

Exposure Assessment and Epidemiological Study of U.S. Workers Exposed to
Carbon Nanotubes and Carbon Nanofibers

Supporting Statement B

Request for Office of Management and Budget (OMB) Review
and Approval for a Federally Sponsored Data Collection

Mary K. Schubauer-Berigan, PhD
and
Matthew M. Dahm, MPH
Project Officers

National Institute for Occupational Safety and Health
Division of Surveillance, Hazard Evaluations, and Field Studies
4676 Columbia Parkway, Mail Stop R-15
Cincinnati, Ohio 45226

MSchubauer-Berigan@cdc.gov

513-841-4251 (phone)

MDahm@cdc.gov

513-458-7136 (phone)

513-841-4486 (fax)

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Section B. Collections of Information Employing Statistical Methods

This information collection does not employ statistical methods to select respondents.

1. Respondent Universe

The respondent universe includes all workers at all companies handling carbon nanotubes (CNT) or carbon nanofibers (CNF) at pilot scale or full scale, and those at the research and development (R&D) scale with plans to scale up within five years. We identified, using these criteria, 50 eligible companies across the U.S. in 2008 (Schubauer-Berigan et al., *J Occup Environ Med* 2011;53:S62-S67), that are producing, using, or distributing CNT or CNF. All eligible companies still in operation as of mid-2010 were invited to participate in exposure assessment and epidemiologic research. Initial site visits were done at the 16 facilities that indicated interest in participating, to verify that workers at the company were handling CNT or CNF, to determine the best procedures for assessing exposure to CNT and CNF, and to discuss the industrywide study with employees and managers. In preliminary site visits, we determined that there were an average of 9 employees at each site, working with or around these nanomaterials. Because these are small companies, with every employee having some potential for direct or indirect exposure to CNT or CNF, all employees at all participating facilities will be invited to participate in the study.

A power analysis conducted for the epidemiologic study determined that 100 workers would be necessary to observed associations between CNT or CNF exposure and loss of lung forced vital capacity. Therefore, 10 companies would be required to have a study with sufficient power. Of the 16 companies initially visited by NIOSH, 10 expressed interest in participating in the industrywide study. Thus, the site selection process may be described as a convenience sample (companies could not be compelled to participate) of

an exhaustive sample of all U.S. facilities making or using CNT or CNF, as of December 2011. All workers at each facility will be invited to participate in the industrywide study.

2. Procedures for the Collection of Information

The proposed research is a cross-sectional study of the small current workforce involved with CNT and CNF in manufacturing and distribution. The study involves an industrywide exposure assessment study to evaluate worker exposure and further development and refinement of measurement methods for CNT and CNF. This component will refine sampling and analysis protocols previously developed for the detection and quantification of CNT and CNF in US workplaces. The study also involves a cross-sectional study relating the best metrics of CNT and CNF exposure to markers of early pulmonary or cardiovascular health effects. After the sampling and analysis protocols have been established to measure CNT and CNF, concurrent with the industrywide exposure assessment study, several biomarkers of early effect (for pulmonary fibrosis, cardiovascular disease, and genetic damage) will be measured in blood and sputum for workers exposed to a range of CNT and CNF levels. A questionnaire will also be administered, as described below.

For the industrywide study, exposure measurements will be done for each participant at each study workplace for two days. During this period, study participants will be asked to wear a vest containing three small sampling pumps. Study participants are asked to wear the pumps for the purpose of determining the amount of CNT or CNF in the air around them. The sampling pumps pull air through (1) a filter to measure amounts of elemental carbon (a marker for CNT or CNF exposure) that may reach two different areas of

the respiratory tract and (2) a filter used to count the number of structures containing CNT and CNF in the air participants are breathing.

Concurrent with the industrywide exposure assessment study, a medical examination will be conducted by a NIOSH physician (to measure height and weight, waist circumference, and to review information obtained from the questionnaire) to ensure that the participant is healthy enough to take part in the spirometry and biospecimen collection. Then, lung function will be assessed using spirometry, and blood and induced sputum specimens will be collected. Several biomarkers of early effect (for pulmonary fibrosis, cardiovascular disease, and genetic damage) will be measured in the biospecimens for workers exposed to a range of CNT and CNF levels. This will be accompanied by a questionnaire, administered as a computer-assisted personal interview (CAPI) by NIOSH personnel, with a three-fold purpose: (1) to determine whether study participants have any contraindications for the medical procedures to be conducted (spirometry and sputum induction), (2) to assist in interpretation of the medical tests and biomarker results, and (3) to inquire about current and past exposure to CNT, CNF, and other chemicals, dusts, and fumes, so that estimates of exposure can be made for use in data analysis. After administration of the CAPI, medical examinations will be conducted and biospecimens will be collected. A complete blood count will be conducted on the blood samples, and several biomarkers (looking at inflammation, oxidative stress, early indications of pulmonary fibrosis, cardiovascular effects, and genetic damage) will be measured on both the blood and sputum samples.

As indicated above, a large number of the questions included in the CAPI are for the protection of the participant, to ensure that he or she is healthy enough for the spirometry and biospecimen collection procedures. As such, these questions will not be used in any data analyses. Statistical analyses will be conducted to determine the nature of the relation between exposure

to CNT and CNF and the outcome measures of interest. These outcome measures are: systolic and diastolic blood pressure; lung function metrics, including forced vital capacity and forced expiratory volume in one second; and each measured biomarker of early health effects, including biomarkers of inflammation, oxidative stress, pulmonary fibrosis, cardiovascular disease and cancer. These analyses will be based on multiple linear or logistic regression analyses to determine the nature of relation between quantitative metrics of exposure to CNT and CNF (based on elemental carbon measurements and CNT or CNF structure counts via transmission electron microscopy) and each outcome measure listed above. The statistical models will adjust for important potential confounding factors such as tobacco and alcohol consumption history, age, gender, body mass index, waist circumference, use of certain medications, and workplace or hobby co-exposures, including non-engineered nanoscale particulate matter.

3. Methods to Maximize Response Rates and Deal with Nonresponse

This study does not use statistical sampling methods, so most of these items do not apply. Company and employee participation is entirely voluntary. However, we have attempted to maximize participation by working with the companies to provide information on occupational exposure levels and control methods that are useful for their understanding of how to minimize exposure, and by undertaking the study entirely at the workplace, so that the participant does not need to use personal time to participate. We have streamlined the questionnaire and the medical and biospecimen collection procedures to minimize the inconvenience to the participant and to the employer. We are using the NIOSH Field Evaluations and Response Vehicle (a large, lab-equipped trailer) to conduct all medical exams and biospecimen collections in a clean, private space.

4. Tests of Procedures or Methods to be Undertaken.

The procedures used in the study, including the CAPI questionnaire, have been tested on a group (fewer than 10) of NIOSH volunteers, to ensure clarity and understandability of questions, and to minimize the inconvenience of the procedures undertaken.

5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data.

A protocol was prepared describing all aspects of the study, including data collection instruments and statistical analysis. This protocol was reviewed by Dr. Elizabeth Whelan, the Industrywide Studies Branch Chief of NIOSH's Division of Surveillance, Hazard Evaluations, and Field Studies (DSHEFS), as well as Dr. Douglas Trout, Associate Director for Science of NIOSH's DSHEFS. As part of the NIOSH peer review process, in 2012, the protocol, including the data collection and statistical data analysis methods, was peer reviewed by:

- (1) Sara Brenner, MD, MPH
Assistant Vice President for NanoHealth Initiatives and Assistant Professor
University of Albany College of Nanoscale Science and Engineering
NanoFab East
257 Fuller Road, Rm 4406
Albany, NY 12203
518.956.7224
sbrenner@albany.edu
- (2) James Lockey, MD, MS
Professor of Occupational, Environmental and Pulmonary Medicine
University of Cincinnati Department of Environmental Health
Kettering Laboratory
3223 Eden Ave
Cincinnati, OH 45267
513.558.0030
lockeyje@ucmail.uc.edu
- (3) Thomas M. Peters, PhD, MS, CIH
Associate Professor
University of Iowa School of Public Health
Department of Occupational and Environmental Health

CPHB S331
105 River Street
Iowa City, IA 52242
319.335.4436
Thomas-m-peters@uiowa.edu

Comments received by all these reviewers led to changes that were incorporated into the protocol. The data will be collected by NIOSH personnel, including Mary Schubauer-Berigan, PhD (Principle Investigator, CAPI data), Matthew Dahm, MPH (Co-Principle Investigator, exposure data), Douglas Evans, PhD (Co-Investigator, exposure data), Marie de Perio, MD and Douglas Trout, MD (NIOSH physicians, medical data), and technicians from NIOSH's Division of Applied Research and Technology (spirometry and biospecimens). All data will be statistically analyzed by the NIOSH employees listed above and by a NIOSH statistician (James Deddens, PhD).