

**Attachment F, part 1: Example draft notification letter for individual biomarker results**



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service  
Centers for Disease Control and  
Prevention  
National Institute for Occupational  
Safety and Health

Robert A. Taft Laboratories  
4676 Columbia Parkway  
Cincinnati, OH 45226-1998

Name (first, last)  
Street Address  
City, State, Zip

Dear Mr. (Ms.) (last name):

Thank you again for taking part in the National Institute for Occupational Safety and Health (NIOSH) Study of U.S. Workers Exposed to Carbon Nanotubes and Nanofibers. During our visit to (company name) on (date range), we conducted a number of assessments for our study, including (*choose the consented and completed evaluations from among the following list*) body measurements, blood pressure and heart rate measurements, spirometry, a complete blood count, and collection of specimens (blood and sputum) for future analysis of other biomarkers. We have already sent you and (*if applicable*) your doctor your results for the (*choose the consented and completed evaluations from among the following list*) body measurements, blood pressure and heart rate measurements, spirometry, and the complete blood count.

This letter includes your personal results from the biomarker measurements that we made in your (*choose the consented and completed biospecimens from among the following list*) blood and sputum. As we explained to you at the start of the study, these biomarker tests do not have direct clinical (medical) meaning for you and your doctor. The biomarkers we measured are proteins produced by your body, which are markers or indicators of your body's response to exposures to many possible agents, including exposures in your environment or your workplace. Their levels in your body may be affected by your exposure to tobacco smoke or your level of alcohol consumption. They can also vary depending on the presence of other health conditions (like autoimmune disease or cystic fibrosis), independently of your exposure to carbon nanotubes or nanofibers. As we explained previously, in our research study we will be evaluating whether the levels of these biomarkers are different among groups of participants with higher workplace exposure to carbon nanotubes and carbon nanofibers, compared to workers with lower exposure.

While we do not yet have the research study results available, we wanted to give you your individual results for these biomarker measurements. Although there is no direct medical meaning for these biomarkers, we have provided your results for each measurement, along with the average, lowest and highest measurement for all the participants in our study. We also include the average, lowest and highest measurement for the participants in our study who had no measureable workplace exposures to carbon nanotubes or carbon nanofibers. Having a biomarker measurement at the extreme of or outside these ranges does not mean that you have a health problem.

*(if applicable)* Your results for the biomarkers in blood are shown in Table 1, *(if applicable)* and your results for the biomarkers in sputum are shown in Table 2. *(For those who did not consent to having results sent to their personal physician)* Your individual results have been sent only to you. *(For those who consented to having results sent to their personal physician)* Your individual results have been sent to you and, at your request, to your personal physician.

Your individual results are important because they contribute to our evaluation of occupational exposure to carbon nanotubes or nanofibers. Only the grouped results for all worksites that participated in the study will be shared with your workplace.

We encourage you to discuss all of your test results with your personal physician. If you or your physician has any questions about these results or our study, please feel to contact me at 513-841-4251.

Sincerely yours,

Mary K. Schubauer-Berigan, PhD, MS  
Senior Research Epidemiologist  
Division of Surveillance, Hazard  
Evaluations and Field Studies

Enclosures





Attachment F, part 2: Example draft notification of study findings to individual participants



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Dear Mr. (Ms.) (last name):

Thank you again for taking part in the National Institute for Occupational Safety and Health (NIOSH) Study of U.S. Workers Exposed to Carbon Nanotubes and Nanofibers. During our visit to (company name) on (date range), we conducted a number of assessments for our study, including (*choose the consented and completed evaluations from among the following list*) body measurements, blood pressure and heart rate measurements, spirometry, a complete blood count, and collection of specimens (blood and sputum) for future analysis of other biomarkers. We have already sent you and (*if applicable*) your doctor your results for the (*choose the consented and completed evaluations from among the following list*) body measurements, blood pressure and heart rate measurements, spirometry, the complete blood count, your exposure measurements, and your biomarker results.

We have now completed the research study, which looked at a small group of 100 workers to assess the possible relationship between workplace exposure to carbon nanotubes (CNT) and carbon nanofibers (CNF) and some health outcomes and biomarkers of interest. I am writing to you to let you know what we found overall in the study.

1. We looked at workplace exposure levels to CNT and CNF:

- We found that the background-corrected respirable exposure levels to CNT and CNF among the entire study group were generally (*choose one*) below/above the NIOSH recommended exposure limit, based on elemental carbon measurement. The average exposure value in our study was  $x \mu\text{g}/\text{m}^3$ , and the lowest and highest values were  $y \mu\text{g}/\text{m}^3$  and  $z \mu\text{g}/\text{m}^3$ , respectively.
- For the background-corrected inhalable exposure levels to CNT and CNF, no recommended exposure limit exists, based on elemental carbon measurement. The average exposure value in our study was  $x \mu\text{g}/\text{m}^3$ , and the lowest and highest values were  $y \mu\text{g}/\text{m}^3$  and  $z \mu\text{g}/\text{m}^3$ , respectively.

- For the CNT and CNF electron microscopy counts, no recommended exposure limit exists. The average structure counts we found in our study were  $x$  structures/cm<sup>3</sup>, and the lowest and highest values were  $y$  structures/cm<sup>3</sup> and  $z$  structures/cm<sup>3</sup>, respectively.
2. We looked at possible statistical associations between CNT or CNF exposure and clinical measures of interest. In doing this, we adjusted for factors other than CNT or CNF exposure that might have influenced these results, such as body mass index, waist circumference, smoking levels, alcohol consumption, and exposure to other chemicals or ultrafine particles in your workplace:
- We found that CNT or CNF exposure was significantly associated with (*choose from among the following list*) lung forced expiratory volume in one second; lung forced vital capacity; systolic blood pressure; diastolic blood pressure; heart rate; neutrophil (a type of white blood cell) level. This finding does not mean that CNT or CNF exposure causes changes in these health outcomes. Such a determination can only be made after several similar studies confirm what we found here.
  - We found that CNT or CNF exposure was not significantly associated with (*choose from among the following list*) lung forced expiratory volume in one second; lung forced vital capacity; systolic blood pressure; diastolic blood pressure; heart rate; neutrophil (a type of white blood cell) level. This finding does not mean that CNT or CNF exposure does not cause changes in these health outcomes. Such a determination can only be made after several similar studies confirm what we found here.
3. We looked at possible statistical associations between CNT or CNF exposure and biomarkers of interest. In doing this, we adjusted for factors other than CNT or CNF exposure that might have influenced these biomarker levels, such as body mass index, waist circumference, smoking levels, alcohol consumption, and exposure to other chemicals or ultrafine particles in your workplace:
- We found that CNT or CNF exposure was significantly associated with (*choose from among the list in Table 1*). These biomarkers are possible early indicators of (*choose from among the following list*) inflammation, oxidative stress, cardiovascular or coagulation effects, pulmonary fibrosis, DNA damage, in the body. This finding does not mean that CNT or CNF exposure causes changes in these biomarkers or causes any health effects. Such a determination can only be made after several similar studies confirm what we found here. In addition, the biomarkers themselves have no direct medical meaning. Rather, they are useful in learning more about the possible mechanisms for exposure or disease pathways, especially when compared to animal toxicology studies.
  - We found that CNT or CNF exposure was not significantly associated with the other biomarkers that we studied. This finding does not mean that CNT or CNF exposure does not cause changes in these biomarkers. Such a determination can only be made after several similar studies confirm what we found here.

These overall study findings are important because they contribute to our knowledge about occupational exposure to and possible health effects of exposure to carbon nanotubes or nanofibers. These overall study findings will be shared with others in your workplace. *(For those who consented to having results sent to their personal physician)* These study findings have also been sent, at your request, to your personal physician. For more information about what we found, we have attached references to the scientific publications describing these findings.

We encourage you to discuss these study findings with your personal physician. If you or your physician has any questions about these findings or our study, please feel to contact me at 513-841-4251.

Sincerely yours,

Mary K. Schubauer-Berigan, PhD, MS  
Senior Research Epidemiologist  
Division of Surveillance, Hazard  
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**Table 1. Description of circulating biomarkers to be measured for early effect of exposure†.**

Marker	Sample Matrix	Rationale
<b>Inflammation</b>		
Interleukin-1 $\beta$	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	
TNF $\alpha$	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.
<b>Oxidative stress</b>		
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	
<b>Cardiovascular / Coagulation</b>		
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	
<b>Cancer / Fibrosis</b>		
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	
<b>Genetic Damage</b>		
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.