.1200(h)] and the Hazardous Waste Operation and Emergency Response Standard [29 CFR 1910.120].
- Identify and characterize processes and job tasks where workers encounter bulk ("free-form") CNT or CNF and materials that contain CNT/CNF (e.g., composites).
- Substitute, when possible, a nonhazardous or less hazardous material for CNT and CNF. When substitution is not possible, use engineering controls as the primary method for minimizing worker exposure to CNT and CNF.
- Establish criteria and procedures for selecting, installing, and evaluating the performance of engineering controls to ensure proper operating conditions. Make sure workers are trained in how to check and use exposure controls (e.g., exhaust ventilation systems).
- Routinely evaluate airborne exposures to ensure that control measures are working properly and that worker exposures are being maintained below the NIOSH REL of 1 μg/m^3 using NIOSH Method 5040 (Section 6 and Appendix C).

- Follow exposure and hazard assessment procedures for determining the need for and selection of proper personal protective equipment, such as clothing, gloves, and respirators (Section 6).
- Educate workers on the sources and job tasks that may expose them to CNT and CNF, and train them about how to use appropriate controls, work practices, and personal protective equipment to minimize exposure (Section 6.3).
- Provide facilities for hand washing and encourage workers to make use of these facilities before eating, smoking, or leaving the worksite.
- Provide facilities for showering and changing clothes, with separate facilities for storage of nonwork clothing, to prevent the inadvertent cross-contamination of nonwork areas (including take-home contamination).
- Use light-colored gloves, lab coats, and workbench surfaces to make contamination by dark CNT and CNF easier to see.
- Develop and implement procedures to deal with cleanup of CNT and CNF spills and decontamination of surfaces.
- When respirators are provided for worker protection, the OSHA respiratory protection standard [29 CFR 1910.134] requires that a respiratory protection program be established that includes the following elements:
  - A medical evaluation of the worker's ability to perform the work while wearing a respirator.
  - Regular training of personnel.
  - Periodic workplace exposure monitoring.
  - Procedures for selecting respirators.
  - Respirator fit testing.
  - Respirator maintenance, inspection, cleaning, and storage.
- The voluntary use of respirators are permitted, but must comply with the provisions set forth in CFR 1910.134(c)(2)(i) and CFR 1910.134(c)(2)(ii).
- Information on the potential health risks and recommended risk management practices contained in this CIB should, at a minimum, be used when developing labels and Safety Data Sheets (SDS), as required [http://www.osha.gov/dsg/hazcom].

1.1 Medical Screening and Surveillance

The evidence summarized in this document leads to the conclusion that workers occupationally exposed to CNT and CNF may be at risk of adverse respiratory effects. These workers may benefit from inclusion in a medical screening program to help protect their health (Section 6.7).

1.1.1 Worker Participation

Workers who could receive the greatest benefit from medical screening include the following:

- Workers exposed to concentrations of CNT or CNF in excess of the REL (i.e., all workers exposed to airborne CNT or CNF at concentrations above 1 μg/m^3 EC as an 8-hr TWA).

- Workers in areas or jobs that have been qualitatively determined (by the person charged with program oversight) to have the potential for intermittent elevated airborne concentrations to CNT or CNF (i.e., workers are at risk of being exposed when they are involved in the transfer, weighing, blending, or mixing of bulk CNT or CNF, or the cutting or grinding of composite materials containing CNT or CNF, or workers in areas where such activities are carried out by others).

1.1.2 Program Oversight

Oversight of the medical surveillance program should be assigned to a qualified health-care professional who is informed and knowledgeable about potential workplace exposures, routes of exposure, and potential health effects related to CNT and CNF.

1.1.3 Screening Elements

Initial Evaluation

- An initial (baseline) evaluation should be conducted by a qualified health-care professional and should consist of the following:
  - An occupational and medical history, with respiratory symptoms assessed by use of a standardized questionnaire, such as the American Thoracic Society Respiratory Questionnaire [Ferris 1978] or the most recent.
  - A physical examination with an emphasis on the respiratory system.
  - A spirometry test (Anyone administering spirometry testing as part of the medical screening program should have completed a NIOSH-approved training course in spirometry or other equivalent training; additionally, the health professional overseeing the screening and surveillance program should be expert in interpreting spirometry testing results, enabling follow-up evaluation as needed.).
  - A baseline chest X-ray (digital or film-screen radiograph). All baseline chest images should be clinically interpreted by a board eligible/certified radiologist or other physician with appropriate expertise, such as a board eligible/certified pulmonologist. Periodic follow up chest X-rays may be considered, but there is currently insufficient evidence to evaluate effectiveness. However, if periodic follow up is obtained, clinical interpretation and classification of the images by a NIOSH-certified B reader using the standard International Classification of Radiographs of Pneumoconioses (ILO 2011 or the most recent equivalent) are recommended.
  - Other examinations or medical tests deemed appropriate by the responsible health-care professional (The need for specific medical tests may be based on factors such as abnormal findings on initial examination—for example, the findings of an unexplained abnormality on a chest X-ray should prompt further evaluation that might include the use of high-resolution computed tomography scan of the thorax.).

Periodic Evaluations

- Evaluations should be conducted at regular intervals and at other times (e.g., post-incident) as deemed appropriate by the responsible health-care professional based on data gathered in the initial evaluation, ongoing work history, changes in symptoms such as new, worsening, or persistent respiratory symptoms, and when process changes occur in the workplace (e.g., a change in how CNT or CNF are manufactured or used or an unintentional "spill"). Evaluations should include the following:
  - An occupational and medical history update, including a respiratory symptom update, and focused physical examination—performed annually.
  - Spirometry—testing less frequently than every 3 years is not recommended [OSHA NIOSH 2011]; and
  - Consideration of specific medical tests (e.g., chest X-ray).

Written reports of medical findings

- The health-care professional should give each worker a written report containing the following:
  - The individual worker's medical examination results.
  - Medical opinions and/or recommendations concerning any relationships between the individual worker's medical conditions and occupational exposures, any special instructions on the individual's exposures and/or use of personal protective equipment, and any further evaluation or treatment.
- For each examined employee, the health-care professional should give the employer a written report specifying the following:
  - Any work or exposure restrictions based on the results of medical evaluations.
  - Any recommendations concerning use of personal protective equipment.
  - A medical opinion about whether any of the worker's medical conditions is likely to have been caused or aggravated by occupational exposures.
- Findings from the medical evaluations having no bearing on the worker's ability to work with CNT or CNF should not be included in any reports to employers. Confidentiality of the worker's medical records should be enforced in accordance with all applicable regulations and guidelines.

1.1.4 Worker Education

Workers should be provided information sufficient to allow them to understand the nature of potential workplace exposures, potential health risks, routes of exposure, and instructions for reporting health symptoms. Workers should also be provided with information about the purposes of medical screening, the health benefits of the program, and the procedures involved.

1.1.5 Periodic Evaluation of Data and Screening Program

- Standardized medical screening data should be periodically aggregated and evaluated to identify worker health patterns that may be linked to work activities and practices