Engineered Carbonaceous Nanomaterials Manufacturers in the United States

Workforce Size, Characteristics, and Feasibility of Epidemiologic Studies

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Objective: Toxicology studies suggest that carbon nanotube (CNT) exposures may cause adverse pulmonary effects. This study identified all US engineered carbonaceous nanomaterial (ECN) manufacturers, determined workforce size and growth, and characterized the materials produced to determine the feasibility of occupational ECN exposure studies. **Methods:** Eligible companies were identified; information was assembled on the companies and nanomaterials they produced; and the workforce size, location, and growth were estimated. **Results:** Sixty-one companies manufacturing ECN in the United States were identified. These companies employed at least 620 workers; workforce growth was projected at 15% to 17% annually. Most companies produced or used CNT. Half the eligible companies provided information about material dimensions, quantities, synthesis methods, and worker exposure reduction strategies. **Conclusions:** Industrywide exposure assessment studies appear feasible; however, cohort studies are likely infeasible because of the small, scattered workforce.

Uses of engineered nanomaterials represent a fast-growing but ill-characterized aspect of many industrial sectors. Application of nanotechnology is spreading unevenly across these sectors, with manufacturing proliferating earliest, followed by electronics and information technology applications and, lastly, health care and life sciences applications. On the basis of a recent report by the International Council on Nanotechnology,[1] more than 30% of nanomanufacturers worldwide participating in their voluntary survey create and handle engineered carbonaceous nanomaterials (ECN) [eg, carbon nanotubes (CNT), fullerenes, graphene, and carbon black]. Human health effects from workplace exposures to ECN are uncertain, but toxicological studies suggest that they may include harmful pulmonary and extrapulmonary effects. Studies in mice and rats suggest that single-walled and multiwalled CNT exposures may result in pulmonary inflammation and fibrosis[2–4] and some may also penetrate the pleural mesothelium.[5] Possible extrapulmonary effects under investigation include cardiovascular inflammation,[6] immunological effects,[7] systemic exposure (accompanied by lack of clearance from the body),[8,9] and penetration of the blood-brain barrier.[10–12] A recent systematic review of laboratory toxicology studies suggests that in experimental treatments, cell viability is lower and cell death is higher than among controls.[13]

Unique properties of engineered nanomaterials, such as high particle number per equivalent mass, size, surface area, surface charge, and shape, may be of greater importance than particle mass and bulk properties in determining exposure and toxicity. Despite the growing evidence for possible hazards from occupational exposure to ECN, little information exists on actual workplace exposure,[14–17] and no epidemiologic studies have been conducted.[18] Future evaluation of potential health risks, such as cancer and cardiovascular or immunological disease, associated with occupational exposure to engineered carbonaceous nanomaterials will require improved characterization of the workforces and workplaces involved in this industry.

The purpose of this study was to enumerate the companies directly manufacturing (or using in other manufacturing processes) engineered carbonaceous nanomaterials in the United States, and to estimate the US workforce size and characteristics of nanomaterials manufacturers. The project was initiated on the basis of evidence of pulmonary fibrosis and other lung effects observed in experimental animal studies exposed to carbon nanotubes and nanofibers. The information gathered through these surveys will be used to identify possible candidate industries or workplaces for occupational epidemiology and worker exposure assessment studies.

The specific objectives of the overall study were threefold: (1) to collect and compile information on US ECN workforce size and growth in recent years; (2) to estimate, by workplace and year, the quantity and type of nanomaterials produced by manufacturers of ECN; (3) to collect and compile available information concerning presence or absence of exposure controls and on types of controls in place, to the extent feasible. The findings related to the third goal are described elsewhere.[19] This information was then used to determine the feasibility and potential timing of industrywide exposure assessment and epidemiology studies, as well as health outcome surveillance, in the ECN industry.

METHODS

Identification of Potentially Eligible Companies

Industry profiles[20,21] and internet searches were used to identify companies potentially producing ECN in the United States. Information from these and other sources was assembled on the basis of characteristics of the companies and of the nanomaterials produced as well as the workforce size, location, and estimated growth. Information needed to carry out the feasibility study was collected and compiled using the following sources: (1) Volume I of The Nanotech Report, Vols 4 and 5,[20,21] a comprehensive nanotechnology industry characterization report, used to identify the key companies and personnel producing or using ECN; (2) internet searches for suppliers and manufacturers of each type of ECN in the United States; and (3) information from personal contacts and colleagues. The completeness of this original search, which was conducted in late 2008, was assessed by comparing the list of CNT producers to

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health (NIOSH).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.joem.org).

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DOI: 10.1097/JOM.0b013e31821b1e2c

the companies identified by the state of California during mandatory registration of companies producing CNT there, and also by the NIOSH nanotechnology coordination group, which was separately identifying companies willing to participate in field surveys of ECN production.

Collection and Confirmation of Information on Companies, Materials, and Workforce

It was then determined whether companies initially identified were eligible for participation. To be eligible, at the time of the survey (October 2008 to May 2009), the company must be manufacturing (or applying in other manufacturing processes) ECN in the United States either at full-scale, at pilot-scale, or at research scale with plans to scale-up within 5 years. Redistributors and repackagers, and companies exclusively operating at research-scale, were excluded. Volume II of The Nanotech Report, Vols 4 and 5, supplemented with a search of Dun & Bradstreet (www.dnb.com), was used to obtain information for each of these companies on company size, location, and materials produced. This source was also used to determine whether the manufacturing conducted by each of these companies was primary (ie, directly manufacturing ECN), secondary (ie, using ECN in a separate manufacturing process), or both.

Process engineers, chief technical officers, or health and safety managers at each company were contacted to confirm the information collected from the Lux and Dun & Bradstreet reports. A telephone questionnaire (see Appendix for the data collection form, http://links.lww.com/JOM/A53) was administered to collect additional information: types of engineered carbonaceous nanomaterials produced; size, shape, and quantities of nanomaterials produced; location of facility and pertinent contact information; size of population working with ECN; mass of ECN materials produced or used. In a few instances, a written survey was administered at the request of the company contact. Information was compiled using a relational database to track company contacts and survey results. The annual industry growth among all facilities was estimated by measuring annual change in workforce size over a 3-year period (2004 to 2006 for eligible companies that did not participate in the survey or 2006 to 2008 for companies that did participate in the survey). Overall growth was collated into Year 1, Year 2, and Year 3 estimates to combine information across participating and nonparticipating eligible companies with workforce estimates.

The work practices and engineering controls reported by these companies, associated with their engineered carbonaceous nanomaterials production processes, are described in the companion article.[19]

RESULTS

A total of 139 potentially eligible companies were identified, of which 61 (44%) were determined to be eligible. Of the 78 ineligible companies, 32 (41%) were not handling ECN, 14 (18%) were doing bench-scale research and development work only, 11 (14%) had non-US carbon nanomaterials manufacturing operations only, 9 (12%) were solely distributors or repackagers, 8 (10%) were no longer in business at the time of the survey, and 4 (5%) were nanomaterials consultants or handling intellectual property and patents.

The most common material produced by eligible companies was CNT (72%), followed by graphene (16%), fullerene (15%), and carbon or polymer nanofibers (15%) (Table 1). Other carbon nanomaterials produced in the United States less commonly included diamond films, nanoporous carbon, carbon quantum dots, and dendrimers. Eligible companies were most likely to be manufacturing or using ECN in the northeastern and western United States (Table 1), and were most common in California, Massachusetts, Texas, and Ohio. Geographic heterogeneity in the production and use of different types of engineered carbonaceous nanomaterials was also observed. For example, CNT and fullerene manufacturers were predominantly located in the northeastern and western regions of the United States, while graphene manufacturing occured primarily in the midwest and west. Vapor-grown carbon nanofibers were most frequently produced in the midwest and west, and electrospun polymer fibers and "other" carbonaceous nanomaterials were produced most frequently in the midwest.

Overall, 34% of eligible companies were reported to be exclusively primary manufacturers of ECN, while 26% were solely secondary manufacturers, and 39% were both primary and secondary manufacturers. These percentages did not vary substantially by ECN type (Table 2). Regarding the scale of manufacturing among the companies, 59% were at full manufacturing scale (either primary

TABLE 1. Locations of Companies Manufacturing or Using Engineered Carbonaceous Nanomaterials in the United States

	US Region (%)*				
Nanomaterial Type	Northeast	Southeast	Midwest	West	Total†
Carbon nanotubes	18 (41%)	4 (9%)	5 (11%)	17 (39%)	44
Graphene	1 (10%)	1 (10%)	4 (40%)	4 (40%)	10
Fullerenes	4 (44%)	1 (11%)	1 (11%)	3 (33%)	9
VGCNF	1 (17%)	0	2 (33%)	3 (50%)	6
EPF	0	1 (33%)	2 (67%)	0	3
Other‡	4 (27%)	1 (7%)	6 (40%)	4 (27%)	15
Total§	21 (34%)	6 (10%)	15 (25%)	19 (31%)	61§

EPF, electrospun polymer fibers; VGCNF, vapor-grown carbon nanofibers

*Northeast includes CT, DE, MA, NH, NJ, NY, PA, VT; southeast includes GA, MD, NC, SC, TN, VA; midwest includes IL, MI, MN, OH, WI; and west includes AZ, CA, NM, OK, TX, WA. No eligible manufacturers or users were identified in AK, AL, AR, CO, DC, FL, HI, IA, ID, IN, KY, KS, LA, ME, MI, MO, MS, MT, ND, NE, NV, OR, RI, SD, UT, WV.

†Companies were counted once for each type of material produced and for each region in which it was produced.

‡Includes dendrimers, diamond-like, nanoporous carbon, carbon quantum dots, and others.

§Each company producing multiple materials was counted only once.

TABLE 2. Primary or Secondary Manufacturing Status by Nanomaterial Type

	Manufacturing Status			
Nanomaterial type	Primary	Secondary	Primary & secondary	Total*
Carbon nanotubes	14 (33%)	18 (42%)	11 (26%)	43
Graphene	4 (40%)	4 (40%)	2 (20%)	10
Fullerenes	3 (38%)	3 (38%)	2 (25%)	8
VGCNF	3 (50%)	3(50%)	0	6
EPF	0	1 (33%)	2 (67%)	3
Other†	6 (40%)	5 (33%)	4 (27%)	15
Total‡	21 (34%)	16 (26%)	24 (39%)	61‡

EPF, electrospun polymer fibers; VGCNF, vapor-grown carbon nanofibers.

*Companies were counted once for each type of material produced.

†Includes dendrimers, diamond-like, nanoporous carbon, carbon quantum dots, and others.

‡Each company producing multiple materials was counted only once.

or secondary), 11% were at pilot-scale, 11% were at research and development-scale with plans to scale up, and 18% (primarily, the nonparticipating companies) operated at unknown scale.

About half ($n = 30$) of the eligible companies agreed to be interviewed and provided information about material quantities, dimensions, and methods employed to reduce workers' exposures. The number of employees reported to be handling ECN at the 36 manufacturers with workforce size estimates (from all sources) ranged from three to 100 (476 total, not including 11 companies for which estimates were not available) and at the pilot scale operations from one to 30 employees (144 total, not including 1 company for which estimates were not available). Thus, the eligible companies employed a total of about 620 workers directly using ECN (Table 3). Most ($n = 375$) worked with single-walled or multiwalled CNT. Companies handling carbon nanomaterials in manufacturing, pilot scale, and R&D operations preparing to scale-up in the near future have all seen growth in the industry during 2006, 2007, and 2008. Employee numbers increased by roughly 14% in manufacturing, 74% in pilot plant operations, and 44% in R&D operations preparing to scale-up in the next 5 years. The estimate for manufacturers includes participating and nonparticipating companies with employee data available over a 3-year period. Though the time periods for ascertaining the number of workers employed differed by 2 years for the participating (2006 to 2008) and nonparticipating companies (2004 to 2006), only one out of the five nonparticipating companies had a notable change in employee numbers over the 3-year period. Twenty-two participating companies and five nonparticipating companies were used for the growth estimate. Employee counts for the nonparticipating developmental/small sales companies were only available for 1 year, so they were not included in the above growth estimates.

The overall ECN workforce growth between Year 1 and Year 3 was 34%: 17% from Year 1 to Year 2, and 15% from Year 2 to Year 3 (Table 4). Comparing the growth in CNT manufacturing operations with that in those involving all other types of ECN, the industry growth picture is similar. The number of employees in manufacturing operations involving CNT increased 44% over the 2-year period; from 192 employees to 276 in 22 companies. Manufacturers of other ECN experienced a 16% increase in growth over the 2-year period: from 109 to 126 employees in nine companies.

The growth in pilot operations is due primarily to CNT operations. Throughout the 3 years of interest, approximately 90% of employees working in pilot operations worked for companies involved with CNT. In research and development operations preparing to scale-up, both fullerenes and CNT play a role in the growth. There was an 88% increase in the number of employees in CNT operations and a 13% growth in fullerene operations.

The quantities produced annually as reported by the manufacturers ranged from 0.9 to 10,000 kg (roughly 18,000 kg total; Table 3). Quantities handled at the pilot plant sized operations were reported to range from 0.2 to 3000 kg (3350 kg total). No quantity data were available for the nonparticipating developmental scale companies. Three companies considered the quantities they produced to be business sensitive information; one would not provide any quantity information though the other two were willing to provide "less than" estimates. Although CNT producers comprised the largest group of ECN manufacturers, they produced the second-highest quantity of material: greater than 3472 kg (14 CNT manufacturers did not provide quantity information). Electrospun polymer fibers were produced in 40,000 linear yard quantities, and 10,000 kg of carbon nanofibers were reported to be produced annually. Quantities of other ECNs were much lower: 700 kg of dendrimers, 40.3 kg of graphene, and 14.6 kg of fullerenes. At least 4000 kg of "other" nanomaterials were produced annually.

Overall, 87% of companies completing the questionnaire provided information on synthesis methods. Among CNT manufacturers ($n = 13$), 62% reported chemical vapor deposition, 23% reported using arc discharge, 15% reported flame combustion, 8% reported using laser ablation, and one company did not report (some reported more than one method).

Our comparisons of the list of CNT producers against both the contacts made by the NIOSH nanotechnology coordination group and in response to the state of California's request for notification of CNT production in the state found no companies that were not captured by our study.

DISCUSSION

This study attempted to identify all companies producing ECN in the United States. The number of companies is large, with more

TABLE 3. Number of Employees and Quantity Produced by Nanomaterial Type Eligible Companies (Participants and Nonparticipants)

	Manufacturers		Pilot/Developmental Scale	
Type of Carbon Nanomaterial	No. of Employees Per Company	Quantity (kg/yr) Produced Per Company	No. of Employees Per Company	Quantity (kg/yr) Produced Per Company
Carbon nanotubes	2–100	0.2–2500	1–30	0.1–300
Vapor grown nanofibers	5	10,000	NA	NA
Polymer fibers electrospun	10–18	40,000 linear yards	NA	NA
Fullerenes	4–23	1–13.5	NA	0.1
Graphene	8	ND	3–20	0.001–40
Dendrimers	3–19	700	NA	NA
Diamond-like	5	1200 wafers/yr	NA	NA
Nanoporous carbon	NA	NA	ND	3000
Other	9	1000	NA	NA
No data	5–100	ND	NA	NA

ND, no data; NA, not applicable.

TABLE 4. Industry Growth—Employee Count by Manufacturer and Nanomaterial Type, Among Eligible Companies With Workforce Size Information

Nanomaterial CNT or Other	Production Scale	Employee Count, Year 1*	Employee Count, Year 2† (% Change From Year 1)	Employee Count, Year 3‡ (% Change From Year 2)
CNT	Manufacturing	172	196 (14%)	214 (9.2%)
CNT	Pilot	20	43 (115%)	62 (44%)
Total CNT	All combined	192	239 (24%)	276 (15%)
Other	Manufacturing	89	80 (−10%)	100 (25%)
Other	Pilot	20	32 (60%)	26 (−19%)
Total other	All combined	109	112 (2.7%)	126 (13%)
Total ECN	All combined	301	351 (17%)	402 (15%)

CNT, carbon nanotubes; ECN, engineered carbonaceous nanomaterials.
*Year 1 was 2004 for nonparticipating companies ($n = 5$) and 2006 for participating companies ($n = 26$).
†Year 2 was 2005 for nonparticipating companies and 2007 for participating companies.
‡Year 3 was 2006 for nonparticipating companies and 2008 for participating companies.

than 60 represented. The ECN workforce identified in this study, however, is small, with an average of about 10 workers handling ECN per company. By far, single-walled and multiwalled CNT were the most common substances produced, with the 43 eligible companies employing at least 375 workers by our estimate (see Table 2). The strengths of this study include the systematic evaluation of ECN producers in the United States in 2008 and 2009. Consistent information was collected on workforce size and characteristics across the entire industry. Comparison to data collected by other groups suggests that this study's sampling method adequately captured carbon nanotube producers.

However, this study has a number of limitations that affect interpretations of the feasibility of epidemiologic studies in this workforce and that could be used to design improved surveys in the future. The participation rate was suboptimal. This may have been affected by companies' concerns over recent interest among regulatory agencies in listing CNT as a hazardous substance. Responsiveness might have been improved if NIOSH rather than a contractor had made the contacts (eg, several nonparticipants reported concerns in sharing data with potential competitors). It was necessary to rely on self-report for information. In addition, the time period of survey (October 2008 to May 2009) occurred during a severe global economic recession, which may have affected companies' plans to expand at the time of the survey. This likely led to an underestimate of the workforce size in future years, as the rate of growth may appear lower than reality with economic recovery. It is also clear that this study underestimated the research and development workforce size, because such groups were excluded if they did not express a plan to move to at least pilot scale in the next 5 years. Furthermore, a number of research and development institutions in government, academia, and private industry were excluded at the outset (ie, they were not captured in our initial examination of 139 potentially eligible companies) because they were known to be involved only in research and development and were thought likely to have smaller workforces exposed to a wide variety of materials. It appears that 34 companies initially queried that were ineligible for this study are actually handling ECN either in the United States or elsewhere. Lastly, the number of companies no longer in business at the time of the survey illustrates the fact that the ECN workforce is small and fluid: many new companies either fail or are acquired by other companies if successful. Business relationships (eg, company buyouts and supply chains) were recorded when possible in our database, which may be valuable for tracking these workers for any future epidemiologic studies.

Industrywide exposure assessment studies are likely feasible at this time; however, they are subject to a number of challenges. Studies of the US ECN workforce will likely be hampered by limitations in the measurement capabilities for these materials. While a mass-based method has been developed for assessing elemental carbon exposure in diesel-exposed occupations,[22] it cannot differentiate between nano-sized particles and those of larger size (a potentially important toxicological consideration). In addition, the method's limit of quantitation for single-walled and multiwalled carbon nanotubes may approach workplace equivalent mass concentrations that have been shown to cause adverse effects in animal studies.[23] At present, investigations are being carried out on the most appropriate particle size–based analysis methods for CNT and other ECNs.[15–17] Fiber counts and dimensions may also prove useful as metrics, as has recently been described in the asbestos literature.[24] Exposure assessment studies will provide important information regarding tasks and conditions most likely to result in elevated occupational exposures, which will be critical for designing future epidemiologic studies in these emerging industries. Furthermore, these methods should ideally be translated to the toxicology studies, so that findings can be compared between human and animal studies.

In order for optimized exposure assessment methods to be applied by industry-based exposure assessment personnel (which would be required for large-scale epidemiologic research), they must be focused and cost-effective while also measuring toxicologically relevant aspects of exposure. In addition, employers should be encouraged to collect, retain, and share such exposure measurements over the long term, as they may be needed for future epidemiologic studies.[25] Exposure registries and large exposure databases may be useful tools to retain institutional knowledge about ECN workers and exposures.

A challenge affecting both exposure assessment and epidemiologic studies of occupational exposures to ECN will be consideration of concomitant exposures at these facilities. ECN synthesis methods may involve exposures to other hazardous materials, such as heavy metals used as catalysts, or hydrocarbons used as feedstock or precursor.[17] A recent study estimated that 11 potentially hazardous exposures existed within a carbon nanofiber manufacturing facility, including several types of carbon nanofibers, the precursor material and intermediates of pyrolysis (often, simple polycyclic aromatic hydrocarbons), methane, propanol, and high heat.[26] Not all of these are hazards for the same outcome (eg, cancer or nonmalignant respiratory disease). Furthermore, this phenomenon is not unique to the study of ECN—most studies of long-term health impacts from occupational exposures must contend with multiple exposures. However, epidemiologic studies should assess exposures to other substances that potentially cause the disease of interest, so that they may be treated statistically as confounders, or (more importantly) that their joint effects with ECN may be investigated.

Large-scale cohort studies of the US ECN workforce are likely infeasible because of the small workforce (causing low power) and short follow-up time available for diseases with long latency.[18] However, potential cross-sectional studies and utility of pooling internationally, particularly of CNT and carbon nanofiber manufacturers, should be considered. At least ten additional companies, many of them large multinational corporations, are involved in ECN manufacturing outside the United States. It is unclear how large the US workforce may become, given the typical patterns of manufacturing in the high-technology manufacturing;[27,28] thus, international pooling of cohorts may offer the most promise for large-scale studies. In the meantime, cross-sectional studies may be the most feasible epidemiologic design. Such studies should consider evaluating pulmonary function as well as biomarkers of exposure or early effect, in relation to various aspects of measured exposure. Relevant biomarkers of early effect could include endpoints related to genotoxicity (eg, spectral karyotyping or multiphase fluorescence in-situ hybridization), given recent evidence regarding interference of CNT with mitotic spindle formation, biomarkers of oxidative stress (glutathione and malondialdehyde in mouse studies[29]), or markers of pulmonary fibrosis. These could include serum immunoproteins IL-6, KL-6, SP-A, and SP-D, which have shown promise as markers of pulmonary inflammation and fibrosis in studies of workers exposed to indium compounds and cobalt-tungsten-carbide.[30,31] Of great need are biomarkers of systemic exposure, such as genes expressed in circulating lymphocytes or soluble serum proteins[32] that have been identified from animal studies. Such biomarkers could complement industrial hygiene-based sampling to identify workers at higher risk of effects from exposure, as well as confirm results from toxicology studies.

CONCLUSIONS

This study identified a small (>600) but growing workforce within 61 companies manufacturing and using engineered carbonaceous nanomaterials in the Unites States. The materials most commonly produced include single-walled and multiwalled carbon nanotubes. Industrywide exposure assessment studies will be useful in identifying the extent of occupational exposure to these materials. Epidemiologic researchers should consider the feasibility of cross-sectional studies using biomarkers of exposure and early pulmonary effect, along with industrial hygiene sampling, as well as the potential for pooled international studies of carbon nanotube manufacturing workers.

ACKNOWLEDGMENTS

This study received partial funding from the National Toxicology Program (Interagency Agreement 97-04M21). The authors thank Drs John McKernan and Douglas Trout for assistance in conceptualizing the project; Kevin H. Dunn for contributing valuable comments on the questionnaire; Dr Amy Heintz, Candace Mayweather Hunter, and Kellie Fay for helping to identify potentially eligible companies; Jean Busto for contacting companies to determine eligibility and arrange for interviews; Christine Gersic and Denise Giglio for providing clerical assistance with the study; and Lian Luo for developing the database used at NIOSH for the study.

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