Carbon Nanotube Risk Assessment

Implications for Exposure and Medical Monitoring

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Objective: Quantitative risk estimates using toxicology data provide information for risk management to protect workers with potential exposure to carbon nanotubes (CNTs). **Methods:** Dose–response data from subchronic inhalation studies in rats were used in benchmark dose modeling. Dose was airborne mass concentration of multiwalled CNTs. Responses included pulmonary inflammation, lipoproteinosis, and fibrosis. **Results:** Estimated human-equivalent concentrations to the rat lowest observed adverse effect levels were similar to some workplace airborne concentrations of CNTs. Working lifetime risk estimates of early-stage adverse lung effects were more than 10% at the limit of quantification (7 $\mu g/m^3$) of the National Institute for Occupational Safety and Health analytical method for measuring CNT airborne concentrations. **Conclusions:** Exposure monitoring and control are the primary occupational health measures to protect workers from potential exposure to CNT. Medical monitoring for early detection of occupational respiratory diseases may also be warranted.

Although carbon nanotubes (CNTs) may be thought of as a recent discovery, the first images of CNTs were apparently first published in Russia in the early 1950s.[1] In the 1990s, enhanced production methods were developed,[2] enabling commercial production and interest in applications of CNTs. CNT structures consists of single or multiple graphene sheets, resulting in single-wall or multiwall CNTs (SWCNTs and MWCNTs, respectively). The diameter of individual SWCNT is approximately 1 nm and the diameter of individual MWCNT is approximately 2 to 100 nm. Both SWCNTs and MWCNTs tend to form agglomerated structures of up to several micrometers in diameter. The length of individual CNT can be a few micrometers up to several millimeters. Nanotubes have been constructed with length-to-diameter ratio of 132 million,[3] substantially greater than any other material. There are many variations of CNTs including different metal content. CNTs are of high commercial interest due to their unique properties. CNTs are several times stronger than steel at the same weight; and they provide excellent thermal and electrical conductivity. CNTs are used in composites, aerospace, electronics, and energy applications. Production volumes are anticipated to increase,[4] and consequently the number of workers with potential exposure to CNTs is also likely to increase.

National Institute for Occupational Safety and Health (NIOSH) is a leading institute in assessing workplace hazards including that from CNTs. NIOSH is authorized by the Occupational Safety and Health Act of 1970 to develop recommended occupational safety and health standards.[5] NIOSH conducts toxicological research, risk assessment, exposure assessment, and health surveillance, and develops criteria for recommended standards. These recommended standards are formally transmitted to Occupational Safety and Health Agency, which is the agency responsible for promulgating occupational safety and health regulations in the United States. The risk assessment process provides input to developing occupational safety and health, including occupational exposure limits (OELs).

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METHODS

Critical Dose Estimation

Two examples of using toxicological data from animal studies in risk assessment are illustrated in this article, which involve estimating a critical dose of either (1) a lowest observed adverse effect level (LOAEL) or (2) a benchmark dose (BMD). The LOAEL approach is used here to estimate equivalent exposures in workers to those associated with adverse effects observed in animal studies. This approach provides estimates of the level of exposure that indicates potential adverse effects in humans. Comparison with occupational exposure data provides information on whether the potential exposure in workers may be sufficient to indicate the need for medical monitoring.

The identification of a LOAEL or NOAEL (no observed adverse effect level) is dependent on the probability of detecting an effect, which depends on the sample size (number of individuals), sensitivity of the analytical method, and the probability of disease (which depends on dose and potency). A *LOAEL* is the lowest dose associated with a statistically significant increase in an adverse response in an exposed group. A LOAEL depends on the dose spacing in the experiment and the number of animals. An adverse effect is often (but not always) nonreversible and associated with a functional impairment or development of a chronic adverse health outcome. The effect concentrations (eg, LOAELs) in subchronic (13-week) studies tend to be higher than those in chronic studies.[6] In the analyses shown here, the subchronic effect concentrations are converted to the estimated equivalent lung doses, accounting for duration of exposure, so may better estimate the chronic effects than did concentrations without consideration of duration as reported by Kalberlah et al.[6]

BMD methods are used to estimate doses associated with specified risk (eg, 10%) and to provide a standardized method of estimating a point of departure for extrapolation to lower risk levels (which may be acceptable or feasible), and to estimate exposure limits for up to a full working lifetime. A benchmark response (BMR) is an adverse effect level (eg, 10%) that is considered biologically and statistically significant, and which may include early subclinical effects linked to increased risk of developing chronic adverse effects and disease. A BMD is the dose associated with a specified level of risk of the BMR. Thus, although the response endpoint associated with a LOAEL may be qualitatively similar to a BMR, a BMR is linked to a risk estimate, and is less dependent on the dose spacing and the slope of the dose–response relationship. BMD methods can be used in quantitative risk assessment, which is defined as an estimation of the severity and likelihood of an adverse effect associated with exposure to a hazardous agent.[7,8]

The steps in estimating occupational risks from animal dose–response data are illustrated in Fig. 1. For occupational aerosols, such

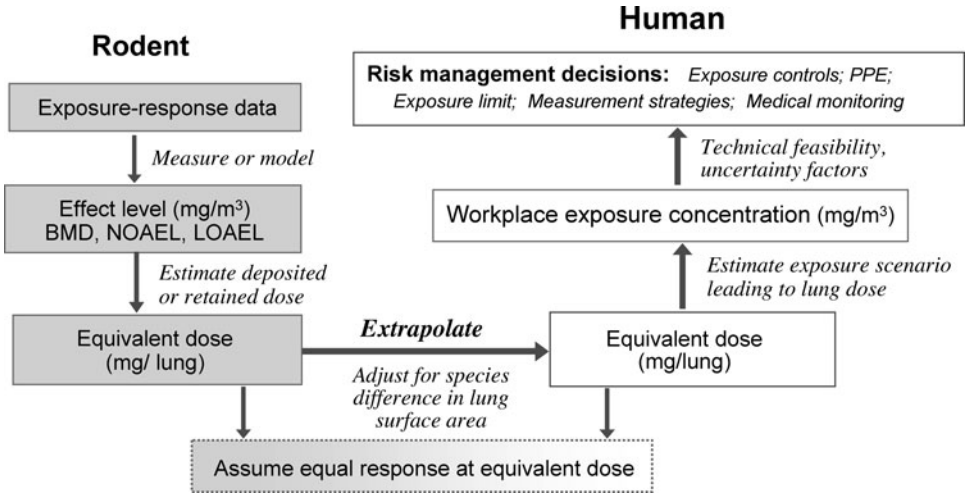

FIGURE 1. Risk assessment methods using animal data of airborne particles, for example, carbon nanotubes. BMD, benchmark dose; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; PPE, personal protective equipment.

as airborne CNTs, the animal dose–response data are extrapolated to predict risk in workers if exposed up to a full (45-year) working lifetime. This requires estimation of the human lung dose corresponding to a critical (adverse) effect (BMR or LOAEL response) or absence of effect (NOAEL) in the animal. The animal lung dose (measured or estimated) is extrapolated to humans using data on factors that influence species-specific lung dose (particle size-specific regional deposition in the lungs, breathing rates, exposure scenario). In the absence of other data, it is assumed that, at an equivalent dose, the human and animal response is equal. The workplace exposure scenario (concentration and duration) that would result in the human-equivalent lung dose is estimated using a human lung dosimetry model. Currently, these models have not been evaluated for CNTs. Nevertheless, according to aerosol physics principles, for particles larger than approximately 500 nm in diameter, the aerodynamic diameter (which accounts for inertial behavior regardless of density and shape) accurately predicts the particle deposition efficiency in the respiratory tract regions.[9,10] Although individual CNTs have diameters from 1 to 10s of nanometers, the airborne CNT structures are often large heterogeneous agglomerates made up of individual CNTs. The physical size of these airborne CNT agglomerates are typically in the micrometer size range. For example, the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the aerosolized CNTs in the Ma-Hock et al[11] study were approximately 1.2 and 2.7, respectively, and in the Pauluhn[12] study were approximately 2.74 and 2.11, respectively. Furthermore the aspect ratio, based on the overall envelop size of the CNT structures, is typically less than 10.[13] Therefore, it is reasonable to assume that the spherical particle-based lung deposition models, though not yet validated for CNT, should provide reasonably accurate estimates of their deposition efficiency. The lung clearance model predictions may be more uncertain, however, given that CNT clearance has been shown to be slower than expected for a given mass of poorly soluble low-toxicity spherical particles.[12,14]

The estimated equivalent workplace exposure concentration (to that associated with a critical effect in the animal studies) is used to develop OELs and to develop other risk management strategies such as engineering control requirements, use of personal protective equipment, and need for medical monitoring. For example, if workplace exposures are demonstrated to be considerably below the health-based OEL, then the engineering controls typically would be considered to be effective, and periodic exposure monitoring may be sufficient to verify the continued effectiveness of controls. However, if exposures are above the OEL, then additional measures are clearly needed to reduce exposures including improved engineering controls and interim use of respirators (until exposures are demonstrated to be maintained below OELs). In addition, medical monitoring may be indicated for early detection of any adverse effects from exposure. Medical monitoring decisions depend on many factors, including the availability of appropriate medical tests, the potential for accidental exposures (even in a well-controlled workplace), and the concerns of workers.[15]

Animal Data

Risk assessment methods are illustrated using two recent subchronic (13-week) inhalation studies of MWCNTs in rats.[11,12] The exposure concentrations in Ma-Hock et al[11] were 0, 0.1, 0.5, and 2.5 mg/m^3; the LOAEL (as reported by the authors) was 0.1 mg/m^3 for granulomatous inflammation, of which 30% of rats had developed a minimal or higher grade based on histopathology. At 0.5 mg/m^3, 85% of the rats had developed lipoproteinosis (0% at 0.1 mg/m^3). The exposure concentrations in Pauluhn[12] were 0, 0.1, 0.45, 1.62, and 5.98 mg/m^3. A NOAEL was identified at 0.1 mg/m^3 and the LOAEL was 0.4 mg/m^3 for pulmonary inflammation (based on elevated polymorphonuclear leukocytes in bronchioalveolar lavage fluid) and alveolar interstitial thickening (a measure of pulmonary fibrosis) of which 90% of rats had developed a minimal or higher grade based on histopathology. Although alveolar interstitial thickening was not evaluated in the Ma-Hock et al[11] study, the findings of granulomatous inflammation and lipoproteinosis are consistent with the development of pulmonary fibrosis (silicosis) in rodents and humans from exposure to respirable crystalline silica.[16–18]

Concerning the severity of biological response, it is useful to evaluate where along the biological continuum from exposure to disease[19] would these subchronic responses in rats (or human equivalent) lie. Pauluhn[12] showed the persistence of alveolar interstitial thickening at 26 weeks after the end of the 13-week exposure (ie, at week 39). On the contrary, these effects are relatively early-stage (minimal or mild fibrosis in Pauluhn[12] and Ma-Hock et al[11] studies, and there has not been an evaluation of whether these effects are associated with functional impairment in the animals or would be clinically significant in humans. The rat exposures were only for 13 weeks and there is uncertainty about the chronic consequence of these persistent effects. Nevertheless, alveolar interstitial

thickening observed in animal studies has been considered relevant to humans and to indicate "fundamental structural remodeling."[20,21] Thus, these effects observed in the rat subchronic studies appear to be early biological effects that could result in altered structure and function.[19]

Risk Assessment Examples

The following examples of risk estimation methods are intended to describe simple, data-based estimates using minimal assumptions.

Example 1: Human-Equivalent LOAEL

The purpose of this exercise is to estimate the exposures in workers that are equivalent to the rat subchronic LOAELs, using data from the Ma-Hock et al[11] study as an example.

The first step is to estimate, as follows, the deposited lung dose of MWCNTs in rats at the end of the 13-week exposure:

$$\text{airborne concentration} \times \text{duration} \times \text{ventilation rate} \times \text{deposition fraction} = \text{deposited dose} \quad [1]$$

eg, 0.1 mg/m^3 × (6 hr/d × 5 d/wk × 13 wk) × 0.013 m^3/hr × 0.072 = 0.035 mg/rat lung, where the ventilation rate in the rat is 0.21 L/min × 0.001 m^3/L × 60 min/hr. The ventilation rate is based on species and body weight,[22,23] assuming 300 g average body weight for male and female rats in Ma-Hock et al.[11] The deposition fraction was estimated on the basis of particle size distribution (MMAD and GSD) in the Multiple-path Particle Dosimetry (MPPD) 2.0, lung dosimetry model, assuming unit density (to be consistent with the definition of aerodynamic diameter).[24] [Note: These same calculations were applied to the Pauluhn,[12] except using values of 0.015 m^3/hr (ventilation rate for rat of body weight 369 g at 0.25 L/min) and 0.046 deposition fraction based on the reported MMAD and GSD. In addition, these MPPD 2.0 estimates of MWCNTs retained in rat lungs after 13 weeks of inhalation exposure were found to be fairly similar (about 15% to 40% higher) than those approximated from a graph of the measured matrix-bound cobalt that was retained in rat lungs[12]].

The next step, as follows, is to extrapolate the rat lung dose (Equation 1) to humans:

$$\text{human lung dose} = \text{rat lung dose} \times \text{human/rat alveolar surface area } (102\ \text{m}^2/0.4\ \text{m}^2) = 9.0\ \text{mg in human lungs}, \quad [2]$$

where average human and rat alveolar epithelial surface area estimates are from morphometric analyses[25] (although estimates vary for the average adult human alveolar surface area, for example, US Environmental Protection Agency[22] cites 54 m^2). Normalizing on surface area of the respiratory tract region(s) is typically used for insoluble particles, which deposit and clear along the respiratory tract surface.[22] In this case, the alveolar surface area is used because it is a primary site of respirable particle deposition and also the target tissue for development of pulmonary fibrosis.

Finally, the workplace exposure scenario that would result in the human-equivalent lung dose is estimated. In this example, the occupational duration approximately equivalent to a 13-week exposure in animals is used in estimating the human-equivalent exposure scenario to that associated with the rat LOAEL. That is, 13 week is to 104 week (2-year chronic bioassay in rats) as 5.6 years is to a 45-year working lifetime (given that an animal chronic bioassay is typically assumed in occupational risk assessment to be equivalent to a 45-year working lifetime). The estimated human 8-hour time-weighted average (TWA) concentration over 5.6 years that would result in the human-equivalent lung dose in the pulmonary (alveolar) region is then calculated as follows:

$$\text{human-equivalent lung burden (mg)}/[\text{air intake} \times \text{exposure} \times \text{deposition fraction}] = 9.0\ \text{mg}/[9.6\ (\text{m}^3/\text{d}) \times (5\ \text{d/wk} \times 50\ \text{wk/yr} \times 5.6\ \text{yr}) \times 0.099] = [0.00676\ \text{mg/m}^3 \quad [3]$$

where the human-equivalent lung burden is from (Equation 2); the air intake is for the reference worker;[26] and the alveolar deposition fraction is based on the MMAD (GSD) as in (Equation 1), estimated in MPPD 2.0 (Yeh and Schum deposition model).[24]

Thus, exposure to 6.8 μg/m^3 (as 8-hour TWA concentration in air) for a duration of 5.6 years is estimated to be equivalent to a subchronic (13-week) LOAEL of 0.1 mg/m^3 in rats (for granulomatous inflammation of minimal or greater severity) in Ma-Hock et al,[11] based on the estimated deposited lung dose. Using this same approach, the human-equivalent concentrations to the other LOAEL responses were estimated at approximately 6 to 35 μg/m^3 (Table 1). Concerning potential workplace exposures, it is relevant to note that the limit of quantification of the method used to measure airborne CNTs is 7 μg/m^3 (as an 8-hour TWA airborne concentration).[27] This finding indicates a critical need to develop more sensitive methods for measuring workplace airborne exposures to CNTs.

Example 2: BMD Estimation

The subchronic inhalation data in rats[11,12] are used to illustrate BMD modeling and estimation of working lifetime risk estimates. Figures 2 and 3 show the fit of a multistage (polynomial degree 2) model to the rat exposure-response data to estimate a 10% excess (added) risk of the BMR (granulomatous inflammation or pulmonary fibrosis of minimal or higher grade). The multistage model was the only one of the BMD software dose–response models[28] that converged and provided adequate fit ($P > 0.1$ in a goodness of fit test)[29] to these sparse data (which have only one dose each between 0% and 100% response) (Figs. 2 and 3).

In this example, the BMD is an exposure concentration (also known as benchmark concentration) because it is based on exposure data rather than lung dose data. The BMD is the maximum likelihood estimate, and the BMDL is the lower 95% confidence limit estimate.

TABLE 1. Human-Equivalent Estimated Concentrations to Effect Levels Observed in Rat Subchronic Inhalation Studies of MWCNTs

Compound and Study	Adverse Effect	Rat Effect Concentration (mg/m^3)	Human- Equivalent 8-hr TWA Concentration in 5.6 yrs (μg/m^3)
MWCNT 9.6% Al_2O_3, 0.5% Co (Ma-Hock et al[11])	Granulomatous inflammation	0.1 LOAEL	6.8
	Lipoproteinosis	0.5 LOAEL	35
MWCNT 0.5% Co (Pauluhn[12])	Pulmonary inflammation	0.1 NOAEL	5.9
	Alveolar interstitial thickening	0.45 LOAEL	27

LOAEL, lowest observed adverse effect level; MWCNT, multiwalled carbon nanotube; NOAEL, no observed adverse effect level; TWA, time-weighted average.

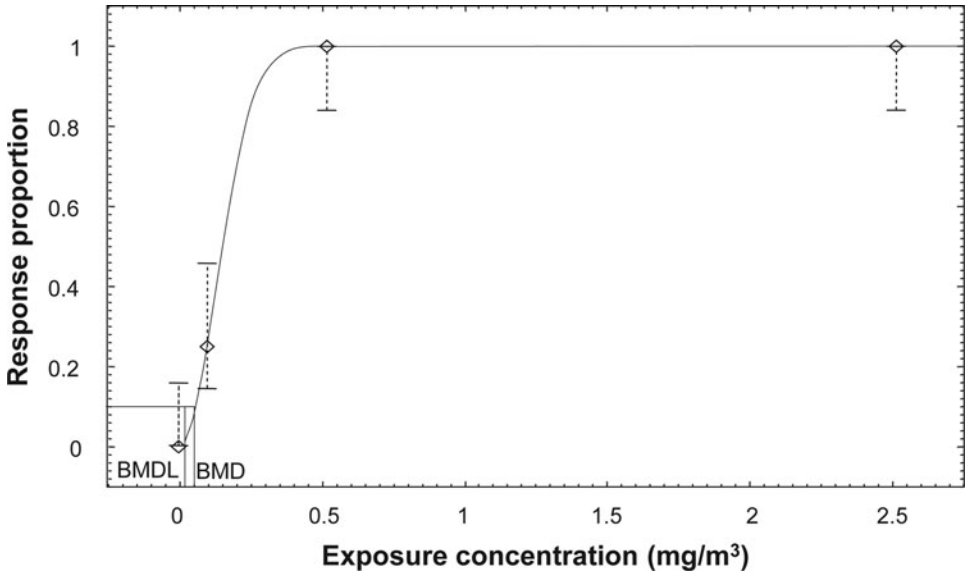

FIGURE 2. BMD estimation—granulomatous inflammation in rats.[11] Multistage model, polynomial degree 2; $P = 0.99$. BMD(L), 10% excess risk = 0.06 (0.02) mg/m^3. BMD, benchmark dose maximum likelihood estimate; BMDL, BMD lower 95% confidence limit.

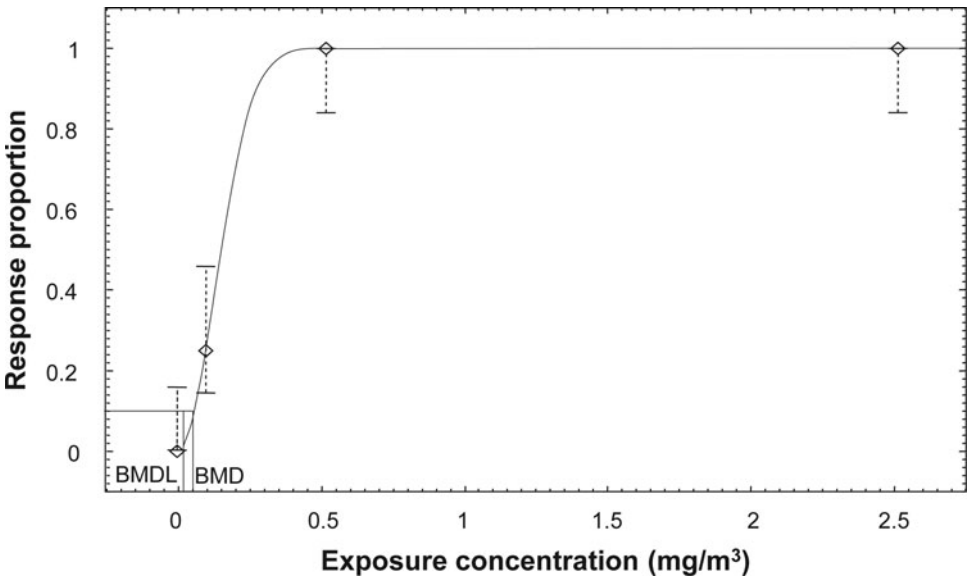

FIGURE 3. BMD estimation—alveolar interstitial thickening in rats.[12] Multistage model, polynomial degree 2, $P = 0.88$. BMD(L), 10% excess risk = 0.1 (0.05) mg/m^3. BMD, benchmark dose maximum likelihood estimate; BMDL, BMD lower 95% confidence limit.

BMD(L) is used here to indicate both the BMD and the BMDL estimates. The BMD(L) estimates corresponding to a 10% BMR are 0.06 (0.02) mg/m^3 in Ma-Hock et al[11] and 0.1 (0.05) mg/m^3 in Pauluhn[12] (Figs. 2 and 3). Because these dose–response data are sparse near the 10% BMR, especially in the Pauluhn,[12] it is necessary to evaluate further whether these BMD(L) estimates are reasonable. Given that the model optimization algorithm seeks the best fit to all the data including the maximum (100%) responses, a common approach is to drop the highest dose group and refit the model to evaluate the effect on the BMD(L) estimates.[29] The results of these model refits showed little effect (up to four decimal places) on the BMD(L) estimates. In addition, as would be expected, these BMD(L) estimates are similar to or lower than the LOAELs and NOAEL in those studies; LOAEL of 0.1 mg/m^3 in Ma-Hock et al;[11] and LOAEL of 0.4 mg/m^3 and NOAEL of 0.1 mg/m^3 in Pauluhn.[12] Thus, the BMD(L) estimates appear to be reasonable despite the less-than-ideal dose–response relationships (Figs. 2 and 3).

Next, the BMD(L) estimates (as exposure concentration) are used to estimate an equivalent lung dose in rats, in this case, either the deposited or the retained lung burden at the end of the 13-week study. These lung dose estimates were obtained by using data on the MWCNT particle size MMAD (GSD) and unit density in the rat model in MPPD 2.0;[24] and the rat lung doses were extrapolated to humans by normalizing on lung surface area (as in example 1).

In this example, a 45-year working lifetime exposure concentration associated with human-equivalent lung doses (deposited dose or retained dose) was estimated using the same particle size data (as in the rat model) for the human model in MPPD 2.0 (Yeh and Schum deposition model).[24] This method provides estimates of the working lifetime exposure concentration associated with a 10% excess risk of early-stage adverse lung effects.

In the final step to develop a health-based OEL, the 10% BMDL would be used as the point of departure to extrapolate to lower doses and risks (eg, model-based or linear extrapolation, or uncertainty factors). However, this step is beyond the scope of this example.

RESULTS

On the basis of the methods and assumptions described in example 1, Table 1 gives the estimated human-equivalent concentrations to the NOAEL or LOAEL from the rat subchronic inhalation studies of multiwall CNTs.[11,12] No uncertainty factors were applied to these estimates. These are not considered safe levels, but are the levels estimated to be associated with the effect levels in the animal studies. These estimates are based on the equivalent deposited lung dose.

Results from example 2, based on BMD(L) estimation and extrapolation to humans over a full (45-year) working lifetime are shown in Table 2. In this case, the human-equivalent BMDL estimates indicate that working lifetime exposure concentrations to approximately 0.2 to 2 $\mu g/m^3$ would be associated with a 10% excess risk of early-stage adverse lung effects (pulmonary inflammation and fibrosis) in workers.

Published exposure measurements of workplaces producing or using CNTs are provided in Table 3. These airborne concentrations ranged from not detected to more than 8000 $\mu g/m^3$, with many concentrations in the 10s of micrograms per cubic meter. Although most of these samples were short-term (eg, 30-min), task-based measurements of total carbon (not specifically CNTs), these data indicate the potential for workers to be exposed to airborne concentrations at or above those associated with early-stage adverse lung effects in rats.

DISCUSSION

Workplace exposures to 8-hour TWA airborne concentrations of approximately 6 to 35 $\mu g/m^3$ MWCNTs over 5.6 years were estimated to be equivalent to the LOAEL or NOAEL in the two rat subchronic inhalation studies[11,12] (Table 1). Working lifetime (45-year) equivalent airborne concentrations associated with 10% excess risk of early-stage adverse lung responses were approximately 0.2 – 2.0 $\mu g/m^3$ (BMDL estimates) (Table 2). Limited workplace exposure data indicate the potential for workers to be exposed to MWCNTs, SWCNTs, and carbon nanofibers (CNFs) at these concentrations or higher (Table 3). Although the MWCNT data from the rat subchronic inhalation studies are used in this paper to illustrate risk estimation, additional animal studies of SWCNTs and CNFs (with routes of exposure by pharyngeal aspiration, intratracheal instillation, or short-term inhalation) have shown similar lung responses also at low mass doses (recently reviewed by NIOSH[27]). Thus, until more data are available, it is considered prudent to use extra precaution in controlling exposures to all types of CNT and CNF.[27]

The risk estimates for MWCNTs are based on early-stage adverse effects (e.g., alveolar interstitial thickening indicating early-stage fibrosis); however, those effects persisted up to four months after the end of exposure.[12] These findings indicate the potential for

TABLE 2. Working Lifetime 8-Hour TWA Concentration Associated With 10% Excess Risk

		Human-Equivalent 8-hr TWA Concentration Over 45-yr Working Lifetime	
Study	**Response**	**BMD_{human} ($\mu g/m^3$)**	**$BMDL_{human}$ ($\mu g/m^3$)**
Deposited lung dose*			
Ma-Hock et al[11]	Granulomatous inflammation	0.51	0.19
Pauluhn[12]	Alveolar interstitial thickening	0.77	0.38
Retained lung dose*			
Ma-Hock et al[11]	Granulomatous inflammation	2.7	1.0
Pauluhn[12]	Alveolar interstitial thickening	4.2	1.9

*Using aerodynamic size data reported in subchronic studies, assuming spherical particle lung deposition and clearance kinetics (Multiple-path Particle Dosimetry version 2.0).[24]

Limit of quantification of analytical method to measure exposure is approximately 7 $\mu g/m^3$ as an 8-hr TWA concentration.[27]

BMD, benchmark concentration maximum likelihood estimate; BMDL, BMD lower 95% confidence limit; TWA, time-weighted average concentration.

TABLE 3. CNT Occupational Exposure Data

Material and Process	**Concentration($\mu g/m^3$)***	**Reference**
SWCNT—production facility	10–53	Maynard et al[30]
MWCNT—research laboratory, before and after controls	37–434 ND–39	Han et al[31]
CNF composite—weighing, mixing, cutting	64–1094	Methner et al[32]
MWCNT composite—wet or dry cutting	54 2110–8380	Bello et al[33]

*Most are short-term (eg, 30-min) samples of total carbon.

CNF, carbon nanofiber; CNT, carbon nanotube; MWCNT, multiwalled carbon nanotube; ND, not detected; SWCNT, single-walled carbon nanotube.

chronic lung disease and need for effective measurement and control of workplace exposures. They also suggest that medical monitoring may be needed to detect early-stage adverse lung effects, including pulmonary inflammation and fibrosis, which workers may be at risk of developing at potential workplace exposures in certain jobs.

It should be noted that no uncertainty factors were used in these risk estimation examples. According to standard occupational health practice, a human-equivalent exposure to a NOAEL, a LOAEL, or a BMD(L) associated with a 10% excess risk would not be used directly to develop an OEL for humans. Instead, these estimates would typically be used as points of departure to estimate lower levels of risk or to apply uncertainty factors.

To reduce the uncertainty in risk estimation of CNTs, additional information and research are needed in several areas. For example, additional information is needed to assess whether the observed rat subchronic lung responses would correspond to functionally or clinically significant responses in humans. In addition, it is unclear whether these early responses would be detected in standard medical tests. Fibrosis in human lungs is generally detected by chest radiography or computed tomography. Yet, there is no information at this time to determine whether the amount of pulmonary fibrosis (alveolar interstitial thickening) observed in the animal studies (eg, Pauluhn[12]) would be readily detectable in humans. More sensitive medical screening or biomarker tests may be needed to detect these early effects and to intervene to prevent potential development of occupational lung disease in workers producing or using CNTs.

Research is needed on the chronic effects of exposure to CNTs, including potential carcinogenic effects. Studies are needed on the effect of dose rate on the development of adverse lung effects from CNT exposure. For example, it is not known whether the cumulative lung doses associated with adverse lung effects in the rat subchronic studies would be associated with more or less severe responses if the same dose were received over a longer period of time (eg, biological adaptation and/or residence time may affect the long-term lung response to a given dose). It is also uncertain whether human lungs and rat lungs have similar sensitivity to CNTs, as humans are known to be more sensitive to some pulmonary toxicants.[6]

Because CNTs are produced with varying physical-chemical characteristics, data are needed on the extent to which these various factors may influence the hazardous properties of the CNT, in addition to the effect of the carbon composition of all CNTs. Evidence that particle shape, size, and surface area influence the lung response to carbon particles is seen in the comparison between the lung responses to ultrafine carbon black (ufCB)[34] versus MWCNTs[11,12] based on the same study design (13-week inhalation) and animal species (rat). Comparing the study LOAELs, the MWCNT was at least 10 times more potent than the ufCB (LOAEL of 7 mg/m^3 for ufCB vs 0.1 or 0.4 mg/m^3 for MWCNTs).[11,12] Although LOAELs and NOAELs are dependent on dose spacing, the NOAEL of 0.1 mg/m^3 in one study of MWCNTs[12] was an order of magnitude lower than the NOAEL of 1 mg/m^3 in a study of ufCB.[34]

Measurements of CNT airborne characteristics are needed to determine the extent to which CNT particle size and morphology may influence lung deposition and retention, after accounting for aerodynamic diameter. It would be useful to know how the characteristics of CNT materials in the workplace compare with those in the animal studies, and to have sufficient data to link those characteristics to the hazardous properties of the CNTs in order to prevent adverse health effects in workers. For example, in a recent study in mice, dispersed SWCNT structures were associated to a greater extent with interstitial fibrosis whereas the agglomerated structures were more clearly associated with granulomas.[35] Until specific particle size characteristics are linked to qualitative and quantitative differences in toxicity, it would be prudent to apply the available CNT data (which include studies in rats and mice exposed to SWCNTs or MWCNTs with different metal content) to the risk assessment and risk management of other CNT materials, erring toward greater precaution in the absence of more specific information.

Finally, there is a critical need for more data on worker breathing zone concentrations of CNTs, including in workers who are using products containing CNTs or the structurally-similar CNFs. Published exposure measurements of airborne concentrations of CNTs, or total carbon in work areas producing or using CNTs (Table 3), indicate the potential for workers to be exposed to levels of CNTs associated with granulomatous inflammation, lipoproteinosis, and early-stage, persistent pulmonary fibrosis in animal studies (Table 1). Workplace exposures to airborne concentrations of approximately 7 to 35 mg/m^3 CNT over 5.6 years were estimated to be equivalent to the LOAELs in the two currently published rat subchronic inhalation studies.[11,12] These limited exposure data in workers indicate the potential for workers to be exposed at airborne concentrations of CNTs exceeding the 8-hour limit of quantification (7 μg/m^3) of the measurement method,[27] which is associated with more than 10% excess risk of early-stage adverse lung effects based on the animal data (Table 2). These findings support the need for effective monitoring and control of CNT exposures as the primary occupational health measure to prevent adverse health effects. Medical monitoring may also be needed as a secondary prevention measure to detect early inflammatory and fibrotic lung effects in workers. Finally, there is a need to develop and validate biomarkers for early adverse biological effects of CNTs.

CONCLUSIONS

MWCNT exposure in rats caused adverse lung effects at exposures at least an order of magnitude lower than did ufCB in subchronic inhalation studies. Current workplace exposures in some jobs or tasks involving production or use of CNTs indicate the potential for early-stage adverse lung effects based on similar estimated lung doses in animals studies. Risks of more than 10% for early-stage pulmonary fibrosis are estimated from animal dose–response data at the limit of quantification of 7 μg/m^3 (as 8-hour TWA concentration) of the measurement method for airborne elemental carbon including CNTs (NIOSH method 5040). These findings have implications regarding the need to develop OELs, improved workplace exposure measurement, and effective engineering controls, and to consider medical monitoring programs for early detection of occupational respiratory diseases in workers producing or using CNTs.

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