



Application and testing of risk screening tools for nanomaterial risk analysis

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1 The Difficulties in Establishing an Occupational Exposure Limit for Carbon Nanotubes

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Abstract

Concern over the health effects from the inhalation of carbon nanotubes (CNTs) has been building for some time, and adverse health effects found in animal studies include acute and chronic respiratory damage, cardiac inflammation, and cancer including mesothelioma, heretofore only associated with asbestos exposure. The strong animal evidence of toxicity requires that the occupational hygiene community develop strategies for reducing or eliminating worker exposures to CNTs; part of this strategy involves the setting of occupational exposure limits (OELs) for CNTs. A number of government agencies and private entities have established OELs for CNTs; some are mass-based, while others rely on number concentration. We review these various proposed standards and discuss the pros and cons of each approach. We recommend that specific action be taken, including intensified outreach to employers and employees concerning the potential adverse health effects from CNT inhalation, the development of more nuanced OELs that reflect the complex nature of CNT exposure, a broader discussion of these issues among all interested parties, and further research into important unanswered questions including optimum methods to evaluate CNT exposures. We conclude that current animal toxicity evidence suggests that strong action needs to be taken to minimize exposures to CNTs, and that any CNT OEL should be consistent with the need to minimize exposures.

Introduction

Concern over the health effects from the inhalation of carbon nanotubes (CNTs) has been building for some time. A review of articles published over the past dozen years (Boxall et al.

2007; Donaldson et al. 2006; Kisin et al. 2007; Kisin et al. 2011; Lam et al. 2006; Legramante et al. 2012; Li et al. 2007; Ma-Hock et al. 2009; Muller et al. 2005; Shvedova et al. 2003; Shvedova et al. 2008a; Shvedova et al. 2005; Shvedova et al. 2008b; Shvedova et al. 2008c; Simeonova 2009; Warheit et al. 2004) outlines the growing concerns regarding the toxicity of CNTs. Recent review papers (Ema et al. 2016; Gao et al. 2016; Kuempel et al. 2016; Ong et al. 2016; Pacurari et al. 2016; Siegrist et al. 2014; Vietti et al. 2016) provide an excellent overview of the current knowledge regarding adverse health effects of single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). The Organization for Economic Cooperation and Development (OECD) has recently published comprehensive summaries of the environmental health and safety aspects of both MWCNTs (OECD 2016a) and SWCNTs (OECD 2016b). Rodent studies have found an acute inflammatory response, granulomas, fibrosis, and decreased rates of respiration and bacterial clearance from the lungs. Importantly, the National Institute for Occupational Safety and Health (NIOSH) (NIOSH 2013) concluded that "...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, and the effects, including fibrosis, developed soon after exposure and persisted." Adverse impacts on other organ systems, including cardiac inflammation, have also been found (NIOSH 2013). Such a wide range of acute and chronic health effects associated with CNTs, particularly the strong fibrogenic potential, are reason enough for concern – but even more serious concerns have arisen. Almost twenty years ago, the morphological similarity between CNTs and other fibrous materials, such as asbestos, raised concerns as to whether exposure to CNTs could cause lung cancer and/or mesothelioma (Service 1998). Research followed, and two groups observed asbestos-like effects in short-term bioassays when MWCNTs were injected intraperitoneally into mice (Poland et al.

2008; Takagi et al. 2008); subsequently, Ryman-Rasmussen *et al.* (Ryman-Rasmussen et al. 2009) found that inhaled MWCNTs reached the subpleura of mice and Mercer *et al.* (Mercer et al. 2010) found that they penetrated the intrapleural space. Additional research has for the most part confirmed the results of the first studies (Muller et al. 2009; Nagai et al. 2011; Rittinghausen et al. 2014; Schinwald et al. 2012), while others were negative (Muller et al. 2009).

Recently, the International Agency for Research on Cancer (IARC) reviewed the available toxicological studies and classified certain MWCNTs as a Group 2B carcinogen, where Group 2B is defined as “possibly carcinogenic to humans” (Grosse et al. 2014; IARC 2017; Kuempel et al. 2016). IARC based its classification on the Poland and Takagi rodent studies, which used a particular MWCNT designated “MWCNT-7,” and its classification applies only to this particular product. Specifically, IARC found that “inhalation of MWCNT-7 promoted bronchioloalveolar adenoma and carcinoma in male mice” and “MWCNT-7 caused peritoneal mesotheliomas in male and female rats in one intraperitoneal injection study and one intrascrotal injection study, and in male p53+/- mice in two intraperitoneal injection studies”(Grosse et al. 2014). Although rodents were exposed by routes other than inhalation, IARC referenced Mercer *et al.* (Mercer et al. 2010) to conclude that “mechanistic and other data in rodents provided evidence of translocation of three types of MWCNTs (including MWCNT-7) to the pleura.” The Rittinghausen paper (Rittinghausen et al. 2014) was published after the IARC review occurred, and found that four different MWCNTs induced mesothelioma in 40-98% of the rats tested.

All evidence for adverse health effects is based on animal toxicity studies; no case reports or epidemiological studies of CNT-specifically exposed workers have been published. Oberdörster, et al. (Oberdörster et al. 2015) discuss in detail the difficulties in conducting a proper animal inhalation study for CNTs, including e.g. the use of different delivery techniques (instillation,

aspiration, inhalation), high doses, high dose rates, pretreatment with dispersants, poor distribution throughout the respiratory tract, etc. These difficulties and differences between studies make it very difficult to translate results of rodent studies to levels of exposure likely to cause adverse health effects in humans. However, the animal studies, taken together, seem to indicate that at least some MWCNTs cause the same three major diseases associated with asbestos use (pulmonary fibrosis, lung cancer and mesothelioma) and in fact may be a more potent cause of these very serious diseases. The history of asbestos exposure and disease is well-known, and leads to the obvious questions as to whether the occupational and environmental health community can take proper action to prevent another similar pattern of exposure and disease development. Such questions are ones of broad public health policy, with implications well beyond occupational hygiene. We believe that the occupational and environmental health community in particular must act proactively to ensure that workers and members of the public are not needlessly exposed to what may in the future be confirmed as a human carcinogen. The strong animal evidence of toxicity requires that the occupational hygiene community develop strategies for reducing or eliminating worker exposures to CNTs.

This commentary focuses on the issue of setting appropriate occupational exposure levels (OELs) for CNTs, although many issues must be addressed, including exposure assessment methodologies and effective exposure control strategies. We first describe the OELs suggested by government agencies and companies; at this time there are no regulatory OELs specific to CNTs. We then discuss important issues that must be addressed in the setting of an OEL for CNTs, including the more fundamental question about the appropriateness of OELs for suspected carcinogens. We close with some recommendations for actions we believe should be taken in the near future to address this important issue.

137

138 **Recommended OELs**

139 In response to the adverse health effects found in animal studies, several governmental
140 agencies, and one private company, have published occupational exposure limits for CNTs.
141 These are briefly reviewed here.

142 The British Standards Institute (BSI) in 2007 recommended a “benchmark” CNT OEL of
143 0.01 fibers/cm³ (f/cm³), as measured by scanning or transmission electron microscopy (BSI
144 2007). This level is equivalent to the most rigorous exposure limit in Britain for asbestos, *i.e.*, the
145 highest concentration that can be present inside a space after asbestos removal activities (also
146 called the clearance limit, this is the same limit as used by the US EPA for this activity).

147 The German company Bayer Schering Pharmaceuticals studied the toxicity of their
148 MWCNTs, called Baytubes. They concluded that exposure is unlikely to lead to mesothelioma or
149 other chronic conditions because Baytubes are flexible, leading to the formation of relatively
150 large assemblages, or “bird’s nests” of tubes. They set a company OEL for Baytubes of 50
151 µg/m³, based on measured acute toxicity in rats (Pauluhn 2010). Pauluhn stated that their
152 measurements of Baytube mass concentration were made “utilizing cobalt [a catalyst used in
153 Baytube manufacturing] as a tracer (in order to distinguish carbonaceous background dust from
154 Baytubes)” but no more details of the measurement method were provided.

155 The Japanese National Institute of Advanced Industrial Science and Technology (AIST)
156 derived OELs of 30 µg/m³ for SWCNTs and 80 µg/m³ for MWCNTs (Nakanishi 2011), based on
157 studies supported by the New Energy and Industrial Technology Development Organization

(NEDO) of Japan. These limits were based on no observed effect levels (NOELs) calculated for non-carcinogenic effects.

The Swiss Accident Insurance Funds (SUVA) addressed carbon nanotubes and fibers in the Swiss 2011 occupational exposure limit list (SUVA 2011). The document highlighted the structural similarities of CNTs and CNFs to other fibers such as asbestos and noted that these materials lead to inflammation. The document specifically mentioned that studies done with long rigid MWCNTs suggest that they may be carcinogenic; consequently, they recommended an exposure limit of 0.01 f/cm^3 for CNTs and CNFs. This limit corresponds to their threshold value for asbestos fibers and remains in the latest (2015) edition of the occupational exposure limit list.

The German Institute for Occupational Safety and Health (IFA) developed “benchmark” levels for evaluating engineered nanoparticle (ENP) exposures, based on what IFA considers to be likely predictors of ENP toxicity, i.e., size, shape, density and biopersistence. Four groups are defined, each with a “nano reference value (NRV).” Group 1 consists of “rigid, biopersistent nanofibers for which effects similar to those of asbestos are not excluded” (e.g., CNTs) with a NRV of 0.01 f/cm^3 (the same as the BSI recommendation for CNTs and asbestos) (van Broekhuizen and Dorbeck-Jung 2013). It is clear that the NRVs are meant to be differentiated from actual health-based OELs, and are to be used as interim exposure guidelines until OELs can be developed (van Broekhuizen et al. 2012).

After much discussion of an earlier draft, in 2013 NIOSH published Current Intelligence Bulletin (CIB) with a recommended exposure limit (REL) of $1 \mu\text{g/m}^3$ of elemental carbon (EC) (NIOSH 2013). This limit is based on the limit of quantitation (LOQ) of Method 5040, titled “Diesel Particulate Matter (as Elemental Carbon)” (NIOSH 2003). They calculate that the LOQ “can be obtained for an 8-hr respirable sample collected on a 25-mm filter at a flow rate of 4

liters per minute (lpm).” Regarding health effects, for a 45-year lifetime exposure at the REL, NIOSH developed “maximum likelihood estimates” of 2.4 – 33% for “minimal lung effects” and 0.23 – 10% for “slight or mild lung effects” as. The CIB concluded that “NIOSH does not consider a 10% estimated excess risk over a working lifetime to be acceptable for these early-stage lung effects, and the REL is set at the optimal limit of quantification (LOQ) of the analytical method carbon (NIOSH method 5040).”

Carcinogenic potential was not considered in setting the REL. “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 2013).

To summarize, various entities have recommended both mass-based and number-based OELs for CNTs, as shown in Table 1. The number-based recommendations all are consistent with the strictest asbestos OEL of 0.01 f/cm³, whereas the mass-based recommendations range from 1 – 80 µg/m³.

Advantages and Disadvantages of a Mass-Based OEL for CNTs

AIST, Bayer and NIOSH developed mass-based CNT OELs for some very good reasons. One advantage, as discussed above, is that the use of mass concentration correlates well with non-carcinogenic end-points in animal toxicity studies. The primary benefit of this approach, however, is that it uses classic occupational hygiene measurement methods and metrics. Any OEL loses most of its utility if there are no methods to measure worker exposure for comparison

to the standard. For example, the NIOSH REL requires the use of readily-available air sampling equipment and a validated sample analysis method that can be performed by many laboratories at as reasonable price. Thus, any reasonably-proficient field occupational hygienist can collect a valid sample and compare it to the REL. This advantage makes a compelling reason for using this approach.

There are, however, several concerns with using a mass-based OEL for CNTs. First, the risks of developing the most serious adverse health effects, *i.e.*, fibrosis, lung cancer and mesothelioma, are a function not of the *mass* of CNTs inhaled but on the *number* of appropriately-sized fibers inhaled and subsequently depositing in alveoli. Since the mass of any individual CNT can vary greatly, a given mass concentration can have a widely ranging number concentration, so that a mass-based OEL does not correlate well with the property of interest, number. Second, an air sample is likely to collect both CNTs and other particles, but the available analytical methods cannot directly measure the mass of CNTs collected. Available methods rely on a surrogate of CNT mass, such as cobalt for Baytubes and elemental carbon for NIOSH. While it is true that CNTs consist largely of elemental carbon, there may other sources of elemental carbon in the workplace, such as carbon soot formed by incomplete tube formation in a CNT furnace, or diesel exhaust from fork lift trucks in a factory incorporating CNTs into a product.

A third concern with a mass-based OEL is that the actual values proposed correspond to number concentrations that can be much higher than asbestos OELs because they are based either on acute health effects for a specific tested CNT (the AIST OEL of 80 $\mu\text{g}/\text{m}^3$) or on available analytical methods (the NIOSH REL of 1 $\mu\text{g}/\text{m}^3$). The issue was discussed by Schulte, et al. (Schulte et al. 2012), who compare fiber number concentrations for fibers of different

dimensions to a mass concentration of $7 \mu\text{g}/\text{m}^3$ (this was the original proposed REL of NIOSH). Adjusting their conversions to $1 \mu\text{g}/\text{m}^3$, this corresponds to $0.01 \text{ fibers}/\text{cm}^3$ for a very large fiber (2,110 nm diameter x 10,000 nm length) and $300,000 \text{ fibers}/\text{cm}^3$ for a very small fiber (2 nm x 500 nm). These fiber concentrations range from lower than the asbestos PEL of $0.1 \text{ f}/\text{cm}^3$ to much higher than the PEL (OSHA 1994).

Advantages and Disadvantages of a Number-Based OEL for CNTs

The use of a fiber number-based OEL also presents distinct advantages and disadvantages. The primary advantage is that the risk of developing the serious chronic diseases that have been associated with CNT exposure in animal studies – fibrosis, lung cancer, and mesothelioma – are all a function of the number of fibers deposited in the alveolar region of the lung, not the mass. It is for this reason that all asbestos OELs are given in f/cm^3 . The primary disadvantage of a number-based OEL is that it is difficult and costly to obtain exposure measurements. Breathing-zone asbestos concentrations are measured by passing the sampled air through a cellulose ester membrane filter and examining the filter with a phase contrast optical microscope. Unfortunately, CNTs are too small to be seen by an optical microscope, and electron microscopy must be used, increasing the cost of analysis by at least an order of magnitude. Direct-reading particle counters can also be used, but they are expensive and count all particles, not just fibers. We will return to this measurement conundrum in the Recommendations section.

Possible Variations between Different CNT Types

A one-size-fits-all OEL is unlikely to adequately protect workers because the literature suggests that there may be important differences in toxicological response among types of CNTs. In various studies, single wall carbon nanotubes (SWCNTs) have not been found to cause mesothelioma (Kuempel et al. 2016). In addition, thin ($d < 15$ nm) and short [$L < 1$ μ m according to Muller et al. (Muller et al. 2009) and $L < 5$ μ m according to Schinwald et al. (Schinwald et al. 2012) MWCNTs do not cause mesothelioma. SWCNTs and thin MWCNTs, when examined microscopically, tend to curl and form bundles which are not fiber-shaped. Presumably, this shape enhances their clearance from the pulmonary region by phagocytosis. Likewise, very short MWCNTs may be cleared effectively by macrophages (Rittinghausen et al. 2014). As an added complication, Nagai et al. (Nagai et al. 2011) found that very thick MWCNTs ($d > 150$ nm) were less carcinogenic than thinner ones; however, there is evidence that such large-diameter tubes are not important commercially.

The absence of mesothelioma initiation when short tubes are administered to test animals suggests the possibility of treating pristine tubes to shorten them. Ali-Boucetta et al. (Ali-Boucetta et al. 2013) used two different reactions to functionalize pristine long MWCNTs and found that one reaction (functionalization with TEG chains using the 1,3-dipolar cycloaddition reaction) led to a reduction of the effective length of the MWCNTs, while a second reaction (functionalization with octyl chains following the Billups reaction) did not. These results suggest that functionalization needs much further research, and in any case must be used with great care. For example, procedures applied in the laboratory that shorten 100% of the tubes may have lower efficiency when applied at an industrial scale. In addition, many industrial processes may require the use of longer tubes, eliminating this option from consideration.

Another approach that may be effective in certain applications where the MWCNTs are dispersed in water is to coat them with a surfactant. Wang et al. (Wang et al. 2012) found that dispersing MWCNTs in Pluronic F 108, a difunctional block copolymer surfactant, reduced fibrogenic response by reducing damage to the lysosomal membrane.

In any case, MWCNTs subject to any such treatments could never be considered completely safe, since the possible exposure of the workers manufacturing the pristine tubes and functionalizing them would have to be considered. For example, to coat CNTs with a surfactant, the dry tubes would have to be dispersed into the water and surfactant, a potentially hazardous operation.

Agglomerates vs. Individual Fibers

Another significant complication that is not addressed by using a mass-based OEL is that airborne CNTs may exist as individual fibers or as agglomerates or bundles of fibers. The state of agglomeration can influence both the respiratory deposition pattern of the inhaled fibers and the toxicological response. Researchers have found varied changes in toxicity when CNTs agglomerate. For example, Gao et al. (Gao et al. 2016) found that “it clearly appears that aggregation of SWCNTs should be avoided and that nanotube individualization is a key parameter to minimize cellular toxicity.” Wick et al. (Wick et al. 2007) found that agglomerated MWCNTs were more toxic than well-dispersed ones. On the other hand, end effects that depend on the fibrotic nature of CNTs (fibrosis and mesothelioma) should presumably be ameliorated by the formation of non-fiber-shaped agglomerates (Kuempel et al. 2016). Song et al. (Song et al. 2016) summarized the current muddled state of the research on this topic thus: “more efforts should be paid to study the biological effects of agglomeration.” In any case, a significant

shortcoming of mass-based OELs is that the state of agglomeration in the sample would not be known.

From an occupational hygiene viewpoint, agglomeration complicates the use of number-based OELs. Counting schemes need to be developed to address this issue; it is likely that an approach similar to that used for high aspect ratio particles such as bundles of asbestos fibers, where clearly-identified fiber “ends” in fiber bundles are counted, may be needed. NIOSH in 2016 published a draft analytical method titled “Analysis of Carbon Nanotubes and Nanofibers on Mixed Cellulose Ester Filters by Transmission Electron Microscopy” (Birch et al. 2016), which was a modification to NIOSH NMAM 7402, asbestos by TEM (NIOSH 1994). It is an initial attempt to develop an approach in the United States.

Actions by Other Government Agencies

The U.S. Environmental Protection Agency (EPA) regulates CNTs under the Toxics Substance Control Act (TSCA). CNTs were designated as a material requiring a premanufacture notification (PMN), and, as an example, in September, 2017 the EPA issued a significant new use rule (SNUR) for a specific CNTs used in filtration media (EPA 2017). The company-specific SNUR requires the use of protective clothing and NIOSH-approved respirators where there is as potential for exposure, processing and use of only those quantities specified in the consent order, processing only as a aqueous slurry, wet form, or “contained” dry form, prohibits release of CNTs to surface waters, and requires disposal to be done only by landfill or incineration. The SNUR’s restrictions on manufacture, processing, distribution in commerce, and disposal will remain in effect until the results of recommended testing is completed (2-year

inhalation bioassay; daphnid chronic; and algal toxicity). Such actions by EPA, done in consultation with NIOSH and OSHA, serve as an interim approach to worker exposure while awaiting the results of recommended toxicity testing.

The European Union's law regarding Registration, Evaluation, Authorization and Restriction of Chemical substances (REACH), which entered into force on June 1, 2007 (Commission of the European 2007), may also offer some protection to workers potentially exposed to CNTs. TSCA and REACH differ greatly in their approaches to regulating chemical health and safety, and a detailed comparison of the two approaches is beyond the scope of this paper. Readers interested in such a comparison are referred to Chapter 11 of the textbook by Ellenbecker and Tsai (Ellenbecker and Tsai 2015). Briefly, it is fair to say that REACH does not provide the detailed performance standards specified in a SNUR, but rather requires manufacturers to proactively ensure that their products are manufactured and used safely. In addition, the European Commission has promulgated a recommended "code of conduct for responsible nanosciences and nanotechnologies (N&N) research" (EC 2008). Key elements of the code of conduct include:

N&N research activities should be safe, ethical and contribute to sustainable development serving the sustainability objectives of the Community as well as contributing to the United Nations' Millennium Development Goals. They should not harm or create a biological, physical or moral threat to people, animals, plants or the environment, at present or in the future.

N&N research activities should be conducted in accordance with the precautionary principle, anticipating potential environmental, health and safety impacts of N&N outcomes and taking due precautions, proportional to the level of protection, while encouraging progress for the benefit of society and the environment.

Governance of N&N research activities should be guided by the principles of openness to all stakeholders, transparency and respect for the legitimate right of

access to information. It should allow the participation in decision-making processes of all stakeholders involved in or concerned by N&N research activities.

The EC recommends:

That Member States encourage the voluntary adoption of the Code of Conduct by relevant national and regional authorities, employers and research funding bodies, researchers, and any individual or civil society organization involved or interested in N&N research and endeavor to undertake the necessary steps to ensure that they contribute to developing and maintaining a supportive research environment, conducive to the safe, ethical and effective development of the N&N potential.

Other Considerations

Other important CNT occupational hygiene issues, such as exposure assessment and control, depend to some extent on decisions made about appropriate OELs. Methods used to evaluate exposure will differ greatly for a mass-based OEL and a number-based OEL. An advantage of the mass-based OELs when compared to a number-based OEL is that personal samples can be collected and analyzed using readily-available and well-understood equipment and techniques. In contrast, measuring the number concentration and size distribution of nanometer-sized fibers requires expensive, specialized equipment and operator skill and is limited at this time to area samples, with no agreed-upon technique to be used.

The measurement of a very low number concentration of MWCNTs of a certain size will likely require the development and validation of a new method based on transmission electron

microscopy. However, any CNT OEL is likely to require some form of electron microscopy in order to ensure that what is being sampled and analyzed actually contains CNTs. The CIB further recommends that EC and electron microscope samples be collected in parallel and that for each EC sample where the concentration that exceeds the NIOSH REL, the electron microscope sample should be analyzed to confirm that the EC actually came from CNTs.

All of the proposed OELs represent very low levels of exposure, and effective administrative and engineering controls will be required to reduce exposures to acceptable levels. Research has demonstrated that standard control practices, such as local exhaust ventilation and high-efficiency particulate air (HEPA) filtration, when applied with care, can effectively control nanoparticle exposures to minimal level (Golanski et al. 2010; Tsai et al. 2009a; Tsai et al. 2008b; Tsai et al. 2012), and publications on best practices are widely available (BSI 2007; DOE 2008; NCI 2008; NIOSH 2012; Wood 2000). Large MWCNTs will require, however, the highest level of controls to reduce exposures to a concentration such as the BSI benchmark. Sophisticated containment systems, such as those used by the pharmaceutical industry (Wood 2000), may be required.

The recent IARC classification for MWCNT-7 raises a more significant question about establishing OELs, namely, should we even be issuing OELs for carcinogens or suspected carcinogen where the evidence is clear that the “best” exposure limit is no exposure.

Some might argue that the “lowest possible level of exposure” approach be limited to IARC 1A confirmed human carcinogens and thus is overly strict for MWCNTs, an IARC 2B suspect human carcinogen (Grosse et al. 2014; IARC 2017; Kuempel et al. 2016). However, the 1A designation is only given to substances with sufficient positive epidemiologic evidence of an association between the substance and the cancer. Effectively, every new 1A designation

represents a case of evident exposure to workers, since in every case there is evidence of toxicity before the 1A designation and, in spite of that evidence, exposures were allowed sufficient to lead to a statistically significant level of cancer. Recognizing this, the American Conference of Governmental Industrial Hygienists states that for suspected human carcinogens, “worker exposure by all routes should be carefully controlled to levels as low as possible...” (ACGIH 2012) Our goal should be that there is *never* a positive epidemiology study for MWCNTs (or any other engineered nanoparticle, for that matter).

Rather than presuming that we can control workplace exposures to CNTs, especially those with evidence of carcinogenicity, there is a need to redirect technological developments that are venturing down unsafe paths. At a minimum, each potential use of MWCNTs must first undergo a rigorous analysis of the potential benefits versus the possible risks. Two hypothetical examples may illustrate this point. The first is the incorporation of MWCNTs into tennis racquet frames. This would require the use of relatively large amounts of dry MWCNTs being mixed with the polymer in an extruder, with high potential for exposure to workers (Tsai et al. 2008a) and would offer minor benefits to society. The second example is the use of MWCNTs as advanced memory storage devices in electronics. The manufacturing process would use minimal amounts of MWCNTs suspended in water, with minimal potential for worker exposure or environmental release, while potential benefits to society are very large. The first example may fail the risk-benefit test, while the second may pass it.

Such an approach is consistent with the European Union’s 2004 workplace carcinogen directive (EU 2004), which requires that employers replace the use of carcinogens with less dangerous substitutes wherever feasible. History has shown us too many public and occupational

health tragedies where society allowed the proliferation in use of suspected carcinogens by industry while scientists waited for evidence in humans to mount. Is the risk worth the wait?

Recommendations

In response to the concerns discussed above, the following specific actions are recommended:

Intensify outreach to employers and employees

Industry and the research community are in great need of guidance concerning worker exposures to CNTs. Some studies have found elevated exposures in facilities that manufacture CNTs (Baron et al. 2003; Bello et al. 2008; Dahm et al. 2011; Han et al. 2008; Lee et al. 2010; Tsai et al. 2009b) and those that incorporate CNTs into devices (Bello et al. 2009; Cena and Peters 2011; Dahm et al. 2011). Unfortunately, these studies did not evaluate exposures in plants or laboratories subject to TSCA or REACH, so it is difficult at this time to assess either legislations impact on protecting worker health. It is likely that both approaches are having a positive effect on reducing worker exposures in the absence of specific exposure limits, but it is also likely that exposures have not been reduced to the lowest possible level, as would be required for any CNTs that are in fact carcinogens.

It has been our experience that many employers likely have not yet measured their workers' exposures, and those that have made measurements likely are unsure whether their exposures should be of concern. It should be of concern, however, if workers are being exposed to what likely is a potent carcinogen. It is absolutely imperative that the occupational hygiene community

do all it can to ensure that exposure to CNTs is being effectively controlled in workplaces, so that life threatening diseases won't develop in humans.

Provide more nuanced CNT OELs to industry

The mass-based OELs are meant to be protective against the non-carcinogenic adverse health effects from exposure. Referring to CNTs, we should consider 1) what OEL is appropriate to be protective against cancer, remembering that 2) the number concentration corresponding to a mass-based OEL is highly variable depending on the fiber size (Schulte et al. 2012).

Based on the published studies reviewed above, a mass-based OEL *may* be appropriate for SWCNTs and short MWCNTs, based on the lack of current evidence for their carcinogenicity. This approach may prove to be short-sighted, however, if future toxicology and/or epidemiology studies prove otherwise, and is somewhat similar to the seemingly endless debates over the relative carcinogenicity of different asbestos fiber types, lengths and diameters. Although for a period of time the ACGIH had different TLVs for different asbestos fiber types, the occupational hygiene community has in effect made a collective decision to avoid these arguments with respect to asbestos and to issue a single OEL for all asbestos types (but not all fiber lengths). Whether or not this is the proper approach for CNTs must be carefully considered.

In any case, the precautionary approach of reducing exposures to the lowest practical level may need to be applied to long MWCNTs ($d > 15$ nm, $L > 2$ μ m), and, thus they may specifically be exempt from any mass-based CNT OEL. Given the uncertainties in health risk, exposure to all CNTs should be controlled to the lowest possible level. Any discussion of a CNT OEL should include statements that long MWCNTs should not be used unless absolutely necessary, according to current toxicological evidence discussed above, and then if and only if engineering and administrative controls are available to reduce exposure to the lowest possible level.

Although workers manufacturing such CNTs and incorporating them into devices are at the most risk, this precautionary approach shall be applied to all phases of a product's life.

Broaden the discussion

It is critical that decisions regarding the setting of OELs for CNTs involve all parties that have a role in this process. At a minimum in the United States, this should include NIOSH, OSHA, The American Conference of Governmental Hygienists (ACGIH), the American Industrial Hygiene Association (AIHA), and representatives from industry and labor. Appropriate representatives from other countries and areas involved in CNT research and manufacturing (European Union, China, Taiwan, Japan, Korea, *etc.*) should be included for a global perspective. The goals of these discussions should be 1) the setting of a consensus OEL (or OELs) for CNTs, and 2) agreement on a measurement method to be used for evaluating exposures for comparison to the OEL. Meeting these goals likely will require further research, discussed below.

Encourage further research

CNTs often are found as large bundles. However, the stability of these bundles is not well understood. Methods to study the stability of such bundles need to be developed. This method development would be done ideally in parallel with studies on the toxicity of such bundles so that a decision can be made whether bundles should be treated as the sum of many individual fibers or if only the number of free fibers need to be taken into account by a fiber count OEL. Until such a method is developed and tested, the proper procedure will remain a challenge. A conservative approach is to assume that individual fibers can be released into the surrounding tissue after such a bundle was deposited in the lungs; this would lead to the counting of individual fibers inside bundles.

Research is needed into the development of a reliable, cost-effective method to measure exposure to CNTs. Such a method likely would involve the direct collection of an air sample onto a filter or TEM grid, followed by a standardized fiber counting procedure, or a direct reading device that can measure fiber mass and/or volume. Research is needed in both of these areas. Several different techniques are available to directly deposit particles on TEM grids (diffusion, electrostatic and thermal deposition) and the method that best deposits particles of all relevant sizes should be determined. With regard to counting, it would be highly desirable to develop an automated method to scan grids and identify, count and size fibers, since manual counting and sizing is a very costly procedure.

Additional recommendations

CNT Safety Data Sheets, which to date have been seriously deficient (Eastlake et al. 2012), should include sufficient information to communicate the potential hazards discussed in this article. Efforts to prevent release to the environment should also be implemented. Information should also be provided to handlers of wastes containing these materials, including but not limited to personal protective equipment (respirator cartridges, disposable lab coats, gloves, etc.), cleaning wipes, and used air filters from exhaust systems. Manufacturers incorporating any CNT into products should consider appropriate warnings to users, and all products incorporating possibly a more toxic type, e.g. long MWCNTs, should include appropriate warning labels.

CNTs, of course, are only one category among many other nanomaterials either in current use or undergoing research for future use. It is likely that OELs will be needed for many of these materials; some of the difficult issues discussed here are unique to CNTs due to their being fibers, but the use of mass metrics will always present difficulties for nanomaterials. Precisely because they are so small, nanoparticle mass concentrations are typically very low, and masked

by the presence of other, larger particles in the same sample. Thus, we can expect significant difficulties in setting all OELs for nanomaterials. Nonetheless they will be needed, and the occupational health community needs to face this challenge head on.

Conclusion

The association between asbestos exposure and mesothelioma was established more than fifty years ago, but the mesothelioma epidemic continues. An estimated 107,000 people worldwide die from this disease every year; many of those now dying from mesothelioma are family members of the worker who had the primary exposure (Markowitz 2015). It is imperative that this disaster not be seen with other high aspect ratio particles such as CNTs. Strong action needs to be taken to minimize exposures to CNTs type 7 specifically and CNTs in general, and any CNT OEL should be consistent with the need to minimize exposures. The conclusions of Schulte, *et al.*, (Schulte et al. 2012) are worth repeating:

In the evolution of human civilizations, learning from the history and not repeating it has been a key guiding principle. Society can learn from how asbestos was inappropriately considered and not make the same mistake with CNTs. It is possible to safely realize the benefits of CNTs, but it will require rigorous and timely actions. The time to act is now.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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