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

Supporting Statement Section A

New

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)

June 7, 2013

Table of Contents

Section Title

LIST OF ATTACHMENTS

Section A. Justification

A.1. Circumstances Making the Collection of Information Necessary

Background

This is a new information collection request (ICR) from the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC). This data collection is authorized by Section 20(a)(1) of the Occupational Safety and Health Act (29 U.S.C. 669) (**Attachment A**). The 60-day Notice for this collection was published in the Federal Register on September 20, 2012, as required by 5 CFR 1320.8(d) (**Attachment B**).

The mission of the NIOSH is to promote safety and health at work for all people through research and prevention. The Occupational Safety and Health Act of 1970, Public Law 91-596 (Section 20) [a][1] authorizes NIOSH to conduct research to advance the health and safety of workers. In this capacity, NIOSH will conduct an exposure assessment and epidemiological study of U.S. carbon nanotube (CNT) and carbon nanofiber (CNF) workers.

At present, because of the newness of the technology, much of the occupational exposure to engineered nanomaterials occurs at the research and development (R&D) or pilot scale. There have been few reliable surveys of the size of the workforce exposed to nanomaterials. Health effects from exposure to nanomaterials are uncertain, but may be different from larger-sized particles of the same material. This is due to the small size, high surface area per unit mass (i.e., specific surface area) or (in some cases) high aspect ratio of nanomaterials. CNTs and CNFs are among the nanomaterials of greatest interest from a public health perspective because of their potentially asbestiform properties (e.g., high aspect ratio) and toxicological evidence of possible fibrogenic, inflammatory, and clastogenic damage resulting from exposures at occupationally relevant levels. Toxicological studies have demonstrated the occurrence of pulmonary

fibrosis at occupationally relevant exposure levels (DHHS 2013; NIOSH Current Intelligence Bulletin 65). Animal studies have also shown that CNT-induced pulmonary inflammation causes release of inflammatory mediators and activation of leukocytes, which may contribute to cardiovascular disease (CVD) (Simeonova and Erdely; *Inhal Toxicol*. 2009; 21 Suppl 1:68-73). Cytokine profiles & gene expression analysis may provide biomarkers of either pulmonary or cardiovascular effects of CNT exposure (Erdely et al.; *J Occup Environ Med*. 2011;53:S80-6).

In addition to their potential toxicity, the useful properties of CNT and CNF have rendered them among the first nanomaterials to be commercially exploited in manufacturing settings. Thus, an epidemiologic study to evaluate possible early health effects from and biological effects of occupational exposure to CNT and CNF seems warranted.

The proposed project supports the NIOSH legislatively mandated industrywide studies program that conducts epidemiological and exposure assessment research studies to identify the occupational causes of disease in the working population and their offspring and to effectively communicate study results to workers, scientists, industry, and the public.

Several national and international organizations such as the NIOSH, the U.K.’s Health and Safety Executive, the National Cancer Institute, the National Toxicology Program, and the International Agency for Research on Cancer have emphasized the need for basic knowledge about the human health effects of exposures to engineered nanomaterials. This project will investigate the possible associations between exposures to CNT or CNF and blood pressure, loss of lung function, or biomarkers of early health effects, in a relatively small sample of workers. In addition, NIOSH may pool the data obtained in this study with data on other workers to investigate possible associations of CNT or CNF with persistent health effects such as pulmonary fibrosis, cardiovascular disease or cancer. This request also includes the

collection of data that would be useful should NIOSH eventually develop a registry of CNT/CNF exposed workers.

The proposed research is a cross-sectional study of the small current workforce involved with CNT and CNF in manufacturing and distribution, to be conducted in the following phases: 1) Industrywide exposure assessment study to evaluate worker exposure and further development and refinement of measurement methods for CNT and CNF. This component will be based on sampling and analysis protocols previously developed for the detection and quantification of CNT and CNF in US workplaces. 2) A cross-sectional study relating various metrics of CNT and CNF exposure (namely, the inhalable fraction of elemental carbon mass concentration, the respirable fraction of elemental carbon mass concentration, and size-classified CNT- or CNF-containing structure counts) to measures of early pulmonary or cardiovascular health effects. Using established sampling and analysis protocols to measure CNT and CNF, concurrent with the industrywide exposure assessment study, several measures of lung and cardiovascular function will be measured. In addition, 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. These studies are consistent with the recent recommendation in the NIOSH Current Intelligence Bulletin (CIB) to “Conduct cross-sectional and prospective studies of workers exposed to CNT and CNF” (DHHS 2013; NIOSH CIB 65, p.72).

Privacy Impact Assessment

All data collected for this study will be maintained in accordance with the Federal Privacy Act of 1974. Disclosure under the Privacy Act System is permitted to private contractors assisting NIOSH; to collaborating researchers under certain limited circumstances to conduct further investigations; to the Department of Justice in the event of litigation; and to

a congressional office assisting individuals in obtaining their records. Other than disclosures permitted under the Privacy Act System, participants' personal information will not be shared with anyone (except with their personal physician at the participant's request, as noted below) in a way that allows them to be identified. All data for the study will be maintained in accordance with NIOSH and CDC policies on data security for sensitive but unclassified data, including restricted access to study team members with a "need to know" each data source. Hardcopy study records will be maintained in locked rooms or file cabinets with access restricted to study team members with a justified need to maintain access. All study subjects participating in this cross-sectional study will be informed of their individual results of the exposure assessment, medical evaluation, and biomarker measurements. Notification letters will be submitted to the NIOSH Institutional Review Board (IRB) for review. Study participants will be notified within 30 days of clinically relevant medical findings (e.g., blood pressure and spirometry results) and also be sent a summary of study findings at the conclusion of the study. Individual medical results will be sent to the study participants' personal physicians, for participants who consent to this.

The questionnaire will be given by NIOSH personnel as a computer-assisted personal interview (CAPI) encrypted according to applicable Federal Information Processing Standards Publications (FIPS PUBS, see http://www.it1.nist.gov/fipspubs). Information will not be collected through websites.

Overview of the Data Collection System

Data collection for an industrywide exposure assessment and cross-sectional epidemiology study will be done among a convenience sample of 100 workers total over a three year period at approximately 10 workplaces that agree to participate. These workplaces were selected from among 50 eligible

companies, initially identified 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. 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 10 employees at each site, working with or around these nanomaterials. A power analysis conducted for the epidemiologic study determined that 100 workers would be necessary to observe associations between CNT or CNF exposure and loss of lung forced vital capacity. This power analysis takes into account the variability in lung function among healthy persons, as well as several key potential confounders, variability in expected effect and in exposure, and is described in detail in the study protocol (Schubauer-Berigan et al.; NIOSH protocol, pp. 56-61, 2013). Ten or more companies that agree to participate will be included in the study, and all workers will be invited to participate, with a goal of enrolling 100 workers as participants in the study.

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, 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. For this study, we developed a defined list of biomarkers whose analogues have shown responses to CNT exposure in animal toxicology studies, or to ultrafine particulates or occupational heavy metal exposure in human studies. The list of biomarkers to be evaluated is given in Table 1. This will be accompanied by a questionnaire (**Attachment C-1)**, administered as a CAPI by NIOSH personnel, with a three-fold purpose: (1) to determine whether study participants have any contraindications for certain 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. For example, questions about alcohol use, cystic fibrosis, diabetes, cancer, autoimmune diseases and kidney diseases are asked because they may (independent of CNT or CNF exposure) influence the blood pressure, pulmonary function, or the biomarker levels. If these illnesses are present in the study participants, we will adjust for them in statistical analyses of the association between CNT or CNF and blood pressure, pulmonary function, or the biomarkers in Table 1. After administration of the CAPI, medical examinations will be conducted by a physician to evaluate pulmonary function (via spirometry) and blood pressure, and induced sputum and blood 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. Statistical analyses will be conducted to determine the nature of the relation between exposure to CNT and CNF and these indicators or biomarkers of early health effects, considering potential confounding factors such as smoking, age,

gender, and workplace exposures, including non-engineered ultrafine particles.

Items of Information to be Collected

Information in identifiable form (IIF) will be collected including name, date of birth, social security number (SSN), mailing address, telephone number, medical information, biological specimens, employment status, and other information. A detailed justification for the need to collect SSN is provided in section A.11.

The questionnaire will ask workers about their personal and demographic characteristics (date of birth, sex, race and ethnicity, height and weight), history of tobacco and alcohol use, chest symptoms and illnesses, as well as diagnosed autoimmune disease, heart disease, cancer, and other health conditions, which, as noted above, may influence blood pressure or levels of the measured biomarkers, independent of CNT or CNF exposure. Questions are also included about possible contraindications to spirometry or sputum induction, including recent eye, chest or abdominal surgery, stroke, certain forms of heart disease, detached retina, recent history of aneurysm or tuberculosis infection. Participants will also be asked about current and past exposure to CNTs, CNFs, and other chemicals, dusts, and fumes, both in their jobs and (for the past six months) in their hobbies. Information on such exposures for hobbies will be collected for only the past six months in order to reduce the burden of recall and response for the participant, and because these exposures are likely less substantial than workplace exposures.

While conducting the site visits, information will be collected by NIOSH researchers on aspects of the workforce, which will permit the evaluation of factors that may affect health outcomes in epidemiologic studies of CNT and CNF workers. Such information will include an evaluation of potentially confounding workplace exposures for pulmonary and cardiovascular

diseases, the use of personal protective equipment that might attenuate exposure, and any employer-based medical surveillance of the workforce.

These factors include the following:

- Company name and address
- CNT or CNF synthesis method, if a primary manufacturer
- Type and toxicity of raw materials and other potential co-exposures
- Nominal aspect ratio of CNT or CNF (as publicly reported by the company and measured by NIOSH in bulk materials provided by the company).
- Type of processes and tasks performed by employees
- Form of CNT and CNF used—dry powder or liquid emulsion
- Use and adequacy of personal protective equipment
- Length of shift
- Time spent per shift working directly with CNT or CNF
- Time spent per shift potentially indirectly exposed to CNT or CNF
- Cleaning operations and waste disposal

Table 1. **Description of circulating biomarkers to be measured for early effect of exposure†.**

Marker	Sample Matrix	Rationale
Inflammation		
Interleukin-1β	Plasma & Sputum	These 19 analytes are markers of inflammation. As a group, the analytes chosen represent a thorough early screen of effect for exposure to CNT/CNF. These markers have been shown to be increased in animal models of CNT exposure or associated pulmonary exposure studies.
Interleukin-2	Plasma & Sputum	
Interleukin-4	Plasma & Sputum	
Interleukin-5	Plasma & Sputum	
Interleukin-6	Plasma & Sputum	
Interleukin-8	Plasma & Sputum	
Interleukin-10	Plasma & Sputum	
Interleukin-12p70	Plasma & Sputum	
Interleukin-18	Plasma & Sputum	
Interleukin-6 receptor beta	Plasma & Sputum	
Alpha-2-Macroglobulin	Plasma & Sputum	
Complement C3	Plasma & Sputum	
C-Reactive Protein	Plasma & Sputum	
TNFα	Plasma & Sputum	
GM-CSF	Plasma & Sputum	
Macrophage derived chemokine	Plasma & Sputum	
Eotaxin-1	Plasma & Sputum	
Apolipoprotein A-I	Plasma & Sputum	
Apolipoprotein A-II	Plasma & Sputum	
CBC with Differential	Whole Blood	Increased neutrophils following concentrated ambient particles or welding fume exposure.
Oxidative stress		
Myeloperoxidase	Plasma & Sputum	These markers will indicate the presence of local and systemic oxidative stress. These markers have been indicated following pulmonary toxicant exposures and/or are being analyzed in other nanomaterial epidemiological studies
SOD activity	Plasma & Sputum	
GPx activity	Plasma & Sputum	
8-OHdG	Plasma & Sputum	
8-isoprostane	Plasma & Sputum	
Cardiovascular / Coagulation		
ICAM-1	Plasma & Sputum	These markers represent a group of cardiovascular and coagulation specific markers. The analytes have been increased following pulmonary inflammatory exposures.
VCAM-1	Plasma & Sputum	
Endothelin-1	Plasma & Sputum	
Fibrinogen	Plasma & Sputum	
von Willebrand Factor	Plasma & Sputum	
PAI-1	Plasma & Sputum	
t-PA	Plasma & Sputum	
Cancer / Fibrosis		
KL-6	Serum & Sputum	These analytes represent markers of fibrosis and/or cancer. KL-6 and MMPs correlate with pulmonary fibrosis. Some can be increased in incidences of lung cancer.
MMP-1	Plasma & Sputum	
MMP-2	Plasma & Sputum	
MMP-7	Plasma & Sputum	
MMP-9	Plasma & Sputum	
TIMP1	Plasma & Sputum	
Osteopontin	Plasma & Sputum	
Genetic Damage		
Comet Assay	Serum and either sputum, nasal or buccal cells	Marker of DNA strand breaks and misrepairs; found to be elevated in Taiwanese CNT workers.
M-FISH	Serum and either sputum, nasal or buccal cells	Marker of chromosome translocations

† All except GPx and SOD expected to increase with CNT or CNF exposure. GPx and SOD expected to decrease.

This information will be collected via the CAPI questionnaire for each participant, supplemented with direct observations by the study team (observation recording sheet is shown in **Attachment C-2**) and evaluation of workplace-supplied information and records.

Identification of Website(s) and Website Content Directed at Children Under 13 Years of Age

The proposed research will not involve the collection of information through websites, and will not direct any website content at children under 13 years of age.

A2. Purpose and Use of Information Collection

All information collected will be used to assess possible associations between workplace exposure to CNT and CNF and early or late health effects. Health effects that will be assessed include pulmonary and cardiovascular function. Biomarkers of pulmonary, cardiovascular and genetic damage will also be measured. Several national and international organizations have emphasized the need for basic knowledge about the human health effects of such exposures. Without this information, the human health effects of exposure to CNT and CNF will continue to be unknown.

Engineered nanomaterials represent a fast-growing, but ill-characterized industry. Health effects from exposure to nanomaterials are uncertain, but may be different from from larger-sized particles of the same material. This is due to the small size, high surface area per unit mass (i.e., specific surface area) or (in some cases) high aspect ratio of nanomaterials. Carbon nanotubes and nanofibers are among the nanomaterials of greatest interest from a public health perspective because of their potentially asbestiform properties (e.g., high aspect ratio) and toxicological evidence of possible fibrogenic, inflammatory, and clastogenic damage resulting from exposures

at occupationally relevant levels. In addition, the useful properties of CNT and CNF have rendered them among the first nanomaterials to be commercially exploited in manufacturing settings. Thus, an epidemiologic study to assess possible associations between occupational exposure to CNT or CNF and health effects or biomarkers is justified, and is consistent with recommendations by NIOSH and other governmental and non-governmental organizations.

The exposure data collected will be used to make recommendations to the companies employing workers in the study on how to improve their risk management practices, if warranted. The results will also be relevant to other companies that manufacture, distribute, or use CNT or CNF. The data collected may also assist in developing recommendations and regulations regarding workers exposed to CNT and CNF.

This information collection is being conducted under the authority of U.S. Code Title 42 (Public Health and Welfare) PART 85a—OCCUPATIONAL SAFETY AND HEALTH INVESTIGATIONS OF PLACES OF EMPLOYMENT which are conducted by NIOSH under the authorization of sections 20 and 8 of the Occupational Safety and Health Act of 1970.

The industrywide exposure assessment study has established and will apply sampling and analysis protocols for the quantification of CNT and CNF in US workplaces. These are described in the approved protocol for the study (Schubauer-Berigan et al.; NIOSH protocol, pp. 19-25, 2013). Concurrent with the industrywide exposure assessment study, several biomarkers of early effect (for pulmonary fibrosis, cardiovascular disease, and genetic damage) will be measured for workers exposed to a range of CNT and CNF levels. This will be accompanied by a questionnaire to assist in interpretation of the biomarker results and medical examinations to evaluate pulmonary function and cardiovascular health. Statistical analyses will then be conducted to determine the nature of the relation between exposure to

CNT and CNF and these biomarkers of early effect, considering potential confounding factors such as smoking, age, gender, and workplace co-exposures, including non-engineered particulate matter.

The information collected will also be used for additional components planned for the future (which will be covered under a separate OMB data collection request), including the development of an industrywide exposure registry of CNT and CNF workers, and the identification of a cohort of these workers to be followed on a prospective basis for a variety of health outcomes, including incidence and mortality from pulmonary disease (e.g., fibrosis), cardiovascular disease, and cancer. The participants included in the present cross-sectional study will be invited to participate in this future study. To the extent that questions overlap between the two data collection instruments, NIOSH plans to minimize burden to the future participants who also participated in the present data collection by using the same format for overlapping questions, with pre-loaded information for previous participants who choose to participate in future studies.

Privacy Impact Assessment Information

IIF will be collected as part of the informed consent forms (**Attachment D)** and questionnaire (**Attachment C-1**) for this study. Study participants will be identified only using unique identifiers (created by NIOSH) to track the responses of the participants during the study; however, IIF will be retained and used to permit the notification of participants in the study of findings related to their individual medical examination and exposure assessment and biomarker results, and of overall study findings. Examples of the notification letters for clinically relevant medical results and exposure assessment results are provided in the protocol (Schubauer-Berigan et al.; NIOSH protocol, pp. 122-129, 2013). Examples of the notification letters for the biomarker results (which have no direct clinical interpretation) and the overall study findings are given in Appendix F.

Individual participants' personal information will not be published in any identifiable form and will be protected to the extent allowed by law (Freedom of Information Act and the Privacy Act). Information will be maintained for the length of time required by law. The IIF data will only be used by NIOSH researchers for the purposes outlined below. The impact on the privacy of the individual is considered to be minimal if there were a breach of security. Stringent safeguards will be used to protect the confidentiality of each participant's SSN (e.g., it will be encrypted to meet Federal Information Processing Standards 140-2 encryption standard). All Privacy Act-protected electronic data will be stored on encrypted, CDC-issued, secure laptop computers (while in the field) and will be stored on secure, password-protected network servers inside CDC's firewall after returning from the field. Paper records containing Privacy Act-protected data (e.g., signed consent forms) will be stored in locked file cabinets or locked offices in access-controlled Federal buildings. Access to all Privacy Act-protected data will be restricted to those with a need to access the data for purposes of conducting the study.

IIF Being Collected	**Purposes**
First and last name of individual participant	The participant's fist and last name (in combination with their birth date) will be used to link a unique identifier (created by NIOSH) to track the questionnaire responses, exposures, medical findings, and biomarker results of the participant over the course of the study. The name will also be used to send results of the pulmonary function test, blood pressure and heart rate tests, complete blood count tests, and other tests using blood and sputum, and to invite the participant to take part in future planned phases of the study (i.e., the exposure registry and prospective cohort study), as described in A.1 and A.2 above.
Mailing address of individual participant	The mailing address will be used to send results of the pulmonary function test, blood pressure and heart rate tests, complete blood count tests, and other tests using blood and sputum, as well as the exposure measurements for the individual, and to invite the participant to take part in future planned phases of the study, as applicable.
Phone number of individual participant	The telephone number will be used to obtain current address information for the participant for purposes of notifying him or her about medical test results, and biomarker findings, and the overall study results, which may require several years to be completed.
Date of birth	The participant's date of birth (in combination with their first and last name) will be used to link to a unique identifier (created by NIOSH) to track the responses of the participant over the course of the study. The date of birth is also required to interpret the spirometry findings and the results of some of the medical tests and biomarker results.

IIF Being Collected	Purposes
Social Security Number	The Social Security number will be used to link the participant's information to workplace records and to link to the Internal Revenue Service[1] and other sources to obtain current address information in order to notify the participant about the medical test results, biomarker findings, and the overall study results, which may require several years to be completed.
Medical information	Medical information will be used to evaluate whether workplace exposure to CNT or CNF is associated with early or late health effects. Medical information will also be used to identify contraindications to spirometry and sputum induction.
Biological specimens	Biological specimens (blood and sputum) will be analyzed to measure several biomarkers of potential early health effects. This information will be used to explore whether workplace exposure to CNT or CNF is associated with early possible health effects.
Employment history	Information on the current and past places of employment will be collected to identify other potentially confounding workplace exposures.

[1] Title 26 – Internal Revenue Code 6103(m)(3), (http://www.irs.gov/irm/part11/irm_11-003-029.html) as amended and Public Law 96-128, title V, Sec. 502, as amended, (http://thomas.loc.gov/cgi-bin/bdquery/z?d096:HR02282:@@@D&summ2=m&) allows the IRS to disclose address information upon written request solely for the purpose of locating individuals who are, or may have been, exposed to occupational hazards, in order to determine the status of their health or to inform them of the possible need for medical care and treatment. These provisions also require the Director of NIOSH, upon request by the VA (or other federal department, agency, or instrumentality) to request the current mailing address from the IRS of persons whom the Administrator or other department, agency, or instrumentality head certifies may have been exposed to occupational hazards during military service.

IIF Being Collected	Purposes
Other	Information on the companies employing workers in the study will be collected so that the companies can be informed of the study findings. Information will also be collected on risk management practices so that recommendations for improvements can be made, if warranted.

Written consent to participate in the study will be obtained for each participant before administering the questionnaire. The consent form is included as **Attachment D**. This consent document describes the uses that will be made of the data obtained in the study, plans for publishing the aggregate data from the study, and plans for notifying the participant about both his or her individual results and about the overall results from the study (as described in section A2 above). During the consent process and before administering the questionnaire, study participants are informed that their participation is entirely voluntary, that they may refuse to answer any question without penalty, and that they may refuse to participate in any other aspect of the study without jeopardizing their participation in other aspects of the study. They are informed that the Privacy Act applies to the information being collected for the study, and that the information they provide will be kept private and not disclosed unless compelled by law, using all available safeguards for protecting inadvertent disclosure.

A3. Use of Improved Technology and Burden Reduction

The majority of the data collection will be accomplished through computer-assisted personal interview. The interviewer-administered format reduces respondent burden by removing the need for the respondents to read the questions, and by ensuring that respondents do not spend time reading and

responding to questions that do not apply to them. It also ensures that low-literacy individuals are not barred from participation in the survey. The data collection instrument has been through multiple iterations of review and revision, with the goal of excising any questions that were not essential to the survey's purpose.

A4. Efforts to Identify Duplication and Use of Similar Information

We have searched the published literature and consulted with colleagues in other Federal agencies. There are at present no published or in-progress studies of possible health effects from exposure of US workers to CNT or CNF. Thus, this study does not duplicate any other known study being conducted in the U.S.

A5. Impact on Small Businesses or Other Small Entities

More than 30% of nano-manufacturers worldwide participating in a voluntary survey indicated that they create and handle carbonaceous nanomaterials (e.g., CNT, fullerenes, and carbon black) (Gerritzen G, Huang L-C, Killpack K, Mircheva M, Conti J. 2007. A Review of Current Practices in the Nanotechnology Industry; Survey of Current Practices in the Nanotechnology Workplace. University of California, Santa Barbara in collaboration with the International Council on Nanotechnology. Accessed November 15, 2007. http://icon.rice.edu). A recent NIOSH feasibility study of companies manufacturing or using engineered carbonaceous nanomaterials in the US (above R&D scale) found that 50 (82%) of 61 were handling CNT or CNF (Schubauer-Berigan et al., *J Occup Environ Med* 2011:53:S62-S67). Most of these companies were small, with an average of about 10 workers per company. As mentioned above in Section A1, participation in the survey is voluntary and questions have been held to the minimum required for the intended use of the data. NIOSH researchers conducting this study will minimize the burden to small companies by collecting most information through direct observation at the workplace. Small businesses involved in

the study will benefit by learning about actual CNT exposures in their workplaces and about proven methods to reduce these exposures. They will also benefit by learning from this study whether any early health effects are discernible from CNT exposures in U.S. workplaces.

A6. Consequences of Information Collected Less Frequently

This request is for a one-time data collection. If this data collection does not take place, our understanding of whether or not exposure to CNT or CNF may be associated with early signs of health effects in U.S. workers will not be possible.

There are no legal obstacles to reduce the burden.

A7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

There are no special circumstances associated with this data collection activity. This request fully complies with regulation 5 CFR 1320.5.

A8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A. A 60-day Federal Register Notice was published in the *Federal Register* on September 20, 2012, vol. 77, No. 183, pp.58396-58397 (see **Attachment B**). There were no public comments.

B. As part of the NIOSH peer review process, in 2012, the protocol, including the data collection instrument, 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

As a result of the comments made by these peer reviewers, the questionnaire has been modified slightly from the version that underwent the 60-day Federal Register Notice, to incorporate questions about specific exposure to diesel exhaust (a potential confounder in the epidemiologic study) and history of forms of tobacco use other than smoking and of secondhand smoke exposure in the home.

A9. Explanation of Any Payment or Gift to Respondents

No payments will be offered to survey participants as remuneration for their participation.

A10. Assurance of Confidentiality Provided to Respondents

The interview will collect IIF and potentially sensitive information about health status. NIOSH has extensive systems in place to protect IIF collected for its many health studies. Respondents will be informed that their participation in this study is voluntary and that they may withdraw consent and discontinue participation in this study at any time without penalty or loss

of benefits to which they are otherwise entitled. CDC/NIOSH is authorized to collect this information, including the social security number, under provisions of the Public Service Act, Section 301 (42 U.S.C. 241); Occupational Safety and Health Act, Section 20 (29 U.S.C. 669). The information supplied by participants is voluntary and there is no penalty for not providing it. The data will be used to evaluate associations of pulmonary and cardiovascular disease and other health effects and exposure to carbon nanotubes and carbon nanofibers. Data will become part of CDC Privacy Act system 09-20-0147, "Occupational Health Epidemiological Studies and EEOICPA Program Records and WTC Health Program Records" and may be disclosed to private contractors assisting NIOSH; to collaborating researchers under certain limited circumstances to conduct further investigations; to the Department of Justice in the event of litigation; and to a congressional office assisting individuals in obtaining their records. An accounting of the disclosures that have been made by NIOSH will be made available to participants upon request. Except for these and other permissible disclosures expressly authorized by the Federal Privacy Act, no other disclosure may be made without the participant's written consent.

Institutional Review Board approval

This study, including the CAPI data collection instrument, was approved by the NIOSH Institutional Review Board (IRB) on November 13, 2012. The NIOSH IRB approval letter is shown in **Attachment E**.

Privacy Impact Assessment Information

A. This submission has been reviewed by the Information Collection Review Office (ICRO), who determined that the Privacy Act does apply. The applicable System of Records Notice is 09-20-0147.
B. Data will be treated in a secure manner and will not be disclosed, unless compelled by law. Access to individual data will be limited to

authorized NIOSH researchers and contractors. NIOSH facilities have 24-hour security guards, and key card ID badges must be used to enter the buildings. Data in hardcopy form will be stored in locked rooms or cabinets. Questionnaire data will be collected at the worksites using a laptop encrypted according applicable Federal Information Processing Standards Publications (FIPS PUBS, see http://www.it1.nist.gov/fipspubs). After the data are transported to NIOSH facilities, all electronic data will be stored on secure servers that are protected with firewalls and passwords.

C. Written consent to participate in the study will be obtained for each participant before administering the questionnaire. The consent form is included as **Attachment D**. This consent document describes the uses that will be made of the data obtained in the study, plans for publishing the aggregate data from the study, and plans for notifying the participant about both his or her individual results and about the overall results from the study.

D. During the consent process and before administering the questionnaire, study participants are informed that their participation is entirely voluntary, that they may refuse to answer any question without penalty, and that they may refuse to participate in any other aspect of the study without jeopardizing their participation in other aspects of the study. They are informed that the Privacy Act applies to the information being collected for the study, and that the information they provide will be kept private and not disclosed unless compelled by law, using all available safeguards for protecting inadvertent disclosure.

A11. Justification for Sensitive Questions

Potentially sensitive information about a study participant's race and ethnicity, body mass index and waist circumference, history of tobacco and alcohol use, health status, personal habits, work history and exposure

information, and medications used is required to conduct a scientifically valid study evaluating the association between occupational exposure to CNT or CNF and possible early health effects. For example, information on smoking history is needed to interpret whether obstructive or restrictive spirometry patterns are explained by smoking patterns, rather than by CNT or CNF exposure. Information on certain health conditions (e.g., cystic fibrosis, autoimmune disease, diabetes, cancer or kidney disease), body mass index, waist circumference, tobacco use history, alcohol consumption patterns and current medications is needed to statistically adjust for these factors (as potential confounders) in analyses of the association between CNT or CNF exposure and the health outcomes of interest (i.e., clinical measures such as blood pressure, lung function, or neutrophil count, or the biomarker levels).

NIOSH is mandated by law to conduct research to assure safe and healthful working conditions for working men and women. To meet this mission, NIOSH collects information on exposure and health effects and provides the individual and summary findings to all individuals who participate in our studies. In this study, SSNs are needed to ensure that participant information is matched to workplace records for the correct individual and to allow NIOSH to locate current addresses of participants so that we can provide them with information on their health status, possible need for medical care, workplace exposure levels, and summary findings of the study. Because some of this information will not be available for several years, it will be necessary to trace some individuals who have participated in the study. The Internal Revenue code (IRC 6103(m)(3)) specifically allows disclosure of the mailing address of taxpayers to NIOSH solely for the purpose of locating individuals who are, or may have been, exposed to occupational hazards in order to determine the status of their health or to inform them of the possible need for medical care and treatment (see http://www.irs.gov/irm/part11/irm_11-003-029.html). In order to obtain the taxpayer address, the IRS requires that NIOSH provide the SSN and last

name of each individual we are trying to locate. The SSN and last name provided by NIOSH are sent to IRS (and addresses returned to NIOSH) via a secure, encrypted, FTP site.

A12. Estimates of Annualized Burden Hours and Costs

A. Annualized Burden to Respondents

No direct costs will accrue to respondents other than their time to complete the questionnaire, the consent form, and the medical examinations and biospecimen collection. The industrywide exposure assessment and cross-sectional epidemiology study will be done among 100 workers total over a three year period at approximately 10 workplaces that agree to participate (approximately 33 respondents per year). The questionnaire, consent form, medical examination, and biospecimen collection will be administered to each participant during his or her regular workday, resulting in no individual cost to the participant. The time required to complete the questionnaire and the consent form was estimated from a pretest of these items among fewer than ten individuals. The estimated annualized burden hours is 66.

Table A.12.1. Estimated Annualized Burden to Respondents

Type of Respondents	Form Name	No. of Respondents	No. of Responses per Respondent	Average Burden per Response (in hours)	Total Burden (in hours)
Nanomaterials Workers	Questionnaire	33	1	22/60	12
Nanomaterials Workers	Informed Consent	33	1	20/60	11
Nanomaterials Workers	Medical examination, biospecimen collection,	33	1	1.3	43

	and exposure monitoring				
	Total		66		

B. Estimated Annualized Cost to Respondents

The total estimated annualized cost to respondents is $2640, as summarized in Table A.12-2. The average hourly wage rate is $40 per worker (the 75th percentile hourly wage rate among U.S. Materials Engineer-II in the U.S. as obtained from http://www1.salary.com/Materials-Engineer-II-salary.html).

Table A.12.2. Annualized Cost to Employer

Type of Respondent	No. of Respondents	Number of Responses Per Respondent	Average Burden Per Response (in hrs.)	Total Burden (in hrs.)	Hourly Wage Rate	Total Respondent Cost
Nanomaterials Workers (Questionnaire)	33	1	22/60	12	$40	$480
Nanomaterials Workers (Consent Form)	33	1	20/60	11	$40	$440
Nanomaterials Workers (Medical Examination, Biospecimen Collection, and Exposure Assessment)	33	1	1.3	43	$40	$1720
Total	$2640					

A13. Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

There are no capital or maintenance costs to respondents.

A14. Annualized Cost to the Government

Total costs include work performed by CDC/NIOSH researchers including a research epidemiologist (co-project officer), research industrial hygienist (co-project officer), aerosol scientist, research chemist, electron microscopist, phlebotomist, industrial hygiene technician and spirometry technician and will require 2.5 years of full-time effort for each of two fiscal years. There will be total average costs in the amount of $429,415 for each of the two fiscal years to conduct the work (including personnel and travel costs for the research team, contracts for some of the biomarker analyses, and supplies

and materials). There will be additional dissemination costs to NIOSH (not yet determined) for preparing reports and publications that NIOSH anticipates following analysis of the data captured in this survey. CDC personnel costs are estimated at $263,000 per year for all project staff.

Estimated annualized costs to the Federal Government for the survey period are presented in Table A.14-1 below.

Table A.14.1. Estimated Annualized Cost to the Federal Government

	FY 2013 $	FY2014 $
CDC Personnel	263,000	263,000
NIOSH Travel	41,495	79,564
Use of FERV*	2,517	3,443
Overtime/Drive FERV after regular hrs. (contracts)	2,340	2,340
Supplies & Materials	24,000	5,900
Equipment Purchases	0	0
Shipping of specimens to NIOSH and contract labs.	1,500	1,500
Contract for sample analysis & calibration	82,500	85,730
Total	417,352	441,477

*The NIOSH Field Evaluations and Response Vehicle (FERV) will be used at each site to conduct medical examinations, spirometry, and biospecimen collection (serum, sputum, buccal cells), and to administer a questionnaire to participating workers.

A15. Explanation for Program Changes or Adjustments

This is a new data collection.

A16. Plans for Tabulation and Publication and Project Time Schedule

As described in the study protocol (Schubauer-Berigan et al. NIOSH protocol. Pp. 54-56, 2013), statistical analyses will be conducted to explore whether exposure to CNT and CNF is associated with 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 assess whether quantitative metrics of exposure to CNT and CNF (based on elemental carbon measurements and CNT or CNF structure counts via transmission electron microscopy) are related to 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.

In order to carry out the planned statistical analyses, the data from the questionnaire will be combined with the results of the exposure assessment, medical examinations and the biomarker tests as soon as feasible after collection, during FY 13 and FY14, and possibly FY15 (if necessary). Because it will take two to three years to collect all the data necessary for the study, an additional year is required to complete the biomarker analyses and conduct statistical analyses. After analyses are complete, several manuscripts will be published describing the occupational exposure assessment, the measurement methods used in the study, and the results of the analyses of the association between exposure to CNT or CNF and the measures of early health effects in the study participants. We anticipate that these manuscripts will be submitted for publication in FY15 and beyond, and will be followed by notification of workers of the study findings. Workers will be notified of their individual results of clinically relevant medical tests within five days of their completion, and will be notified of their other findings (including exposure assessment measurement results) within one month of the completion of these tests and measurements, which may be up to 1.5 years after the participant is enrolled in the study.

Project Time Schedule

Table A.16-1. Project Time Schedule

Activity	Time Schedule (Months After OMB Approval)
Consent and enroll workers from 10 previously identified workplaces, administer questionnaire, conduct medical examination, collect biospecimens and measure occupational exposure at each workplace	Start within 1 month after OMB approval (completed 24-28 months after OMB approval)
Complete biomarker analyses	Within 30 months after OMB approval
Combine data from questionnaire with results of exposure assessment, medical examination and biomarker tests	Within 32 months after OMB approval
Conduct statistical analyses relating exposure with medical examination and biomarker results	Within 36 months after OMB approval
Prepare survey technical documentation and manuscripts	Within 42 months after OMB approval
Begin notification of workers of the study findings.	Within 48 months after OMB approval

A17. Reason(s) Display of OMB Expiration Date is Inappropriate

There is no request for an expiration date display exemption.

A18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions being sought to the certification statement.