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Carbon nanotube and nanofiber exposure and sputum and blood biomarkers of early effect among U.S. workers

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ABSTRACT

Background: Carbon nanotubes and nanofibers (CNT/F) are increasingly used for diverse applications. Although animal studies suggest CNT/F exposure may cause deleterious health effects, human epidemiological studies have typically been small, confined to single workplaces, and limited in exposure assessment.

Objectives: We conducted an industrywide cross-sectional epidemiological study of 108 workers from 12 U.S. sites to evaluate associations between occupational CNT/F exposure and sputum and blood biomarkers of early effect.

Methods: We assessed CNT/F exposure via personal breathing zone, filter-based air sampling to measure background-corrected elemental carbon (EC) (a CNT/F marker) mass and microscopy-based CNT/F structure count concentrations. We measured 36 sputum and 37 blood biomarkers. We used factor analyses with varimax rotation to derive factors among sputum and blood biomarkers separately. We used linear, Tobit, and unconditional logistic regression models to adjust for potential confounders and evaluate associations between CNT/F exposure and individual biomarkers and derived factors.

Results: We derived three sputum and nine blood biomarker factors that explained 78% and 67%, respectively, of the variation. After adjusting for potential confounders, inhalable EC and total inhalable CNT/F structures were associated with the most sputum and blood biomarkers, respectively. Biomarkers associated with at least three CNT/F metrics were 72 kDa type IV collagenase/matrix metalloproteinase-2 (MMP-2), interleukin-18, glutathione peroxidase (GPx), myeloperoxidase, and superoxide dismutase (SOD) in sputum and MMP-2, matrix metalloproteinase-9, metalloproteinase inhibitor 1/tissue inhibitor of metalloproteinases 1, 8-hydroxy-2′-deoxyguanosine, GPx, SOD, endothelin-1, fibrinogen, intercellular adhesion molecule 1, vascular cell adhesion protein 1, and von Willebrand factor in blood, although directions of associations were not always as expected.

Abbreviations: 8-OHdG, 8-hydroxy-2′-deoxyguanosine; AIC, Akaike Information Criterion; α-2-M, alpha-2-macroglobulin; Apo-AI, apolipoprotein A-I; Apo-AII, apolipoprotein A-II; CRP, C-reactive protein; CNF, carbon nanofibers; CNT, carbon nanotubes; CNT/F, carbon nanotubes and carbon nanofibers; CHM, cardiovascular health metric; C3, complement C3; CPC, condensation particle counter; CI, confidence interval; ELPI, electrical low-pressure impactor; EC, elemental carbon; ECN, engineered carbonaceous nanomaterials; GPx, glutathione peroxidase; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM-1, intercellular adhesion molecule 1; IL-1 β, interleukin-1 beta; IL-2, interleukin-2; IL-4, interleukin-4; IL-5, interleukin-5; IL-6, interleukin-6; IL-6R-β, interleukin-6 receptor subunit beta; IL-8, interleukin-8; IL-10, interleukin-10; IL-12p70, interleukin-12 subunit p70; IL-18, interleukin-18; IARC, International Agency for Research on Cancer; IQR, interquartile range; LDD, least detectable dose; MDC, C-C motif chemokine 22/macrophage derived chemokine; MMP-1, interstitial collagenase/matrix metalloproteinase-1; MMP-2, 72 kDa type IV collagenase/matrix metalloproteinase-2; MMP-7, matrilysin/matrix metalloproteinase-7; MMP-9, matrix metalloproteinase-9; MUC-1/KL-6, mucin-1/Krebs von den Lungen-6; MWCNT, multi-walled carbon nanotubes; MPO, myeloperoxidase; NCI, National Cancer Institute; NIOSH, National Institute for Occupational Safety and Health; NMAM, NIOSH Manual of Analytical Methods; Ln, natural logarithm of linear; NSAID, non-steroidal anti-inflammatory drugs; OEL, occupational exposure limits; $PM_{2.5}$, particulate matter mass with an aerodynamic diameter ≤ 2.5 μm; PBZ, personal breathing zone; DustTrak, photometer/optical particle counter; PAI-1, Plasminogen activator inhibitor 1; EDN1, endothelin-1; REL, recommended exposure limit; SPP-1, osteopontin/Secreted phosphoprotein 1; SWCNT, single-walled carbon nanotubes; SOD, superoxide dismutase; TIMP-1, metalloproteinase inhibitor 1/Tissue inhibitor of metalloproteinases 1; t-PA, tissue-type plasminogen activator; TEM, transmission electron microscopy; TNF-α, tumor necrosis factor alpha; U.S., United States; U.S. EPA, U.S. Environmental Protection Agency; VCAM-1, vascular cell adhesion protein 1; vWF, von Willebrand factor

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Conclusions: Inhalable rather than respirable CNT/F was more consistently associated with fibrosis, inflammation, oxidative stress, and cardiovascular biomarkers.

1. Introduction

Carbon nanotubes (CNT) and carbon nanofibers (CNF; collectively CNT/F) are increasingly used in many novel applications spanning several products and industries such as manufacturing, electronics, information technology, healthcare, and life sciences (National Institute for Occupational Safety and Health, 2013; Schubauer-Berigan et al., 2011). Although the number of workers involved in the manufacture and use of CNT/F is relatively small, it is growing steadily (Schubauer-Berigan et al., 2011). In addition, recent exposure assessment studies have documented exposure to CNT/F among workers who manufacture these materials or use them in downstream applications including incorporation in semiconductors, polymers, composites, or other products (Debia et al., 2016; Guseva Canu et al., 2016).

There is concern regarding possible health effects of exposure to CNT/F because of their physical similarities to workplace or environmental particulate matter and asbestos (National Institute for Occupational Safety and Health, 2013; Oberdörster et al., 2015). Workplace and environmental exposure to airborne particulate matter such as diesel emissions and ultrafine air pollution has been associated with cancer, cardiovascular and respiratory diseases, and eventual mortality (Brook et al., 2010; International Agency for Research on Cancer Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012, 2016; Kuempel et al., 2017; U.S. Environmental Protection Agency, 2009). CNF and a few types of multi-walled CNT (MWCNT; Mitsui-7 and similar materials) are physically similar to asbestos. Kasai et al. (2016) found that one type of MWCNT (MWCNT-7, Mitsui Ltd., Japan) is carcinogenic to the lungs of rats. In addition, the International Agency for Research on Cancer (IARC) classified MWCNT-7 as possibly carcinogenic (IARC Group 2B) to humans (Grosse et al., 2014; Kuempel et al., 2017). Evidence for the carcinogenicity of single-walled CNT and other types of MWCNT was insufficient (Grosse et al., 2014; Kuempel et al., 2017), but other potential adverse effects are a concern (Aragon et al., 2017; Erdely et al., 2011; Kuempel et al., 2017; National Institute for Occupational Safety and Health, 2013).

The health effects of CNT/F are difficult to assess as a general class because of the diversity of these materials. Toxicity may be affected by their different physical and chemical properties such as their shape, aspect ratio, size, structure, surface area and chemistry, number of particles for a given mass, purity, functionalization, and tendency to agglomerate (National Institute for Occupational Safety and Health, 2013; Oberdörster et al., 2015). Animal studies suggest that exposure to CNT/F may cause oxidative stress and fibrotic, inflammatory, and cardiovascular health effects locally and systemically (Erdely et al., 2009; Oberdörster et al., 2015). The few human epidemiological studies that have been conducted, however, have typically been small, confined to single workplaces, and limited in exposure assessment (Fatkhutdinova et al., 2016; Kuijpers et al., 2018; Lee et al., 2015; Liou et al., 2015; Shvedova et al., 2016; Vlaanderen et al., 2017). Therefore, we conducted an industrywide cross-sectional epidemiological study of 108 workers from 12 sites across the U.S. to evaluate associations between occupational exposure to CNT/F and human health effects (Schubauer-Berigan et al., unpublished results[2]).

The latencies for overt health effects such as pulmonary fibrosis, other respiratory diseases, cardiovascular diseases, cancer, or other chronic diseases are likely several years or decades. The majority of workers included in our study likely have not been exposed to CNT/F long enough or at high enough levels to cause overt health effects at this time. For these reasons, we evaluated relationships between occupational CNT/F exposure and early sputum and blood biomarker responses and patterns. We included biomarkers that have been positively associated with pulmonary fibrosis or that were increased in animal models of CNT/F exposure, pulmonary toxicant exposure studies, and lung cancer (Brook et al., 2010; Erdely et al., 2009, 2011; Ichiyasu et al., 2012; Liou et al., 2012; Pine et al., 2011). Virtually all of the biomarkers we evaluated, however, have no known clinical significance. Therefore, associations we observed between CNT/F exposure and biomarkers may reflect short-term reactions and may not indicate future chronic diseases. Nevertheless, evaluating biomarkers may be useful for elucidating possible mechanisms for CNT/F exposure or disease pathways, especially when compared to animal studies. For the current analysis, we focused on biomarkers of fibrosis, inflammation, oxidative stress, and cardiovascular effects.

2. Materials and methods

2.1. Study population

We have previously described how we identified companies manufacturing, using, or distributing CNT/F (Dahm et al., 2011; Schubauer-Berigan et al., 2011). Briefly, we initially identified companies via industry profiles (Dun, and Bradstreet, Inc., 2016; Lux Research, Inc., 2006, 2007), internet searches, and personal contacts or colleagues (Dahm et al., 2011; Schubauer-Berigan et al., 2011). Of 139 companies we identified in 2008 that worked with various types of engineered carbonaceous nanomaterials, 59 met the inclusion criteria of manufacturing, using, or distributing CNT/F in the U.S. at full-, pilot-, or research-scale (Dahm et al., 2011; Schubauer-Berigan et al., 2011) (Fig. 1). We included companies at research-scale only if they had plans to scale up within 5 years (Dahm et al., 2011; Schubauer-Berigan et al., 2011). We identified an additional seven eligible companies in 2012 by updating the original search (Fig. 1). The eligible companies employed over 500 workers who work with CNT/F (Fig. 1). For the current cross-sectional epidemiological study, we visited the facilities of 12 companies between December 2012 and September 2014, and 108 workers participated (75% of the 144 invited workers) (Fig. 1).

The Human Subjects Review Board of the U.S. Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (NIOSH), approved this study. All workers provided written informed consent after the study was explained to them.

2.2. Sputum and blood collection and biomarker assessment

Workers underwent a limited in-person clinical exam conducted by a physician at the middle or end of the midweek shift for which we collected their personal breathing zone exposure measurements (see Section 2.3) (Schubauer-Berigan et al., unpublished results). As part of this exam, we collected induced sputum from each worker. We followed the procedure outlined in an induced sputum evaluation among popcorn manufacturing workers (Akpinar-Elci et al., 2005), but modified to use isotonic saline at lower nebulizer output rate. This modification reduces the occurrence of side effects while producing sputum of acceptable quality (Loh et al., 2004). Five workers had contraindications for sputum induction and were ineligible (Fig. 1). In addition, five workers declined to provide sputum samples and we did not try sputum

[2] Citations to "Schubauer-Berigan et al., unpublished results" refer to a journal article manuscript we wrote that is currently under review for publication. The current citation is Schubauer-Berigan, M.K., Dahm M.M., Erdely, A., Beard, J.D., Birch, M.E., Evans, D.E., et al., Unpublished results. Association of pulmonary, cardiovascular, and hematologic metrics with carbon nanotube and nanofiber exposure among U.S. workers: a cross-sectional study.

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