Annals of Work Exposures and Health, 2019, Vol. 63, No. 2, 158–172
doi: 10.1093/annweh/wxy102
Advance Access publication 4 February 2019
Original Article

Original Article

Predicting Occupational Exposures to Carbon Nanotubes and Nanofibers Based on Workplace Determinants Modeling

Matthew M. Dahm[1*], Stephen Bertke[1] and Mary K. Schubauer-Berigan[1,2]

[1]Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, 1090 Tusculum Avenue, MS-R14, Cincinnati, OH 45226, USA; [2]Present address: Evidence Synthesis and Classification Section, International Agency for Research on Cancer, Lyon, France.

*Author to whom correspondence should be addressed. Tel: +1-513-458-7136; fax: +1-513-841-4486; e-mail: mdahm@cdc.gov

Submitted 12 June 2018; revised 6 November 2018; editorial decision 8 November 2018; revised version accepted 21 November 2018.

Abstract

Background: Recent cross-sectional epidemiologic studies have examined the association between human health effects and carbon nanotube and nanofiber (CNT/F) workplace exposures. However, due to the latency of many health effects of interest, cohort studies with sufficient follow-up will likely be needed. The objective of this study was to identify workplace determinants that contribute to exposure and develop predictive models to estimate CNT/F exposures for future use in epidemiologic studies.

Methods: Exposure measurements were compiled from 15 unique facilities for the metrics of elemental carbon (EC) mass at both the respirable and inhalable aerosol size fractions as well as a quantitative analysis performed by transmission electron microscopy (TEM). These metrics served as the dependent variables in model development. Repeated personal samples were collected from most of the 127 CNT/F worker participants for 252 total observations. Determinants were categorized as company-level or worker-level and used to describe the exposure relationship within the dependent variables. The influence of determinants on variance components was explored using mixed linear models that utilized a backwards stepwise selection process with a lowering of the AIC for model determinant selection. Additional ridge regression models were created that examined predictive performance with and without all two-way interactions. Cross-validation was performed on each model to evaluate the generalizability of its predictive capabilities while predictive performance was evaluated according to the corresponding R^2 value and root mean square error (RMSE).

Results: Determinants at the company-level that increased exposure included an inadequate or semi-adequate engineering control rating, increasing average CNT/F diameter/length, daily quantities of material handled from 101 g to >1 kg and >1 kg, the use of CNF materials, the industry type of hybrid producer/user, and the expert assessment of a high exposure potential. Worker-level determinants associated with higher exposure included handling the dry-powdered form of CNT/F, handling daily quantities of material >1 kg, direct/indirect exposure, having the job title of engineer, using a respirator, using a ventilated or unventilated enclosure, and the job task of powder handling. The mixed linear models explained >60% of the total variance when using all company- and worker-level determinants to create the three exposure models. The cross-validated RMSE values for each of the three mixed models ranged from 2.50 to 4.23. Meanwhile, the ridge regression models, without all two-way interactions, estimated cross-validated RMSE values of 2.85, 2.23, and 2.76 for the predictive models of inhalable EC, respirable EC, and TEM, respectively.

Conclusions: The ridge regression models demonstrated the best performance for predicting exposures to CNT/F for each exposure metric, although they only provided a modest predictive capability. Therefore, it was concluded that the models alone would not be adequate in predicting workplace exposures and would need to be integrated with other methods.

Keywords: carbon nanofibers; carbon nanotubes; cohort; exposure determinants; predictive exposure modeling

Introduction

Carbon nanotube and nanofibers (CNT/F), along with other nanomaterials, have been described as a technology with the capability to transform society at large, with a broad potential for application across the most varied sectors of the economy (Invernizzi, 2011). Carbon nanotube commercial activities have grown over the past several decades with worldwide production capacity increasing at least 10-fold from 2006 to 2013 (De Volder *et al.*, 2013). However, in 2014, The International Agency for Research on Cancer (IARC) concluded that one specific form of multiwalled carbon nanotube (MWCNT) was possibly carcinogenic to humans (Group 2B). Meanwhile, evidence for carcinogenicity of single-walled carbon nanotubes (SWCNTs) and all other types of MWCNTs was insufficient and they were categorized as Group 3, not classifiable as to their carcinogenicity (Grosse *et al.*, 2014; IARC, 2017). Concerns have also risen for other health outcomes from inhalation exposures to CNT/F, which include pulmonary fibrosis and inflammation as well as immunological and cardiovascular effects (Erdely *et al.*, 2009; Mitchell *et al.*, 2009; Simeonova and Erdely, 2009; Pauluhn 2010; Murray *et al.*, 2012; Porter *et al.*, 2013; Oberdorster *et al.*, 2015; Bishop *et al.*, 2017).

The classification by IARC was predominantly based upon animal toxicity studies, since little human health data existed at the time. Since then, several cross-sectional epidemiologic studies have been published which have focused on developing exposure–response relationships between early biological markers of effect and exposures to CNT/F. These studies have generally used consistent exposure metrics which include elemental carbon (EC) mass and some form of microscopy-based structure count (Lee *et al.*, 2015; Fatkhutdinova *et al.*, 2016; Shvedova *et al.*, 2016; Vlaanderen *et al.*, 2017; Beard *et al.*, 2018; Kuijpers *et al.*, 2018; Schubauer-Berigan *et al.*, 2018). However, since these were designed as cross-sectional studies, they inherently lack the ability to demonstrate causality in their findings (Liou *et al.*, 2015).

These cross-sectional studies are an integral first step in determining if exposure to CNT/F can cause health effects, but due to the long latency period for many of the health effects of concern, longitudinal studies are needed featuring consensus data collection and appropriate exposure assessment methodologies. These longitudinal studies will likely rely on current and retrospective CNT/F workplace exposure data, which represents a challenge, as many facilities will have limited or incomplete exposure records (Guseva Canu *et al.*, 2017). To fill this data gap, additional exposure measurements or estimates of worker exposure will need to be made using professional judgment, extrapolating known data, or through the development of quantitative statistical modeling that can incorporate workplace factors and exposure determinants (Seixas and Checkoway, 1995).

As part of an ongoing epidemiologic study of US workers exposed to carbon nanotubes and nanofibers, the objective of this study was to develop and validate predictive models to quantitatively estimate current and historical levels of exposures using the commonly used metrics of EC mass and microscopy-based structure counts for future use in longitudinal (e.g. cohort) studies. An additional objective of this study was to classify common job tasks performed among the various US CNT/F industries.

Methods

Description of exposure database

The exposure database included data on 108 workers from 12 US facilities handling or producing CNT/F that were collected between 2012 and 2014 as part of a cross-sectional epidemiologic study (Beard *et al.*, 2018; Dahm *et al.*, 2018; Schubauer-Berigan *et al.*, 2018). Unpublished data for an additional 23 workers were included in the database from five US facilities visited in 2016. Two of the five facilities were part of the original cross-sectional study, but were re-visited due to significant changes in worker-level determinants. The remaining three facilities had not been previously visited by NIOSH. Additionally, four participants from the exposure database were excluded from the analyses due to insufficient exposure information, leaving a total of 127 participants from 15 unique facilities handling and/or producing CNT/F across the USA.

Repeated measurements were collected as personal samples over two full work-shifts from 117 of the 127 participants, while nonrepeated measurements were collected from seven participants and the remaining three participants had three or four samples collected, creating a total exposure database of 252 personal measurements with observations. Personal exposures were assessed for CNT/F based on three exposure metrics, which served as the dependent variables for each of the three predictive models. The exposure metrics included the mass of elemental carbon (EC) at both the respirable and inhalable aerosol size fractions, reported as $\mu g\ m^{-3}$, as well as a quantitative analysis by transmission electron microscopy (TEM), reported as CNT/F structures cm^{-3}. Data collection and analysis were performed uniformly for the additional facilities visited in 2016 using the sampling and analysis methodologies discussed in Dahm *et al.* (2018).

All values for EC were background-corrected due to the potential for interference by anthropogenic sources of EC following methods outlined in Dahm *et al.* (2015, 2018). Samples below the limit of detection (LOD) [n = 47 (18.7%), respirable; n = 17 (6.7%), inhalable] were substituted with values equal to one-half the LOD. The EC data were then background corrected by subtracting the facility-specific background concentration. In instances where a negative background-corrected concentration was found (background concentration > sample concentration; [n = 70 (27.8%), respirable; n = 77 (30.6%), inhalable]), one-half the lowest background adjusted value from the specific facility was substituted. The TEM concentrations that fell below the LOD [n = 57 (22.6%)], which was defined as 1 CNT/F structure per filter, were substituted with one-half the LOD (0.5 structures per filter). Samples overloaded with material [n = 22 (8.7%)] were estimated by assuming overloaded samples were 50% higher than the largest CNT/F structure count found at that specific facility.

Company- and worker-level determinants

Company- and worker-level determinants used in this study were based upon observations from previously published CNT/F exposure studies (Dahm *et al.*, 2012, 2015), as well as adapted from Woskie *et al.* (2010), and are listed in Table 1. Company-level information was collected during an interview with a site representative or production manager. The information collected included industry type, characterization information on the CNT/F materials produced or used, company policy on personal protective equipment (PPE), engineering control uses, daily production levels or daily quantities handled, and the number of employees on site (Supplementary Appendix I, available at *Annals of Work Exposures and Health* online).

Each of the 15 companies was categorized into one of five distinct industry types based upon the work performed at each site. Four were previously described in Dahm *et al.* (2015, 2018), which include primary manufacturers, hybrid producers/users, secondary manufacturers in the composites/thermoplastics industries, and secondary manufacturers in the electronics industries. An additional company was categorized as a secondary manufacturer in the coatings industry and primarily purchased MWCNT for the creation of advanced corrosion resistant coatings for steel structures. General information regarding each of the 15 unique companies can be found in Supplementary Table S1 (available at *Annals of Work Exposures and Health* online).

Additional company-level determinants included a variable for a subjective assessment of company engineering controls and a variable to denote the company-wide potential for high exposure. The company engineering control variable was categorical with ratings of adequate (appeared to effectively control exposures and used consistently and properly by employees), semi-adequate (many appeared to be effective however some were likely deficient and were not consistently or properly used by employees), and inadequate (lacked proper engineering controls and/or controls present likely did not effectively control exposures). No direct measurements of engineering control efficiency were collected. These ratings were based upon observations and professional judgment from a three-person exposure assessment team that were part of each site assessment.

The company-wide high exposure variable was designed to designate a site that had workplace practices

Table 1. Company and worker-level determinants included in multivariate regression modeling.

Level	Determinant	Determinant categories
Company	CNT/F industry type	Primary manufacturer, hybrid producer/user, secondary manufacturer—coatings, secondary manufacturer—composites/plastics, secondary manufacturer—electronics
	Daily company production level or quantity of material handled	<10 g, 10–100 g, 101 g–1 kg, >1 kg
	Number of employees on site	Continuous variable
	Material type	MWCNT, SWCNT, CNF
	Form of material(s) handled	Dry powder, dispersed in liquid or resin, embedded in composite
	Company engineering controls rating	Inadequate, semi-adequate, adequate
	Average material diameter	Continuous variable (nm)
	Average material length	Continuous variable (μm)
	High exposure potential	Yes/no
Worker	Job title	Administrator, chemist, engineer, maintenance, research and development, technician
	Daily job tasks	See Table 2
	Daily quantity handled	0, <10 g, 10–50 g, 51–100 g, 101–1 kg, >1 kg
	Form of material(s) handled	Dry powder, dispersed in liquid or resin, embedded in composite, none
	Direct CNT/F exposure	Yes/no
	Indirect CNT/F exposure	Yes/no
	Engineering controls	Ventilated or unventilated enclosure, chemical fume hood, local exhaust ventilation
	Half or full-face respirator usage	Yes/no

MWCNT, multi-walled carbon nanotubes; SWCNT, single-walled carbon nanotubes; CNF, carbon nanofibers; CNT/F, carbon nanotubes and nanofibers.

or processes that would likely demonstrate a high potential for exposure over the NIOSH REL of 1 μg m^{-3} at the respirable size fraction of EC (NIOSH, 2013). This variable was created to aid the model in predicting exposures at the company-level that displayed higher than average exposures compared with their industry average from Dahm *et al.* (2015, 2018). Characteristics of these companies included handling large quantities of material, lacking proper engineering controls, and having poor housekeeping protocols. The variable was created post data collection through an independent vote from the exposure assessment team, where one team member had knowledge of the results. This variable is intended for use in future site assessments where little or no exposure data may exist at the time of an initial walk-through, and will be based upon prior observational experiences and professional judgment.

Worker-level determinants were collected on daily-performed job tasks that included the type of job task, direct or indirect exposure to CNT/F, and quantity and form of material handled as well as engineering controls and PPE used throughout the sampling period. The information was collected by NIOSH personnel through a combination of workplace observations and a short in-person interview at the end of each sampled work-shift (Supplementary Appendix II, available at *Annals of Work Exposures and Health* online). Standardized job titles of administrator, chemist, engineer, maintenance, research and development, and technician were assigned to each individual in the exposure database based upon the worker's reported job title and observed daily tasks performed (Dahm *et al.*, 2018). In total, the exposure database included 21 company-level determinant variables and 22 worker-level determinant variables. Additionally, job tasks were standardized into 15 job task variables that are further described in Table 2.

Model Development and Validation

The exposure distributions for all exposure metrics, which served as dependent variables for the three subsequent multivariate regression models, were log-normally distributed and were log transformed before analysis. The median and interquartile ranges (IQR) are reported for each exposure metric across each predictor while the *P*-value was calculated using a simple one-way ANOVA on the log-transformed data.

To control for repeated measures, mixed linear models were created with company- and worker-level

Table 2. Standardized job task descriptions.

Standardized job task[a]	Description
Catalyst preparation	Catalyst used in CNT/F production was prepared before CNT/F production. Note: most facilities used an iron-based catalyst.
Composite cutting/sanding	The testing, cutting, or sanding of any fully cured CNT/F composite or test coupon
Composite fabrication/production	Production or lay-up of any type of CNT/F infused composite material
Equipment maintenance and cleaning	Cleaning equipment or an area possibly contaminated with CNT/F as well as performing maintenance on equipment associated with CNT/F use
Extrusion	Extruding a mixture of CNT/F powder and resin compounds
Liquid intermediate production	The production of a CNT/F dispersion in liquid or resin slurry, which includes any sonication processes, or conducting the process to functionalize CNT/F in a liquid solution
Office/desk work	Performing office or desk related activities
Other work not involving CNT/F	Performing other tasks not directly involving the use of CNT/F
Packaging	Taking CNT/F materials and packaging them for sale or shipment
Powder handling and postprocessing	Includes various powder handling tasks, such as mixing, weighing, transferring, dumping, or sieving of CNT/F powders as well as the postcoating of CNT/F powders
Production/manufacturing	CNT/F synthesis in an enclosed reaction process. The job task generally involves prepping and monitoring the reactor. Note: all facilities used a CVD synthesis process.
Quality control testing	Performing quality control lab analyses on CNT/F materials, typically in small gram quantities.
Reactor harvesting	Removal and collection of CNT/F from the production reactor after the process has been completed
Spray coating	Using a liquid form of CNT/F to spray coat a surface
Wet chemistry lab work	Wet chemistry work within a laboratory not involving the use of CNT/F

CNT/F, carbon nanotubes and nanofibers; CVD, chemical vapor deposition.
[a]All job tasks were coded into the exposure database as a dichotomous variable.

determinants (nested within company) as random effects using the entire exposure database. First, a null model was fit with no fixed effects. Then a backwards stepwise model selection procedure was performed on the mixed linear models with: (i) all company-level determinants only, (ii) all worker-level determinants only, and (iii) all company- and worker-level determinants. A lowering of the AIC was used as the criterion for the variable selection. Modeling was performed separately for each of the three exposure metrics to study the contribution of the determinants to the within-worker (WW), between-worker within-company (BW), and between-company (BC) variance.

Subsequently, to build a generalizable model for prediction, ridge regression was performed. In ridge regression, all predictors are entered into the model and a penalty parameter (λ) is assigned. This helps prevent over-fitting by reducing the size of each coefficient by an amount determined by λ. The exact value of λ was assigned through a grid search by minimizing the root mean square error (RMSE) during cross-validation. To perform cross-validation, one company was removed from the dataset and a model was fit on the remaining 14 companies. The fitted model was then used to 'predict' the dependent variable on the company that was held out. This process was repeated 15 times, once for each site, and resulted in a prediction for each observation in the dataset. The predictive performance of each model was measured by calculating the RMSE:

$$\mathrm{RMSE} = \sqrt{\frac{\sum_{i=1}^{n}(p_i - m_i)^2}{n}}$$

and the R^2:

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(p_i - m_i)^2}{\sum_{i=1}^{n}(\bar{m} - m_i)^2}$$

The RMSE compares the predicted values (p_i) and measured values (m_i) in this exposure database ($n = 252$). These are common definitions, with the exception that they are applied to unseen data through cross-validation. As a result, it is possible to calculate a negative R^2, which would indicate severe over-fitting and a poor predictive performance. In addition, the RMSE does not correct for the number of parameters (k) in the model (by dividing by $n - k$), as is often reported in a traditional ANOVA table. This correction is meant to adjust for over-fitting. However, this is being evaluated by fitting the models on unseen data and as a result, the RMSE reflects the exact average squared error from a model regardless of the number of predictors.

In addition to performing cross-validation to assign the λ in the ridge regression models, cross-validation was also used to evaluate the predictive performance of the mixed linear models using a standard backwards stepwise selection procedure. For each company that was held out during cross-validation, backwards stepwise selection in a traditional linear model was performed on the remaining dataset to predict the dependent variable. Again, performance was evaluated by the RMSE and R^2 and was compared with the performance of the ridge regression results. The model for each exposure metric with the highest R^2 and lowest RMSE value was considered the 'best' model.

In order for ridge regression to perform optimally, all independent variables must have a similar scale. Since the majority of predictors were 'dummy variables' (and took on values of 0 or 1), all continuous variables were also scaled to take on values between 0 and 1. Therefore, the interpretation of the continuous regression coefficients is the change in the log of the dependent variable between the minimum (0) and maximum (1) of the scaled continuous variable. The ridge regression models considered all company-level and worker-level determinants, with and without all two-way interactions.

Creation of the mixed linear models was performed using PROC MIXED in SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). All other modeling and statistical analysis was performed using R 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria) using the caret and penalized packages (Goeman, 2010, 2018; Kuhn, 2017).

Results

The overall exposures for the three exposure metrics within this database were [AM (SD) and GM (GSD)] 0.87 μg m^{-3} (5.5) and 0.07 μg m^{-3} (8.9) for respirable EC, 3.66 μg m^{-3} (17.9) and 0.15 μg m^{-3} (24.6) for inhalable EC, and 0.1679 CNT/F structures cm^{-3} (0.7) and 0.0064 structures cm^{-3} (16.5) for quantitative TEM analysis. Exposures ranged in this database from <0.01 to 80.30 μg m^{-3} for respirable EC, <0.01 to 239.45 μg m^{-3} for inhalable EC, and <0.001 to 5.465 structure cm^{-3} for TEM analysis. Additional descriptive statistics (median, IQR, and *P*-value) for each individual company- and worker-level determinant and job task are provided in Supplementary Tables S2–S4 (available at *Annals of Work Exposures and Health* online).

Table 3 displays the percent of job tasks, material forms, mass quantities handled, and engineering control use by standardized job title and industry type observed within the exposure database. The most common job tasks performed included office work (63%), powder handling/postprocessing (18%), CNT/F production (16%), equipment maintenance/cleaning (15%), liquid intermediate production (13%), and quality control testing (10%). Dry powders were the most common form of material used (51%) followed by CNT/F liquid solutions (20%), and CNT/F in composite forms (8%). The quantities of material typically handled in this exposure database were 0 g (37%), <10 g (19%), 51–100 g (17%), >1 kg (13%), 10–50 g (11%), and 101 g–1 kg (4%). In addition, the most common engineering controls observed in use were ventilated or unventilated enclosures (33%), followed by local exhaust ventilation and chemical fume hoods (19% each). As participants could report more than one type of job task, material form, or engineering control used/performed daily; some totals could be >100%.

Mixed linear models

The results for the mixed linear models are displayed in Table 4. The null models consistently showed the greatest variance was BC (6.34, 2.49, and 4.54) followed by WW (2.53, 2.26, and 2.97) and BW (0.75, 0.12, and 0.45) for inhalable EC, respirable EC, and TEM, respectively. The fixed effects, which included all 58 company- and worker-level determinants, including job tasks, in the inhalable EC model reduced the BC, BW, and WW variances of inhalable EC exposure by 100%, 88%, and 5% compared with the null, respectively ('All Determinants' in Table 4). This model explained 79% of the total variance for inhalable EC exposures. The mixed model using all possible determinants to explain respirable EC exposure reduced the BC, BW, and WW variances by 100%, 100%, and 8% compared with the null, respectively. The selected determinants in the model explained 61% of the total variance for respirable EC exposures. Meanwhile, the mixed model using all possible determinants for estimating TEM exposure reduced the BC, BW, and WW variances by 100%, 100%, and 6% compared with the null, respectively. The fixed effects explained 68% of the total variance in the TEM model. The selected inhalable EC, respirable EC, and TEM determinants from each model, beta coefficients, and significance (*P*-value) are listed in Supplementary Tables S5–S7 (available at *Annals of Work Exposures and Health* online).

Table 3. Percent of job tasks and material uses by job title and industry type.

		Job title (%)						Industry type (%)					Total	Avg. dur.[a]
		Admin.	Chemist	Engineer	Maint.	R&D	Tech	Primary	Hybrid	Coating	Comp.	Elec.	(%)	(min.)
	n	55	18	67	4	34	74	74	97	8	64	9	252	n/a
Daily job task[b]	Catalyst production	0	0	1	0	0	8	7	2	0	0	0	3	360
	Composite cutting/sanding	2	0	0	0	3	5	1	2	13	3	0	2	88
	Composite fabrication/production	5	17	4	0	15	9	5	7	0	16	0	8	154
	Equipment maintenance/cleaning	2	6	22	75	6	22	5	26	50	8	0	15	141
	Extrusion	0	0	4	0	6	5	0	3	0	9	0	4	281
	Liquid intermediate production	2	33	10	0	26	15	8	4	38	25	56	13	234
	Office/desk work	96	61	70	25	68	31	65	54	100	70	44	63	329
	Other work not involving CNT/F	4	11	10	25	15	5	9	6	0	13	0	8	209
	Packaging	4	0	1	0	0	9	1	5	0	6	0	4	93
	Powder handling/postprocessing	4	11	19	0	12	32	4	25	13	27	0	18	160
	Production/manufacturing	4	0	21	50	3	28	18	28	0	0	0	16	271
	Quality control testing	5	22	12	0	6	9	5	15	0	8	0	10	254
	Reactor harvesting	2	0	3	25	0	20	15	8	0	0	0	8	56
	Spray coating	0	0	4	0	0	1	1	0	38	0	0	2	139
	Wet chemistry lab work	4	22	1	0	24	1	18	1	0	3	0	6	279
Material form[b]	Dry	15	33	58	75	50	74	31	73	25	45	33	51	—
	Liquid	7	44	13	0	29	26	11	8	75	36	56	20	—
	Composite	5	0	3	0	15	14	1	4	0	23	0	8	—
	None	78	39	33	25	35	9	61	23	25	30	44	37	—
Mass quantity handled[c]	0	78	39	33	25	35	9	61	23	25	30	44	37	—
	<10 g	13	22	19	0	24	22	12	16	50	25	33	19	—
	10–50 g	5	11	15	0	21	7	14	12	13	3	22	11	—
	51–100 g	0	6	12	75	9	38	14	29	13	6	0	17	—
	101 g–1 kg	0	11	6	0	3	4	0	5	0	8	0	4	—
	>1 kg	4	11	15	0	9	20	0	14	0	28	0	13	—
Engineering controls used[b]	Ventilated/unventilated enclosure	9	11	40	50	29	51	26	40	50	31	22	33	—
	Local exhaust ventilation	5	0	34	0	15	24	8	26	25	25	0	19	—
	Chemical fume hood	5	22	21	0	29	22	9	18	25	25	56	19	—

Admin., administrator; Maint., maintenance; Comp., composites; Elec., electronics; *n*, number of data points within each standardized job title and industry type; n/a, not applicable. Percent = (number of data points per daily job task/material form/mass quantity handled/engineering control) ÷ (*n* from each job title/industry type).

[a]Avg. Dur. = Average duration (minutes) for each of the reported job tasks performed.

[b]Total percent can be >100% because an individual can perform more than one type of daily job task and use more than one type of material form or engineering control.

[c]Total percent will add to 100% for mass quantity handled because each data point could only handle one specified amount.

Table 4. Mixed linear model variance estimates and model fit.

Mixed linear model	Inhalable EC (SE)				Respirable EC (SE)				TEM (SE)			
	BC	BW	WW	R^2	BC	BW	WW	R^2	BC	BW	WW	R^2
Null	6.34 (2.49)	0.75 (0.31)	2.53 (0.32)	0.00	2.49 (1.01)	0.12 (0.11)	2.26 (0.26)	0.00	4.54 (1.82)	0.45 (0.31)	2.97 (0.36)	0.00
Worker-level determinants	4.58 (1.83)	0.32 (0.26)	2.39 (0.30)	0.41	1.66 (0.72)	0.11 (0.21)	2.13 (0.26)	0.31	3.38 (1.41)	0.39 (0.31)	2.89 (0.36)	0.29
Company-level determinants	0.00 (0.00)	0.70 (0.31)	2.54 (0.32)	0.71	0.00 (0.00)	0.00 (0.00)	2.31 (0.21)	0.55	0.00 (0.00)	0.27 (0.30)	3.00 (0.37)	0.61
All determinants	0.00 (0.00)	0.09 (0.24)	2.40 (0.31)	0.79	0.00 (0.00)	0.00 (0.00)	2.08 (0.19)	0.61	0.00 (0.00)	0.00 (0.00)	2.79 (0.26)	0.68

SE, standard error; BC, between company variance; BW, between worker within company variance; WW, within worker variance; EC, elemental carbon; TEM, transmission electron microscopy.

Cross-validated linear and ridge regression models

Since the objective of the study was to estimate exposures for workers at companies or time-periods that would have limited or no sampling data, the predictive capabilities of the models were tested using cross-validation to simulate unseen company data. The cross-validated R^2 values for each of the three mixed linear models examining the effects of company-level, worker-level, and models including all 58 determinant variables ranged from −16.93 to −23.46 with RMSE's ranging from 2.50 to 4.23, as seen in Table 5. These measures of fit and errors indicate severe over-fitting and would provide poor predictive capabilities. Meanwhile, the ridge regression models that included all 58 determinant variables without interactions found cross-validated R^2 values of 0.20, −0.04, and 0.03 with RMSEs of 2.85, 2.23, and 2.76 for the predictive models of inhalable EC, respirable EC, and TEM, respectively. The ridge regression model that incorporated all two-way interactions with each model containing and contained ~1500 variables, found cross-validated R^2 values of 0.18, −0.04, and 0.04 with RMSEs of 2.89, 2.23, and 2.74 for the predictive models of inhalable EC, respirable EC, and TEM, respectively.

The ridge regression models provided the highest cross-validated R^2 values and consistently provided the lowest RMSE among all fitted models. Therefore, the ridge regression models were demonstrated to be the 'best' models for predicting exposures for each of the three exposure metrics in this study. It should be noted that the inhalable EC model that did not include interactions provided the best overall results, but only had a cross-validated R^2 value of 0.20, with a RMSE of 2.85. This indicates that the model would provide only a modest predictive capability. Figure 1 graphically displays the predicted measurement values compared with the actual measured values. Overall, the plots show that the fitted ridge regression models generally over-predicted low exposure concentrations and under-predicted high exposure concentrations.

Table 6 displays the top five strongest positive and negative beta coefficients for each of the ridge regression models that did not include interactions. Seven individual company-level determinants were associated with the highest increased exposure potential and included the engineering control rating of inadequate and semi-adequate, increasing average material diameter, the daily production level or quantity of material handled 101 g–1 kg, handling the material form of CNF, the industry type of hybrid producer/user, and the assessment of a high exposure potential. Fewer worker-level

Table 5. Cross-validated model results and error estimates.

Model		Inhalable EC			Respirable EC			TEM		
		λ	CV R^2	RMSE	λ	CV R^2	RMSE	λ	CV R^2	RMSE
Ridge regression model without interactions		50	0.20	2.85	400	−0.04	2.23	40	0.03	2.76
Ridge regression model with interactions		200	0.18	2.89	3000	−0.04	2.23	90	0.04	2.74
Mixed effects models	Worker-level determinants	—	−18.79	3.78	—	−20.25	2.69	—	−21.05	3.51
	Company-level determinants	—	−22.41	4.13	—	−17.32	2.50	—	−16.93	3.17
	All determinants	—	−23.46	4.23	—	−21.01	2.74	—	−21.77	3.57

λ, penalty parameter used in ridge regression models; CV, cross-validation; RMSE, root mean squared error; EC, elemental carbon; TEM, transmission electron microscopy.

determinants were associated with increased exposure, which included the job title of engineer and the use of a respirator. Meanwhile, only the job task of powder handling and postprocessing was commonly associated with increased exposures across the various models.

Company-level determinants associated with decreased exposure potential included the engineering control rating of adequate and semi-adequate, the daily production level or quantity of material handled 10–100 g, producing or using the material type of SWCNT, the industry type of hybrid producer/user, and handling CNT/F in a liquid suspension or embedded in a composite. The only worker-level determinant associated with a decreased exposure potential was having the job title of administrator and the only job task that was associated with decreased exposure included the tasks of performing office work. All 58 determinant variables and their associated beta coefficients for the ridge regression models that did not include interactions are listed in Supplementary Table S8 (available at *Annals of Work Exposures and Health* online).

Nearly all the top positive and negative beta coefficients were found to be similar when compared with the results of the ridge regression models that included all interactions, which can be found in Supplementary Table S9 (available at *Annals of Work Exposures and Health* online). Several additional company-level determinants were found to increase exposure in these models which included the average CNT/F length and daily quantities of material handled >1 kg. Also, additional worker-level determinants that increased exposure included direct/indirect exposure, handling the dry-powdered form of CNT/F, handling daily quantities of material >1 kg, and using a ventilated or unventilated enclosure. The additional worker-level determinants that strongly reduced exposure included not handling any quantity of CNT/F or handling <10 g of material along with the job tasks of performing other work not involving CNT/F.

Figure 2 presents the predicted exposures from the ridge regression model without interactions for inhalable EC utilizing several realistic workplace exposure scenarios created using the most common job tasks by job title, found in Table 3. All company-level determinants and remaining worker-level determinants were held constant other than job title and the company-level engineering control rating (Fig. 2A). Predicted exposures were highest among the job titles of engineer and technician and decreased as the company engineering control rating improved from inadequate to adequate. Meanwhile, Fig. 2B uses the same determinants as Fig. 2A, but examines the change of inhalable EC exposures for the job title of technician employed in a company with semi-adequate

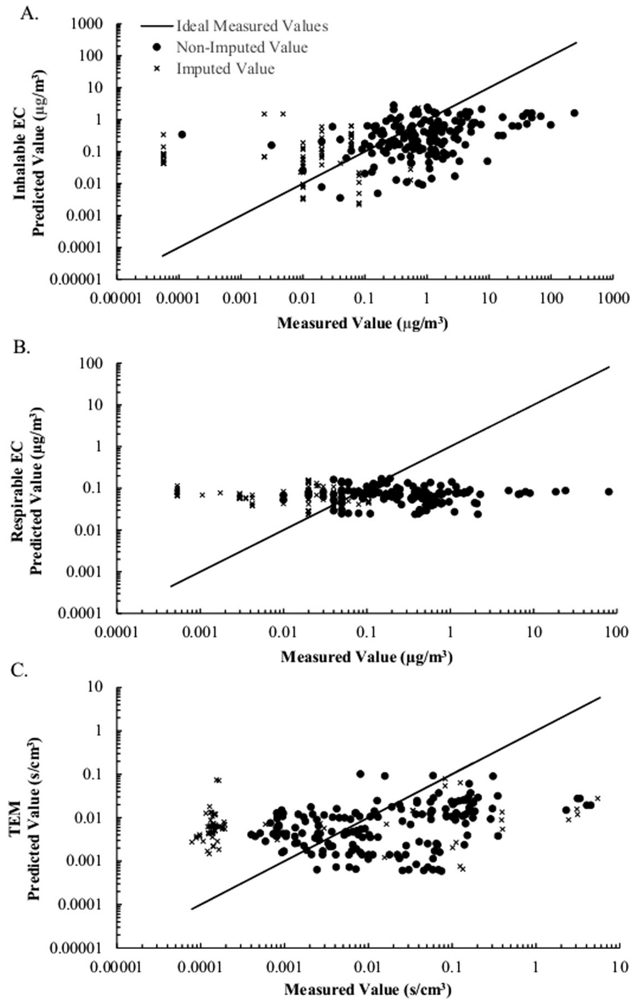

Figure 1. Predicted versus measured values from the ridge regression models, without interactions, for (A) inhalable elemental carbon [R^2 = 0.20], (B) respirable elemental carbon [R^2 = −0.04], and (C) TEM [R^2 = 0.03]. Plotted lines represent ideal measured values. Imputed values were results below the limit of quantitation or were negative after the background correction.

engineering controls as the worker-level determinant of mass quantity handled increases. Predicted exposures increase as the mass quantity handled increases to 101 g–1 kg. However, exposure decreased for masses >1 kg, which may be due to more effective engineering controls and less manual handling of large quantities of CNT/F materials. Full details of the determinants selected for each exposure scenario can be found in Supplementary Table S10 (available at *Annals of Work Exposures and Health* online).

Discussion

The overarching objective of this effort was to develop and validate predictive models using determinants and workplace factors to estimate current and past CNT/F exposures for future use in cohort studies. The validated models could be used to assign exposure levels to workers for whom measurements are not available, but for whom determinant information exists (Burstyn and Teschke, 1999). To date, no other studies have evaluated the use of predictive models for estimating CNT/F exposures, while one other study has identified workplace exposure determinants (Kuijpers *et al.*, 2016). This is likely due to the absence of consensus exposure assessment methods, the limited availability of exposure data, and the relatively recent emergence of these materials in mainstream manufacturing over the past decade. This study used a database of measured exposures and potential determinants to create several

Table 6. Largest positive and negative parameter values from the ridge regression models.

		Inhalable EC		Respirable EC		TEM	
	Rank	Variable	β	Variable	β	Variable	β
Positive effect	1	CL—ECR inadequate	0.60	CL—ECR inadequate	0.13	CL—ECR inadequate	0.83
	2	CL—AM diameter	0.46	WL—respirator use	0.13	CL—AM diameter	0.78
	3	CL—ECR semi-adequate	0.36	CL—IT hybrid	0.12	CL—QMH 101 g–1 kg	0.59
	4	WL—JT engineer	0.36	JTa—powder handling	0.11	CL—high exposure	0.53
	5	CL—high exposure	0.35	CL—high exposure	0.11	CL—MT–CNF	0.52
Negative effect	1	CL—ECR adequate	−0.96	CL—FMH liquid	−0.12	CL—QMH 10–100 g	−0.77
	2	CL—MT SWCNT	−0.83	CL—ECR adequate	−0.11	CL—FMH composite	−0.53
	3	CL—QMH 10–100 g	−0.64	CL—MT SWCNT	−0.11	CL—ECR adequate	−0.45
	4	JTa—office work	−0.55	WL—JT administrator	−0.10	CL—ECR semi-adequate	−0.38
	5	CL—FMH liquid	−0.53	JTa—office work	−0.08	CL—IT hybrid	−0.36

CL, company-level determinant; WL, worker-level determinant; JTa, job task; ECR, engineering controls rating; AM, average material; QMH, quantities of material handled; FMH, form of material(s) handled; JT, job title; MT, material type; IT, CNT/F industry type; EC, elemental carbon; TEM, transmission electron microscopy.

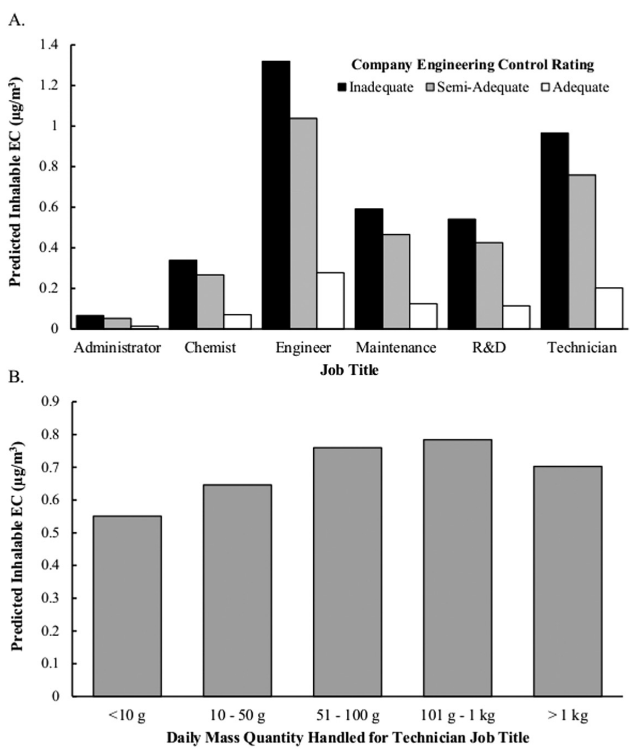

Figure 2. Predicted inhalable EC exposures using the ridge regression model for several realistic workplace exposure scenarios. (A) Workers of all job titles at a hybrid producer/user handling >1 kg daily quantity at the company level with each job title performing 4–5 of the most commonly reported tasks for the average amount of reported times listed in Table 3. All other company- and worker-level determinants were held constant across the job titles, with the exception of the daily quantity of material handled at the worker level for Administrators was 0 g while all other job titles were 51–100 g. (B) The same company and worker level determinants were held constant for the Technician job title from scenario A. This included a hybrid producer/user with a company engineering control rating of semi-adequate, with the exception that the worker level determinant of daily mass quantity handled was changed.

models to evaluate their predictive capabilities and assess potential determinants contributing to CNT/F exposures through cross-validation. The standardized exposure database used in this study provided important insights into commonly performed tasks, material forms used, mass quantities handled, and engineering controls used by the various US industries/job titles that produce or use CNT/F. This is valuable information since few published exposure studies have provided detailed insights regarding these various industries, which include the frequency and duration of exposures.

Model predictive performance

Mixed linear models were created to examine the contributions of variance between-companies (BC), between-workers (BW), and within-workers (WW). It is known that occupational exposures vary greatly both WW and BW in the same job (Rappaport *et al.*, 1999; Friesen *et al.*, 2005). The null models demonstrated that the greatest variance was seen BC. However, when using all company- and worker-level determinants to create the three exposure models, the mixed linear models initially performed well, explaining >60% of the total variance. These models generally explained all of the BC and BW variance, but had limited success in explaining the WW variance. When the models underwent cross-validation to simulate predicting exposures for an unseen company, they performed poorly, and over-fit the data, offering very limited predictive capability for estimating CNT/F exposures.

The ridge regression model that did not incorporate interactions was demonstrated to be the 'best' exposure model based upon its predictive performance for the metric of inhalable EC while the ridge model that incorporated all two-way interactions performed the 'best' for estimating the metric of TEM. However, these models were found to offer only a modest overall predictive capability for CNT/F exposures based upon their overall cross-validated R^2 values and RMSE. Also, these models consistently under-predicted high exposures and over-predicted lower exposures (Fig. 1). Nevertheless, the inhalable EC model that did not incorporate interactions did display the capability to predict reasonable exposure trends based upon actual measured values by worker-level determinants, as seen in Fig. 2 (Supplementary Tables S2–S4, available at *Annals of Work Exposures and Health* online). Therefore, the inhalable model could at least serve as a tool to assist in estimating unavailable worker or workplace exposure data. This may prove to be useful in the future, as several toxicity and epidemiologic studies have found an increased association between the inhalable aerosol size fractions of EC and associated health effects (Bishop *et al.*, 2017; Beard *et al.*, 2018; Schubauer-Berigan *et al.*, 2018).

The inability of the mixed linear models to explain the WW variance may be attributed to the fact that many companies did not fully operate at an industrial level of manufacturing, regardless of industry. It has been previously found that intermittent production processes, as observed in many of these CNT/F workplaces, have a large effect on WW variance (Kromhout *et al.*, 1993). Additionally, many job tasks were similar, and were categorized as such, but there was still a great amount of variation in an individual's daily job tasks due to the lack of standard production line scenarios. Data were pooled in this exposure database to include all industries due to the limited number of unique sites (15) providing company-level determinants and the overall limited number of workers. Therefore, the null mixed linear models demonstrated the greatest amount of variance BC. This is not surprising since these models attempted to predict CNT/F exposures across various industries that were performing somewhat similar basic job tasks (i.e. mixing, weighing), but the execution of these tasks and further downstream processing of materials could be vastly different depending on the industry.

As more unique companies are assessed and additional exposure data are collected or published, future-modeling efforts should focus on individual industries producing or using CNT/F where there would be more standardization among job tasks and job titles. Additionally, these models were created to assist in estimating exposures for use in future cohort studies; however, the data were analyzed in a cross-sectional fashion, which ultimately limits their ability to predict temporal variability. It should also be noted that many of the lower exposure concentrations were imputed values due to samples either being below the limit of quantitation or became a negative value after the background correction (Fig. 1). The derivation of these imputed values was completed using traditional industrial hygiene methods for censored data, which may have provided measurements that were artificially low, possibly weakening each model's predictive capabilities.

Determinants associated with exposure

Company-level determinants were found to be the most important variables associated with both increased and decreased levels of exposure, and was consistently demonstrated across both the mixed linear and regression models for all three exposure metrics. However, it should be noted that only 15 unique sites were included in this exposure database, which limited the confidence in the company-level determinant results, such as the use of CNF materials since only two companies reported consistent use. Additionally, the models generally identified few job tasks that were positively or negatively associated with exposure, which is likely the result of limited observations as nearly half of the job tasks were observed <20 times in the exposure database.

Many of the identified determinants from the models that were found to increase or decrease exposures were expected to contribute to exposure *a priori*. These determinants included variables such as the company engineering control rating, both company and worker daily quantities of materials handled, direct exposure, and material type and form. However, several variables were identified to affect exposures that could not be easily explained, such as the use of ventilated/unventilated engineering controls and the average length and diameter of CNT/F materials. Additionally, the industry type of a hybrid producer/user as well as the use of semi-adequate engineering controls were found to significantly increase and decrease exposure in two separate models.

The ventilated/unventilated enclosures were the most common form of engineering controls used in this study and were generally used in scenarios that had a higher potential for exposure. Consequently, it may be that the positive association was due to the relationship with higher exposure scenarios and not due to the ineffectiveness of these controls. Additionally, increasing material diameter and length have been associated with a decreased ability to agglomerate into larger particles creating unique exposure situations (Murray *et al.*, 2012; Dahm *et al.*, 2018). Therefore, the relationship between CNT/F physiochemical properties and exposure potential should be further investigated. As for the bi-directional findings for the hybrid producer and users, the univariate analysis (Supplementary Table S2, available at *Annals of Work Exposures and Health* online) showed that hybrid sites displayed one of the highest exposures for EC but was one of the lowest average exposures for the TEM metric. This discrepancy within sampling metrics likely caused the determinant to be associated with an increase in exposure within the respirable EC ridge model and a decrease in exposure for the TEM ridge model. Similarly, the bi-directional findings for the semi-adequate engineering control rating can also be attributed to the differences in the semi-adequate control exposures and the inadequate exposures in the univariate analysis between the inhalable EC and TEM models (Supplementary Table S2, available at *Annals of Work Exposures and Health* online).

To date, Kuijpers *et al.* (2016) is the only other study to examine exposure determinants using similar exposure metrics and mixed linear modeling for CNT/F, but focused solely on job tasks related to exposures and included a limited number of measurements from a single site. Common job tasks were found to contribute to exposure, which included workers in direct contact with CNT/F and powder handling processes (Kuijpers *et al.*, 2016). Other methods have been evaluated for semi-quantitatively predicting CNT/F exposures, which include a combination of expert observational assessments and the use of a standardized logbook to document potential exposures to CNT/F (Guseva Canu *et al.*, 2017). Although expert observational assessments were able to identify workstations with potential exposures, it was tested only within a university research laboratory and not compared with any type of quantitative exposure metrics, thus limiting its applicability to industrial settings.

Conclusion

In summary, this study utilized an exposure database to create and validate an exposure model using ridge regression and cross-validation for predicting CNT/F exposures. The 'best' model was identified for the exposure metric of inhalable EC, but only offered an overall limited predictive capability. However, the model demonstrated the capability to identify exposure trends based on realistic workplace exposure scenarios. Therefore, it was concluded that the model alone would not be adequate in predicting workplace exposures, but would need to be supplemented with other methods and additional exposure measurement collection. Other approaches for the prediction of exposures, such as the development of a traditional job exposure matrix (department- and job title-based), assuming adequate work history and exposure information exist, would not be ideal in this situation as there is limited standardization in job tasks or job titles across companies and industries. Improvements to this model may be made as sampling methodologies continue to harmonize and additional exposure data and determinants information become more readily available. Additionally, as manufacturing and downstream uses of CNT/F continue to develop within the various US industries; future predictive models should focus on exposures within these individual trades.

Supplementary Material

Supplementary data are available at *Annals of Work Exposures and Health* online.

Funding

This research was supported by an Interagency Agreement with the National Institute of Environmental Health Sciences (AES 12029-001) and the NIOSH Nanotechnology Research Center.

Acknowledgments

The authors would like to thank the participating workers and facilities for their willingness and commitment to participate in this study. We also thank Kelsey Babik, John Beard, Donnie Booher, Kevin H. Dunn, Douglas Evans, Eric Glassford, and Ken Sparks for their aid in collecting field data as well as Dr Sergey Grinshpun for reviewing the manuscript.

Disclaimer

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC). Mention of any company name or product does not constitute endorsement by NIOSH/CDC.

Conflict of Interest

The authors declare no conflict of interest.

References

Beard JD, Erdely A, Dahm MM *et al.* (2018) Carbon nanotube and nanofiber exposure and sputum and blood biomarkers of early effect among U.S. workers. *Environ Int*; **116**: 214–28.

Bishop L, Cena L, Orandle M *et al.* (2017) In vivo toxicity assessment of occupational components of the carbon nanotube life cycle to provide context to potential health effects. *ACS Nano*; **11**: 8849–63.

Burstyn I, Teschke K. (1999) Studying the determinants of exposure: a review of methods. *Am Ind Hyg Assoc J*; **60**: 57–72.

Dahm MM, Evans DE, Schubauer-Berigan MK *et al.* (2012) Occupational exposure assessment in carbon nanotube and nanofiber primary and secondary manufacturers. *Ann Occup Hyg*; **56**: 542–56.

Dahm MM, Schubauer-Berigan MK, Evans DE *et al.* (2015) Carbon nanotube and nanofiber exposure assessments: an analysis of 14 site visits. *Ann Occup Hyg*; **59**: 705–23.

Dahm MM, Schubauer-Berigan MK, Evans DE *et al.* (2018) Exposure assessments for a cross-sectional epidemiologic study of US carbon nanotube and nanofiber workers. *Int J Hyg Environ Health*; **221**: 429–40.

De Volder MF, Tawfick SH, Baughman RH *et al.* (2013) Carbon nanotubes: present and future commercial applications. *Science*; **339**: 535–9.

Erdely A, Hulderman T, Salmen R *et al.* (2009) Cross-talk between lung and systemic circulation during carbon nanotube respiratory exposure. Potential biomarkers. *Nano Lett*; **9**: 36–43.

Fatkhutdinova LM, Khaliullin TO, Vasil'yeva OL *et al.* (2016) Fibrosis biomarkers in workers exposed to MWCNTs. *Toxicol Appl Pharmacol*; **299**: 125–31.

Friesen MC, Davies HW, Teschke K *et al.* (2005) Predicting historical dust and wood dust exposure in sawmills: model development and validation. *J Occup Environ Hyg*; **2**: 650–8.

Goeman JJ. (2010) L1 penalized estimation in the Cox proportional hazards model. *Biom J*; **52**: 70–84.

Goeman J, Meijer R, Chaturvedi N, Lueder M. (2018) R penalized: L1 (lasso and fused lasso) and L2 (ridge) penalized estimation in GLMs and in the Cox model. CRAN; R package version 0.9-51. Available at https://cran.r-project.org/web/packages/penalized/index.html. Accessed 3 January 2019.

Grosse Y, Loomis D, Guyton KZ *et al.*; International Agency for Research on Cancer Monograph Working Group. (2014) Carcinogenicity of fluoro-edenite, silicon carbide fibres and whiskers, and carbon nanotubes. *Lancet Oncol*; **15**: 1427–8.

Guseva Canu I, Jezewski-Serra D, Delabre L *et al.* (2017) Qualitative and semiquantitative assessment of exposure to engineered nanomaterials within the french EpiNano program: inter- and intramethod reliability study. *Ann Work Expo Health*; **61**: 87–97.

International Agency for Research on Cancer (IARC). (2017) Monographs on the evaluation of carcinogenic risks to humans, vol. 111. Some nanomaterials and some fibres. Lyon, France. Available at http://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Evaluation-Of-Carcinogenic-Risks-To-Humans/Some-Nanomaterials-And-Some-Fibres-2017. Accessed 3 January 2019.

Invernizzi N. (2011) Nanotechnology between the lab and the shop floor: what are the effects on labor? *J Nanopart Res*; **13**: 2249–68.

Kromhout H, Symanski E, Rappaport SM. (1993) A comprehensive evaluation of within- and between-worker components of occupational exposure to chemical agents. *Ann Occup Hyg*; **37**: 253–70.

Kuhn M. (2017) Contributions from Wing J, Weston S, Williams A, Keefer C, Engelhardt A, Cooper T, Mayer Z, Kenkel B, the R Core Team, Benesty M, Lescarbeau R, Ziem A, Scrucca L, Tang Y, Candan C, Hunt T. caret: classification and regression training. R package version 6.0–77. Available at https://CRAN.R-project.org/package=caret. Accessed 3 January 2019.

Kuijpers E, Bekker C, Fransman W *et al.* (2016) Occupational exposure to multi-walled carbon nanotubes during commercial production synthesis and handling. *Ann Occup Hyg*; **60**: 305–17.

Kuijpers E, Pronk A, Kleemann R *et al.* (2018) Cardiovascular effects among workers exposed to multiwalled carbon nanotubes. *Occup Environ Med*; **75**: 351–8.

Lee JS, Choi YC, Shin JH *et al.* (2015) Health surveillance study of workers who manufacture multi-walled carbon nanotubes. *Nanotoxicology*; **9**: 802–11.

Liou SH, Tsai CS, Pelclova D *et al*. (2015) Assessing the first wave of epidemiological studies of nanomaterial workers. *J Nanopart Res*; **17**: 413.

Mitchell LA, Lauer FT, Burchiel SW *et al*. (2009) Mechanisms for how inhaled multiwalled carbon nanotubes suppress systemic immune function in mice. *Nat Nanotechnol*; **4**: 451–6.

Murray AR, Kisin ER, Tkach AV *et al*. (2012) Factoring-in agglomeration of carbon nanotubes and nanofibers for better prediction of their toxicity versus asbestos. *Part Fibre Toxicol*; **9**: 10.

NIOSH. (2013) *Current Intelligence Bulletin 65: occupational exposure to carbon nanotubes and nanofibers*. Publication Number 2013–145. Cincinnati, OH: US Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational safety and Health. DHHS (NIOSH).

Oberdorster G, Castranova V, Asgharian B *et al*. (2015) Inhalation exposure to carbon nanotubes (CNT) and carbon nanofibers (CNF): methodology and dosimetry. *J Toxicol Environ Health B Crit Rev*; **18**: 121–12.

Pauluhn J. (2010) Subchronic 13-week inhalation exposure of rats to multiwalled carbon nanotubes: toxic effects are determined by density of agglomerate structures, not fibrillar structures. *Toxicol Sci*; **113**: 226–42.

Porter DW, Hubbs AF, Chen BT *et al*. (2013) Acute pulmonary dose-responses to inhaled multi-walled carbon nanotubes. *Nanotoxicology*; **7**: 1179–94.

Rappaport SM, Weaver M, Taylor D *et al*. (1999) Application of mixed models to assess exposures monitored by construction workers during hot processes. *Ann Occup Hyg*; **43**: 457–69.

Schubauer-Berigan MK, Dahm MM, Erdely A *et al*. (2018) Association of pulmonary, cardiovascular, and hematologic metrics with carbon nanotube and nanofiber exposure among U.S. workers: a cross-sectional study. *Part Fibre Toxicol*; **15**: 22.

Seixas NS, Checkoway H. (1995) Exposure assessment in industry specific retrospective occupational epidemiology studies. *Occup Environ Med*; **52**: 625–33.

Shvedova AA, Yanamala N, Kisin ER *et al*. (2016) Integrated analysis of dysregulated ncRNA and mRNA expression profiles in humans exposed to carbon nanotubes. *PLoS One*; **11**: e0150628.

Simeonova PP, Erdely A. (2009) Engineered nanoparticle respiratory exposure and potential risks for cardiovascular toxicity: predictive tests and biomarkers. *Inhal Toxicol*; **21** (Suppl. 1): 68–73.

Vlaanderen J, Pronk A, Rothman N *et al*. (2017) A cross-sectional study of changes in markers of immunological effects and lung health due to exposure to multi-walled carbon nanotubes. *Nanotoxicology*; **11**: 395–404.

Woskie SR, Bello D, Virji MA *et al*. (2010) Understanding workplace processes and factors that influence exposures to engineered nanomaterials. *Int J Occup Environ Health*; **16**: 365–77.