A summary of pertinent public and stakeholder comments received on the 2010 draft Current Intelligence Bulletin (CIB): *Occupational Exposure to Carbon Nanotubes and Nanofibers* along with the NIOSH response and subsequent changes to the final document. The complete text of the submitted comments can be found at: http://www.cdc.gov/niosh/docket/archive/docket161A.html

Commenter	Summary of Comments Received	Response	Changes to CIB
DECOS-Health Council of the Netherlands	1) In the Executive Summary, DECOS misses the result of the benchmark dose analyses, revealing working lifetime exposure levels for lung effects (BMDL10) of carbon nanotubes of between 0.2 and 2.0 $\mu g/m^3$, as shown in detail in Appendix A and Section 5. A somewhat more detailed information on results of the benchmark dose analyses in Section 5 would make the discussion and the flow of arguments more understandable. A summary of the information in Annex A could be included in Section 5. The Annex presents useful information for most readers.	1) Agree that adding this information to these sections would be helpful.	1) The BMDL estimates of 0.2 and 2.0 $\mu g/m^3$ (95% LCL estimates associated with 10% excess risk of early stage lung effects), and reference to Appendix A, were added in the Executive Summary. Additional information on the risk assessment was added to Section 5.1.
	2) DECOS notes that the document mainly focused on adverse health effects in the respiratory tract. In addition, DECOS notes that the available information on the adverse health effects of carbon nanotubes and nanofibers mainly showed effects in the respiratory tract. DECOS also expects the lung effects will most likely be the most	2) There are some data which indicate that pulmonary exposure to CNT can affect the cardiovascular and central nervous systems. These results include: A) Li et al, 2007 – SWCNT increase aortic plaques B) Stapleton et al, 2011 – MWCNT	2) The available data on other potential health effects from exposure to CNT and CNF are not sufficiently robust to support an assessment of risk. As additional data on systemic health effects becomes available NIOSH will assess

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DECOS-Health Council of the Netherlands (cont.)	relevant by inhalation of carbon nanotubes and nanofibers. However, the committee feels that other relevant, (systemic) adverse health effects may occur, such as cardiovascular diseases, and diseases related to the immune system. Although no data are yet available on whether or not carbon nanotubes and nanofibers could cause effects, data obtained from exposure to ultrafine particles may be taken to indicate a hazard. Therefore, DECOS would recommend adding a paragraph in Section 4, in which attention is given to this matter, including the state-of-the-art on the matter.	decrease responsiveness of aortic arterioles to dilators. C) Legramante et al, 2009 –SWCNT increase baroreceptor reflex. D) Sriram et al, 2009 – MWCNT increase inflammatory mRNA in certain brain regions. These data are not sufficiently extensive to support a risk assessment.	the information and make appropriate recommendations. A discussion of systemic effects was added to Section 3.
	3) A major issue for DECOS is whether or not inhaled carbon nanotubes and nanofibers can induce cancer, such as mesotheliomas and lung tumors, like in case of asbestos fibers. Although evidence-based animal and human data are still lacking, early indications found in subchronic animal studies, and physicochemical comparisons, do suggest that certain carbon nanotubes and nanofibers may act similarly to asbestos fibers. DECOS recommends that this be discussed in detail in Section 4	3) NIOSH shares this concern and has cited all of the available studies pertaining to cancer potential for CNT and CNF in the CIB. Further study of the potential carcinogenicity of CNT and CNF is listed in the research needs in Chapter 7. As noted, research is needed to develop more sensitive measurement methods of airborne exposure to CNT and CNF, for example using CNT count rather than mass). However, there are	3) The CIB has been updated to include the recent studies on genotoxicity and carcinogenicity of CNT published since the 2010 external review draft document.

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DECOS-Health Council of the Netherlands (cont.)	and/or 5. The discussion should include a state-of-the art on this matter, and a rationale for not taking the possible carcinogenic effects into account as starting point in deriving a REL as a worst-case scenario. Did NIOSH consider using the occupational exposure limit for asbestos fibers for carbon nanotubes and nanofibers?	currently no standard methods for counting CNT structures by electron microscopy. The current data are also insufficient for quantitative risk assessment of CNT cancer risk. For these reasons, NIOSH developed the REL based on airborne mass concentration and reducing exposures and the risk of developing early-stage pulmonary inflammation and fibrosis over a working lifetime. NIOSH also indicated the need to develop more sensitive measurement methods (e.g., based on CNT or CNF structure counting).	
	4) NIOSH advises to use NIOSH method 5040 to measure airborne exposure levels of carbon nanotubes and nanofibers. The method uses the mass concentration of respirable elemental carbon as exposure parameter. With NIOSH method 5040 high risk situations can be identified when the REL is exceeded. However, DECOS would like to emphasize that this method cannot lead to fully conclusive evaluations with regard to CNT and CNF exposure. It is not clear yet what the best and most relevant exposure measure(s) is (are) for nanoparticles and nanofibers. Therefore,	4. We agree that multiple techniques are needed to better characterize exposure. For example, analysis of air samples by transmission electron microscopy (TEM) equipped with energy dispersive x-ray spectroscopy (EDS) can confirm the presence of CNT/CNF and identify other types of particles that may be present. NIOSH researchers applied multiple metrics for a comprehensive study at a CNF manufacturing facility (Birch et al. 2011, Birch 2011, Evans et al.	4) Because the mass of CNT was the dose metric used in animal studies, the risk assessment used the same metric for deriving the REL. NIOSH acknowledges in the CIB that a different exposure metric (e.g., structure count based on dimension) may eventually be determined to be a better measure of health risk once the results of ongoing animal studies are completed. NIOSH recommends in the CIB that

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DECOS-Health Council of the Netherlands (cont.)	DECOS recommends that efforts should be made by occupational hygienists, not only to measure mass concentration, but also to measure other possible parameters. In your document, examples of additional analytical techniques to better characterize exposures are given that could be used. DECOS believes that the same techniques could be valuable if a more detailed risk assessment is needed in specific situations. When using additional analytical techniques in specific working environments (e.g., activities with the highest expected exposure potential) the risk assessment in workplaces can be performed in more detail. DECOS believes that this option could be made more explicit in the document.	2010). Filter, sorbent, impactor, bulk, and microscopy samples, combined with direct-reading instruments, provided complementary information. Organic and elemental carbon (OC and EC), metals, and polycyclic aromatic hydrocarbons (PAHs) were monitored, with EC as a measure of CNFs. Scanning electron microscopy (SEM) and TEM-EDS also were applied. Respirable EC area concentrations were about 6 to 68 times higher than outdoors. Personal breathing zone samples were up to 170 times higher. Iron-rich soot, PAHs, and carbon monoxide were production byproducts. Relatively few studies have reported personal exposure data, and none have addressed complex mixtures. Multiple metrics will be applied to NIOSH surveillance studies at primary manufacturers and secondary users, depending on the processes involved. The purpose of this research is emissions and exposure characterization, and a goal is to collect as much data as practical to characterize health relevant	analysis of airborne samples by electron microscopy for the sizing and counting of tubes may be useful should subsequent animal research results indicate that a dose metric based on tube count and concentration is a better measure of adverse health effects.

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DECOS-Health Council of the Netherlands (cont.)		exposures. NIOSH appreciates that some facilities may not have adequate resources for such extensive characterizations. NIOSH is actively recruiting companies to participate in its surveillance studies and can provide comprehensive workplace assessments in such cases. However, some companies may prefer to conduct monitoring in-house and seek practical monitoring guidance. In this regard, NIOSH Method 5040 should provide a useful estimate of exposure to CNT/CNF when these materials are the main source of EC. As discussed in the CIB, a bulk sample of the CNT/CNF should be analyzed whenever possible to establish the thermal profile for the material(s) and rule out any potential problems in the analysis. A bulk sample also can be used to determine other material properties, such as metal content by inductively coupled plasma (ICP) with detection by atomic emission spectroscopy (AES) or mass spectrometry (MS). Use of a metal catalyst as a surrogate measure of CNT/CNF has been	

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DECOS-Health Council of the Netherlands (cont.)		suggested previously and was considered by NIOSH researchers; however, this approach has limitations. Namely, lack of correlation with the CNT/CNF concentration and inadequate detection limits. Iron was not a useful indicator of CNF exposure in a CNF manufacturing facility. The iron and CNF concentrations were not correlated because the major iron source was not CNF derived. Further, even if a metal is a selective marker of CNT/CNF exposure, the detection limits for ICP/AES will likely not be adequate for quantification at low CNT/CNF concentrations (e.g., the NIOSH REL) due to the low metal contents (e.g., typically $\leq$ 1%) of current products. Currently, a draft (ASTM) TEM-based method for quantitative measurement of CNT/CNF 'structures' is being investigated by NIOSH, but the problem of categorizing the many types of structures has not been adequately addressed. Further, even if the different types of structures can be	

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DECOS-Health Council of the Netherlands (cont.)		consistently sorted (by different analysts), there currently is no basis (e.g., as with aspect ratio for asbestos fibers) for weighting their potential toxicity.	
	5) Editorial comments: pages-18, 21, 23, 27, 29, 29-37, 37-38, 40-41, 43-45, 106, 117, and 120-121.	5) Editorial comments were addressed.	5) All relevant editorial changes were accepted.

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Melius, NYS Laborers Health and Safety Trust Fund	This draft CIB is a scientifically sound review of the current scientific literature on the potential occupational health hazards from exposures to carbon nanotubes and nanofibers. Consistent with previous NIOSH CIB's and similar documents, the document builds on a strong scientific base to make sound recommendations on evaluating and controlling exposures to these materials and on other aspects of an occupational health program.		
	1) The document should clarify that these recommendations not only apply to production of these materials but also to employers utilizing these products. In the past, people working in industries where these products were used often suffered the highest exposures and the highest rate of adverse health effects rather than those employed in manufacturing.	1) Additional clarification provided.	1) The extent of exposure to CNT and CNF was clarified to indicate that worker exposure could occur at any step in the life cycle of CNT and CNF use (i.e., production, product use, recycling, disposal). Recommendations on the control of exposures pertain to all work environments.

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Melius, NYS Laborers Health and Safety Trust Fund (cont.)	2) The CIB needs to include recommendations on labeling and MSDS language for these materials. These are critical elements for making users of these products aware of the potential hazards and the need to take appropriate precautions. Both have been fundamental parts of an overall occupational health program for decades.	2) Agree with commenter.	2) The following statement was included as a recommendation to employers: "Information on the potential health risks and recommended risk management practices contained in this CIB should, at a minimum, be used in the development of labels and Material Safety Data Sheets (MSDS), as required [CFR 1910.1200(b)(1)].
	3) The training recommendations appear to be triggered only by medical surveillance. Employee and user training are also fundamental parts of any occupational health program, and NIOSH needs to make a stronger recommendation regarding training.	3) Specific recommendations for the training and education of workers have been added to the CIB.	3) A new section 6.3 "Worker education and training" was added to the CIB. Specific guidance is given on the education and training of workers including reference to the requirements contained in the OSHA Hazard Communication Standard, Hazardous Waste Operation and Emergency Response Standard, and recent guidelines published by

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Melius, NYS Laborers Health and Safety Trust Fund (cont.)	4) The medical surveillance recommendations also need to be improved. As currently written, they appear to recommend only a baseline exam and then periodically on an ad hoc basis driven mostly by the development of symptoms. While there should be appropriate room for a flexible approach based on exposure levels and other factors, NIOSH should be making recommending a more specific time period and criteria for ongoing medical surveillance. There is much uncertainty about whether the proposed REL is protective. Given the severe consequences and often rapid progression of pulmonary fibrosis, periodic screening including pulmonary function testing and chest X-rays should be provided at least every two years to workers with ongoing exposure to these materials.	4) The reviewer is correct that there is uncertainty concerning whether the proposed REL is protective {there is also uncertainty concerning whether health effects will occur in workers…} The (lack of) specificity of recommendations concerning frequency and content of repeat examinations is related to our knowledge of occupational exposures being associated with health effects – currently this is incomplete. Medical screening recommendations for workers exposed to other substances in the workplace (such as asbestos, silica, or RCF) are at least in part grounded in evidence concerning clinical outcomes resulting from exposure in animal and/or human studies; there are no similar data for CNT/CNF. We feel the current level of medical screening proposed in this CIB is proactive and protective for workers occupationally exposed to CNT and CNF given the absence of data	Kulinowski and Lippy [2011] for workers exposed to Nanomaterials. 4) The medical surveillance recommendations are revised per comments received from the public (see other comments and responses for details)

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Melius, NYS Laborers Health and Safety Trust Fund (cont.)		indicating health effects beyond those effects seen in short term toxicological studies. This CIB attempts to balance the specificity and extent of medical screening with the current evidence indicating that occupational exposures will cause health effects.	
	5) In the section on periodic evaluation of screening data or on research needs, the document should recommend the development of a registry of exposed workers with reporting of adverse medical outcomes among these works. The growing use of these materials in the workplace and the uncertainty about the risk of adverse health effects certainly warrants the development of such a registry.	5) NIOSH agrees that a registry of exposed workers could be an important tool in improving our knowledge concerning potential health effects related to occupational exposures to CNT and CNF. Many issues need to be addressed in order for this type of exposure registry to be feasible, including issues related to: 1) measurement of exposure and determinations of who is exposed; 2) characterization of the nanomaterial(s) for which the registry would apply (for example, CNT/CNF only); and 3) management of the registry including funding and ownership of data.	5) An assessment of the feasibility for establishing exposure registries for workers exposed to CNT and CNF is a research priority identified in Section 7 *Research Needs.*

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O'Connor, ACOEM	Comments regarding medical surveillance (As listed in Sections 1.1, 6.6, and in Appendix B):		
	1) General Comment: The recommended medical screening and surveillance recommendations are not specific for possible pulmonary injuries that may occur from inhalation of carbon nanotubes or nanofibers. The recommendations appear to be generic.	1) This is correct. See response to comments 2 through 4.	1) Revisions made to CIB as noted in response to comments 2 through 4.
	2) Radiographic screening and surveillance: At this time, it is uncertain which specific patterns of pulmonary injury may occur and when they may appear. As a result, it is prudent to recommend that some form of radiologic medical screening and surveillance be performed. However, there is no justification that a NIOSH-certified B-reader must interpret or review the chest radiographs. The presence of acute inflammatory changes (as noted in the aforementioned animal studies) may be seen as different radiographic patterns such as consolidation, ground-glass opacifications, interstitial edema, etc.	2) We agree with the points made here. Background: the ILO has periodically published guidelines on how to classify radiographs for the pneumoconioses – the purpose of the guidelines is to describe and codify radiographic abnormalities of the pneumoconioses in a simple, systematic, and reproducible manner. In concert with the ILO classification, NIOSH formed a proficiency program to provide a pool of qualified readers. The NIOSH B Reader Program is intended to maximize the consistency of the nature and extent of radiologic features associated with the different pneumoconioses,	2) Change to Section 6.7.3 *Screening elements* and also in the Executive Summary. Revised to read: ▪ A baseline chest X-ray (digital or film-screen radiograph). All baseline chest images should be clinically interpreted by board eligible/certified radiologist or other physician with appropriate expertise, such as a board eligible/certified pulmonologist. ▪ Other examinations or medical tests deemed appropriate by the responsible health care professional (The need for

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O'Connor, ACOEM (cont.)	These are not patterns that would be best reviewed by comparison to the standard ILO films. Instead, the finding of any unexplained abnormality on a chest radiograph as interpreted by a radiologist or pulmonologist should prompt further evaluation that might include the use of a high-resolution CT scan of the thorax.	including coal workers' pneumoconiosis, silicosis, and asbestosis. It deals with parenchymal abnormalities (small and large opacities), pleural changes, and other features associated, or sometimes confused, with occupational lung disease. As the reviewer points out, radiologic changes potentially associated with occupational exposure to CNT/CNF may not be restricted to these types of changes.	specific tests may be based on factors such as abnormal findings on initial examination-for example, the finding of an unexplained abnormality on a chest X-ray should prompt further evaluation that might include the use of high-resolution computed tomography scan of the thorax.)
	3) Respiratory Symptom Questionnaires: The presence or development of respiratory symptoms may also be critical to the identification of possible pulmonary injury from exposure to nano-materials. We recommend that a standardized respiratory symptom questionnaire should be used as part of the initial screening and follow-up surveillance examinations; e.g., ATS-DLD-78 or Medical Research Council Questionnaire, etc.	3) Agree. Past NIOSH documents have recommended use of standardized questionnaires and their use for CNT and CNF exposed workers seems reasonable.	3) Change to Section 6.7.3 *Screening elements* and Executive Summary. Revised to Read: ▪ an occupational and medical history, with respiratory symptoms assessed by use of a standardized respiratory symptom questionnaire such as the American Thoracic Society Respiratory Questionnaire [Ferris 1978] or the most recent.

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O'Connor, ACOEM (cont.)	4) Spirometry testing: It is recommended that spirometry testing be administered by an individual who has completed a NIOSH-approved training course in spirometry or other equivalent training. It should also be mentioned that the qualified health professional who is overseeing the screening and surveillance program should be expert in the interpretation of spirometry testing results, enabling them to recommend further medical evaluation if abnormal test results occur; e.g., more complete pulmonary function testing including lung volumes and diffusing capacity measurements.	4) Agree. Revise recommendation on spirometry testing.	4) Change to Section 6.7.3 *Screening elements* and to the Executive Summary. Revised to read: ▪ a spirometry test (Anyone administering spirometry testing as part of the medical screening program should have completed a NIOSH-approved training course in spirometry or other equivalent training; additionally, the health professional overseeing the screening and surveillance program should be expert in the interpretation of spirometry testing results, enabling them to recommend further medical evaluation as needed).
	5) Research needs; we urge NIOSH to initiate at least one prospective cohort study with close follow-up of exposed individuals in order to determine as soon as possible whether occupational	5) NIOSH acknowledges *in Section 7 Research Needs* that exposure data needs to be collected and registries developed so that epidemiologic studies of workers exposed to CNT can be conducted. NIOSH has	5) No revisions required

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O'Connor, ACOEM (cont.)	exposures are associated with adverse health effects and if so, what effects occur. If such a study is also undertaken in order to detect or characterize exposures, in addition to determining adverse health effects, then it is critical that the validity of monitoring methods be separately demonstrated.	initiated a study to identify workplaces where workers are potentially exposed to CNT and CNT. Exposure assessment of workers at these workplaces has begun.	

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Wambach, DOE	1) DOE believes that NIOSH's Recommended Exposure Limit (REL) of 7 $\mu g/m^3$ elemental carbon (EC) as an 8-hr TWA respirable mass airborne concentration measured by NIOSH Method 5040 *Diesel Particulate Matter 5040 (as Elemental Carbon)* is not advisable. That recommended REL is the lowest level that is technically feasible to measured, however, employers cannot implement effective exposure monitoring and control programs if they cannot measure levels below the REL. The Bulletin on page 7 states that 7 $\mu g/m^3$ is a high estimate of the Level of Quantitation (LOQ)." The LOQ is generally understood to be the lowest concentration that can be reported with a defined, reproducible level of certainty. Analytic results less than the LOQ typically are reported as "less than the LOQ" or "non-detect," also referred to as censored results. Setting the REL at the analytic LOQ value is not practical. Exposure control programs require an action level that is lower than the REL. Employers must be able to measure exposures at an action level to have confidence that the REL is not being exceeded. NIOSH	1) However, as explained in the current CIB draft, the proposed REL (7 $\mu g/m^3$) was based on a worst-case estimate of the LOQ. This estimate (7 $\mu g/m^3$, or an LOD of about 2 $\mu g/m^3$) was based on analysis of total carbon (TC). As with all analytical methods, the LOQ (and LOD) CNT is a varying number that was determined from media blanks from different filter lots, over a six month period, and by different analysts at two different laboratories. Further, variability for the TC results, rather than the EC results, was used to estimate the LOD. These combined factors gave a high estimate. In practice, a much lower EC LOD is obtained by NIOSH 5040 than was originally reported in the Method because the variability for EC results for a set of media blanks submitted (with the sample set) for the LOD (LOQ) determination is much lower than that for the TC results. More typical values under different sampling conditions are given in Section 6.1 of the CIB, and even lower values are being found (using media blanks). An LOQ near 1	1) Section 6.1 has been expanded to describe the limitations of Method 5040 for CNT and CNF analysis and provide guidance on how to optimize sample collection.

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Wambach, DOE (cont.)	Method 5040 is not capable of measuring those lower levels. DOE recognizes that a NIOSH method development initiative to lower the LOQ for Method 5040 is not within the scope of this Bulletin. DOE nonetheless respectfully suggests that NIOSH undertake that method development in order to increase the likelihood that a protective action level for CNTs and CNFs can be established used proactively to monitor and control exposures before the exposures exceed the REL. Detailed Technical Comments: On page 42 the bulletin says: *However, NIOSH recognizes that the REL may not be completely health protective, but its use should help to lower the risk for developing lung disease and assist employers in establishing an occupational health surveillance program that includes elements of hazard and medical surveillance. Until improvements in sampling and analytical improvements can be made in measuring airborne exposures to CNT and CNF, continued efforts should be made to reduce airborne concentrations as low as possible below REL by optimizing the sampling and analysis of exposures when possible (Appendix C).*	$\mu g/m^3$ (or lower) can be obtained, and a lower REL that reflects this is now proposed. However, the contribution of environmental background may be significant (e.g., 50%) at concentrations near the LOQ. There are many different "detection limits", and different ways to determine them. Common limits include the instrument detection limit (IDL), method detection limit (MDL), limit of detection (LOD), practical quantification limit (PQL), and the limit of quantification (LOQ). Further, even when the same term is used, there can be differences in the limit estimate, depending on the definition used and the noise contribution. The statement regarding "non-detect" (ND) is incorrect. Results below the *LOD* are reported as ND. Any result above the LOD is considered a 'detectable' level. Results between the LOD and LOQ are considered semi-quantitative. NIOSH and its contract laboratory report results between the LOD and LOQ in brackets to indicate	

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Wambach, DOE (cont.)	NIOSH should acknowledge that compliance with the recommended REL is the highest feasible level of protection employers can provide and refrain from recommending reducing exposures to levels as low as possible below the REL because employers will be unable to implement measures to reduce exposures to levels below the REL if they cannot measure those levels. Exposure assessment methods should aim to limit both false negative and false positive errors that result in unnecessary expenditures of resources on preventive efforts that may have no value. The employer attempting to implement this recommendation would have to make a choice of which of these two types of errors to limit. False positive errors would be limited by taking protective actions only when exposures are above the REL, but because the REL is not a safe level; the false negative error rate would be unknown and uncontrolled. False negative errors could be limited by "continued efforts to reduce airborne concentrations as low as possible below the REL," however because levels below the REL cannot be measured, the false positive error rate would be unknown and uncontrolled. Managers responsible for worker health and	this. [See also discussion of LOD/LOQ in response]. Generally, the LOD is the lowest quantity of a substance that can be reliably detected. That is, it can be distinguished from a *blank* (result for media/matrix without analyte) at a specified confidence limit[1, 2]. The American Chemical Society (ACS Subcommittee on Environmental Improvement 1980) defines LOD as three times the signal-to-noise (S/N) ratio and LOQ as ten times S/N. The LOD can be estimated from the standard deviation for the mean blank response and some confidence factor. The figure below illustrates the relationship between the blanks, LOD, and LOQ. Results are represented as a probability density function for normally distributed measurements. The LOD is defined as $3\sigma_{blank}$ and the LOQ is defined as $10\sigma_{blank}$. These definitions were used to calculate the NIOSH 5040 LOD and LOQ estimates listed in the CIB (based on media blanks). For a result at the LOD, the false positive probability (alpha error) is small (1%). However, the false negative (beta error) probability is 50%, meaning at the LOD, there is a 50% chance that a	

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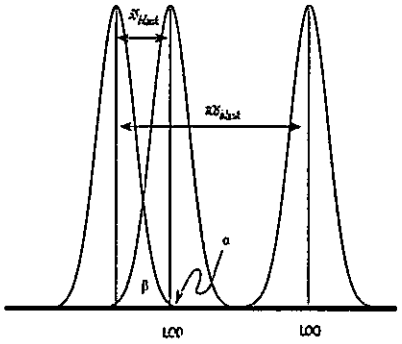
Wambach, DOE (cont.)	safety will have difficulty in securing labor and line management support for protective actions when there is no monitoring or other objective data supporting their need or effectiveness.	measurement would give a result less than the LOD. However, at the LOQ, the chance of a false negative is negligible.  (Fig. from http://www.answers.com/topic/bioinorganic-chemistryrom) http://en.wikipedia.org/wiki/File:LOD.png 1. IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"), Compiled by A.D. McNaught and A. Wilkinson, Blackwell Scientific Publications, Oxford (1997), XML on-line corrected version: http//goldbook.iupac.org(2006) created by M. Nic, J. Jirat, B. Kosata; updates compiled by A. Jenkins. ISBN 0-9678550-9-8, doi:10.1351/goldbook.	

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Wambach, DOE (cont.)		2. MacDougall, Daniel; Crummett, Warren B., et al (1980), Guidelines for Data Acquisition and Data Quality Evaluation in Environmental Chemistry", *Anal. Chem.* 52:2242-49, doi:10.1021/ac50064a004. A result above the LOD is considered 'detectable'. A result ≥ LOQ is considered quantitative. The NIOSH 5040 LOQ is about 1 $\mu g/m^3$. See response and revised CIB for further discussion.	
	2) On page 48, a paragraph that reads: *As part of the initial workplace hazard surveillance, NIOSH recommends identifying those workers with the highest potential for exposure to CNT and CNF [NIOSH 2009a], as well as the tasks and processes associated with those potential exposures. Performing targeted exposure sampling of workers involved in those tasks can be part of an overall exposure sampling strategy to protect workers' health. Although a specific sampling strategy has not been developed for evaluating workplace exposures to CNT and CNF, the same principles developed for the exposure measurement of other aerosols [e.g., NIOSH 1977; Leidel and*	2) The CIB was expanded to include a new Section 6.1.2 *CNT and CNF measurement* that provides more specific guidance on exposure monitoring.	2) Section 6.1.2 *CNT and CNF measurement* provides guidance on exposure strategies acknowledging that workplace airborne exposure concentrations to CNT and CNF can be highly variable and that different strategies may be required depending on the characteristics of the workplace. Several exposure assessment strategies are cited that could be used for evaluating workplace exposures including the AIHA "*A strategy for assessing and managing occupational exposures*". As noted by the commenter, the

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Wambach, DOE (cont.)	*Busch 1994] should apply to workers with potential exposure to CNT or CNF. When the goal of sampling is to determine whether or not worker exposures are being controlled below the REL, initial sampling efforts should focus on those workers thought to have the highest exposure concentrations (i.e., maximum risk worker) [NIOSH 1977; Leidel and Busch 1994]. This type of strategy may be more efficient and require fewer resources for identifying potential exposures above the REL, although periodic sampling of all workers or groups of workers (identified as having similar exposures) should also be performed. The periodic sampling will ensure that the targeted sampling groups include all workers with potential for exposures above the REL. In workplaces where the number of workers potentially exposed is small, consideration should be given to sampling all workers.* The employer must decide which workers and how frequently they should be monitored to determine compliance with the REL. The referenced publication (Leidel and Busch, 1994) Section 5.3 "Exposure Monitoring Strategies," answers this question through the application of		incorporation of an 'Action Level' below the REL would be useful for identifying workers who may require more exposure monitoring and for determining the effectiveness of exposure control measures. However, because the REL is established at the LOQ of the analytical method it's not possible to establish an exposure limit (i.e.,'Action Level') below the REL. It is noted in the CIB that it may be necessary to measure exposures for all workers especially in workplaces where worker exposure concentrations may be highly variable.

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Wambach, DOE (cont.)	hypothesis testing statistics to exposure monitoring results to guide decisions. On page 521 the authors state "Section 2.4 listed two major types of monitoring programs as possible objectives of exposure estimation. The first type is an exposure screening program, which is a limited exposure monitoring program designed to identify target populations of workers with other-than-acceptable exposure distributions for follow up periodic monitoring. The program uses an action level as a screening cutoff to identify appropriate target populations for inclusion in a limited exposure surveillance program or a more extensive exposure distribution monitoring program. The latter program is a more extensive one intended to quantify exposure distributions of target populations." Implementing the screening step requires an action level that is less than the exposure limit since the fact that one day's exposure is less than the REL does not guarantee that all other days' exposures are less than the REL. Appendix L of the NIOSH 1977 reference explains that the distance the action level should be from a limit is highly dependent on the amount of		

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Wambach, DOE (cont.)	day-to-day variation in exposure. The action level should be at least 50 percent the REL even if day-to-day variation is very low (i.e., a geometric standard deviation [GSD] of 1.2 or less) and lower if variation is higher. For moderate variation with a GSD of 2, the action level should be 10 percent of the REL. The AIHA's, *Strategy for Assessing and Managing Occupational Exposures*[1], provides similar but more intuitive guidance as that provided by Leidel and Busch. On Page 89 of the AIHA text states, "If one measurement result is far below 10% of the Occupational Exposure Limit (OEL) threshold or well above 100% of the OEL, then it may be all the monitoring required to judge the exposure acceptable or unacceptable. If the exposure profile is highly variable or positioned within the range of 10% to 100% of the OEL, then more samples might be needed to adequately characterize the exposure profile." If judgment or screenings identify target populations for more extensive exposure distribution monitoring program, then		

[1] Ignacio, J.S. and W.H. Bullock, *A Strategy for Assessing and Managing Occupational Exposures*, Third Edition. AIHA Press, Fairfax, VA. 2006

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Wambach, DOE (cont.)	Leidel and Busch recommend initially collecting 6 to 10 samples per group and using lognormal probability plots or other parametric methods to estimate one-sided tolerance limits and other metrics used to guide decisions on the need for protective actions. If the lognormality of the data is in doubt, they advise much larger sample numbers per group (i.e., 30 to 60). Censoring casts doubt on the fit of data to a parametric model. In Appendix VIII of the AIHA book 20 percent to 50 percent censoring is characterized as medium, 50 percent to 80 percent as high, and 80 percent to 100 percent as severe. In a hypothetical minimally compliant exposure distribution with exactly 5 percent of exposures exceeding the REL and a GSD of 3, a reporting limit that is 50 percent of the REL would result in extreme (≈84 percent) censoring and require use of order statistics. A reporting limit that is 10 percent of the REL would reduce this to medium (≈33 percent) censoring, and use of parametric statistics would still be possible. Monitoring results from environments that are more clearly compliant with the REL would have higher percentages of censored results.		

Commenter	Summary of Comments Received	Response	Changes to CIB
Wambach, DOE (cont.)	3) The Bulletin recommends an exposure assessment strategy that largely depends on having monitoring methods that can detect exposures that are 10 percent of the REL or lower even though, as described above, NIOSH Method 5040 is unable to detect exposures less than the REL. Censoring measurements at the REL limits the choice of strategies to only one of Leidel and Busch's recommended options, the use of nonparametric order statistics. Under most occupational exposure scenarios, order statistics are too inefficient to have much utility. Similarly, exposed groups large enough to produce enough representative samples to support the use of order statistics would be the exception rather than the rule. Under most circumstances, sampling all workers in all shifts would be the only possible method of determining the rate at which the REL is being exceeded.	3) Any result above the LOD is considered a 'detectable' level. The LOD is estimated at about 0.3 $\mu g/m^3$. Results between the LOD and LOQ are considered semi-quantitative, but statistically different from the blank. NIOSH and its contract laboratory report results between the LOD and LOQ. See discussion above of LOD and LOQ in response to comments and the revised CIB.	3) Section 6.1.1 *Exposure monitoring program* was added to provide additional information on the requirements for sampling and analysis of CNT and CNF that will optimize exposure measurement results. Section 6.1.2 *CNT and CNF measurement* which identifies other exposure monitoring strategies with the acknowledgement that all workers may need to be monitored in work environments where airborne exposures to CNT and CNF are highly variable.
	4) The Bulletin provides recommendations to employers to guide decisions on whether additional protective actions are needed. Employers primarily should be concerned with avoiding errors that result in	4) Although it's not possible to establish an 'Action Level' below the REL using Method 5040, exposure measurement results that are below the REL but above the limit of detection (LOD) are	4) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Wambach, DOE (cont.)	concluding that unsafe working conditions are safe. Exposure monitoring methods that are unable to detect levels less than the REL are ill suited to achieving this goal. A consequence of censoring measurements at the REL is that it will limit the use of the monitoring results to support studies of protective exposure levels. Monitoring results from compliant workplaces will be all, or nearly all, labeled non-detects. Even results from workplaces with mean exposure levels near the REL will be highly censored. If the medical surveillance recommended by the Bulletin identifies workers with health effects, it is unlikely that the highly censored monitoring data available would support analyses of the differences in exposure levels between those with health effects and those without even if the exposures had been extensively monitored.	statistically significant. Measurement data between the LOD and LOQ can be informative and help to make decisions as to whether additional protective measures (e.g., engineering controls, PPE) may be required. The commenter is correct in that it may be difficult to associate exposure measurement results with findings of any health effects; however, as acknowledged in the CIB, there remains a residual risk of fibrosis over a working lifetime at the REL and that employers should reduce exposures as low as possible.	
	5) Throughout the Bulletin, there is a statement that: "the LOQ for NIOSH Method 5040 is 7 $\mu g/m^3$." Users of the Bulletin may not understand precisely what NIOSH means by the term "LOQ." There is no standard definition that chemistry laboratories apply to reporting limits, and the limit of quantitation (LOQ)	5) The LOD and LOQ estimates for NIOSH 5040 are normally based on media blanks (supplied by the client). The LOD is defined as 3σblank and the LOQ is defined as 10σblank. See previous response and CIB for discussion of LOD and LOQ.	5) Section 6.1 has been expanded describing the limitations of Method 5040 and provides guidance on how to optimize sample collection.

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Wambach, DOE (cont.)	is not defined in the Bulletin or in referenced documents. For example, what NIOSH calls LOQ other laboratories might call LOD (limit of detection), DL (detection limit), IDL (instrument detection limit), LQ (limit of quantitation), QL (quantitation limit), PQL (practical quantitation limit), EQL (estimated quantitation limit), MDL (method detection limit), or RL (reporting limit). Adding to the confusing variety of these terms is the different procedures and criteria used for their calculation. Most commonly the term LOQ is applied to a metric that conforms to the statistical concept L. A. Currie[2] called the quantifiable level and defined as the true concentration above which the relative standard deviation of the distribution of measured values is less than a specified value (e.g., 10 percent.). This number will depend on several variables, e.g., the concentration of the lowest calibration standard, condition of the analytical equipment, sample matrix, preparation method, number of replicates, etc., and varies over time for a laboratory for each analyte and method. The Bulletin's		

[2] L. A. Currie, Anal. Chem., 1968, 40, 586-593.

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Wambach, DOE (cont.)	recommended use of the fixed number 7 $\mu g/m^3$ is not consistent with Currie's concept of a quantifiable level and how it is determined. 6) The Bulletin suggests that the 7 $\mu g/m^3$ value is the censoring point that NIOSH quality assurance programs have established for reporting results of analyses of full shift personal samples for diesel particulate. It is well suited to assessing diesel particulate exposures against a Mine Safety and Health Administration Permissible Exposure Limit of 160 $\mu g/m^3$. Publishing a REL of 7 $\mu g/m^3$ for CNT and CNF will make it a de facto reporting limit for other chemistry laboratories for CNT and CNF analyses. Labs must establish reporting limits before analyzing the first sample from a customer and will almost certainly choose to establish that they can meet the number NIOSH has shown to be feasible rather than attempt to establish a reporting limit that they could attain that would be lower than the NIOSH LOQ. The discussion in the Bulletin and Chapter Q of the NIOSH Manual of Analytical Methods suggests that lower censoring	6) The LOD and LOQ estimates in the revised CIB are based on typical variability in the EC results for media blanks (with manual OC-EC split). They consider use of a smaller filter (25-mm) and different sample volumes (flow rates). A current limitation is the limited availability of samplers designed to collect respirable dust at higher flow rates. An LOD well below 1 $\mu g/m^3$ is expected, but environmental background may be an issue at concentrations this low.	6) Section 6.1 has been expanded describing the limitations of Method 5040 and provides guidance on how to optimize sample collection.

Commenter	Summary of Comments Received	Response	Changes to CIB
Wambach, DOE (cont.)	points for diesel particulate could have been validated had there been a need.[3] Use of a smaller filter, a size selective sampler that operates at a higher flow rate, and analysis of a larger portion of the sample filter media appear to be straight forward methods of lowering the censoring point. DOE respectfully suggests that NIOSH undertake to enhance Method 5040 to establish a lower LOQ and therefore lower censoring point for CNT and CNF analytic results.		

[3] Birch ME, "Monitoring of Diesel Particulate Exhaust in the Workplace" in *NIOSH Manual of Analytical Methods* http://www.cdc.gov/niosh/docs/2003-154/pdfs/chapter-q.pdf, accessed 2/1/201.

Commenter	Summary of Comments Received	Response	Changes to CIB
Votaw, WilmerHale	1) It is somewhat curious that NIOSH has elected to develop and issue a recommended exposure limit using the Current Intelligence Bulletin (CIB) model rather than developing a Criteria Document. NIOSH typically communicates its recommended standards to regulatory agencies, health professionals and industry by means of Criteria Documents.[4] Criteria documents contain a critical review of the scientific and technical information about the prevalence of hazards, the existence of safety and health risks, and the adequacy of control methods. The Criteria Document provides a comprehensive assessment and analysis of the potential hazards and response options and considerations culminating in a REL for a substance. For example, where NIOSH has recommend medical surveillance in conjunction with a REL, the Criteria Document provides a detailed assessment of the circumstances warranting medical surveillance, and how it should be carried out in light of the particular circumstances (e.g., identifying the particular health end point(s) of	1) The commenter is correct in noting that NIOSH Criteria Documents (CDs) were typically used in the past for communicating recommended exposure limits and other risk management recommendations (e.g., medical surveillance) on a specific health hazard. CDs contained a comprehensive evaluation of all health data on the topic. NIOSH has recently expanded the scope of CIBs to include RELs when appropriate, as well as risk management recommendations (e.g., medical surveillance, exposure monitoring and control measures). Unlike CDs, the CIB on CNT and CNT only focuses on the most relevant health end-point (i.e., respiratory disease). The use of a CIB versus a CD has shortened the time frame in getting important information to the public and stakeholders.	1) No revisions required.

[4] E.g., *Criteria for a Recommended Standard, Occupational Exposure to Refractory Ceramic Fibers*, DHHS (NIOSH) Publication No. 2006–123 (May 2006).

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Votaw, WilmerHale (cont.)	concern, and the suitably sensitive surveillance method(s) to assess the endpoint(s)). In contrast, Current Intelligence Bulletins (CIBs) are more limited instruments. NIOSH uses CIBs to disseminate new scientific information about occupational hazards. "A CIB may draw attention to a previously unrecognized hazard, report new data suggesting that a known hazard is either more or less dangerous than formerly thought, or disseminate information recommending specific controls for a hazard."[5] CIB's provide much less comprehensive analyses and, in the past, have not been the vehicle for developing and recommending exposure limits to other agencies. The number of uncertainties and unanswered questions about CNTs noted in the draft Bulletin suggests that the REL development process may have benefited from the more comprehensive Criteria Document approach typically used for RELs, rather than the "short-form" approach used in the draft Bulletin.[6]		

[5] See e.g., Current Intelligence Bulletin 50, *Carcinogenic Effects of Exposure To Diesel Exhaust*, DHHS (NIOSH) at 1 (Aug. 1988).

[6] Indeed, the Federal Register notice that lead off this effort did not indicate that NIOSH was developing a REL. *Request for Information on Carbon Nanotubes (CNTs) Including Single Walled Carbon Nanotubes (SWCNTs) and Multi-Wailed Carbon Nanotubes (MWCNTs)*, Notice of public comment period; 74 FR 15985 (Apr. 8, 2009).

Commenter	Summary of Comments Received	Response	Changes to CIB
Votaw, WilmerHale (cont.)	Several of the following comments directly support that view. 1) The Analysis Treats All CNT as Being the Same. The draft Bulletin acknowledges the many physical and chemical differences among the several varieties of CNTs used in the studies underlying the draft REL (single wall, multiwall, long, short, thinner, fatter, straight and curly, agglomerated an un-agglomerated; with a range of different chemical catalysts and impurities) and makes the case that these physical and chemical differences affect the relative toxicity of the several materials. Nevertheless, the draft Bulletin persists in drawing inferences about the toxicity of one type of CNT (or all CNT) from the results of studies of other CNT with very different properties.[7]	1) The comment is correct in stating that the CIB describes and evaluates the available data on the effects of physical-chemical properties of CNT on the REL derivation. However, the second part of the comment would be incorrect if it is saying that NIOSH did not take into account the available data on the role of physical-chemical properties on the CNT REL. In Appendix A, NIOSH provided individual estimates of working lifetime risks of early stage lung disease based on the dose-response data in rats and mice exposed to various types of SWCNT and MWCNT from different production methods and with different types and amounts of metal catalysts (Tables A-3 through A-5). Despite the observed variability in response across studies (e.g., human-	1) Text has been added to the CIB (Exec Sum, Section 5, Appendix A) to better communicate the information in this response.

[7] See, e.g., draft Bulletin discussion at 7, 17, 32-33, 112. See also Poland, CA, Duffin R, Kinloch I, Maynard A, Wallace WA, Seaton A [2008]. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. Nat. Nanotechnol 3(7), 423; Pauluhn, J., 2010a. Subchronic 13-week inhalation exposure of rats to multiwalled carbon nanotubes: toxic effects are determined by density of agglomerate structures, not fibrillar Structures. Toxicol. Sci. 113 (1), 226-242.

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Votaw, WilmerHale (cont.)		equivalent BMC(L)s in Tables A-3 to A-5), little evidence was available to indicate any appreciable difference in the variability in estimates across particle type compared to variability in estimates across study and response endpoints (early-stage pulmonary inflammatory and/or fibrotic responses). All of these studies pointed to low mass concentrations relative to other particulate OELs, and would result in a health-based working lifetime REL (8-hr TWA) near the optimal and upper LOQs of 1 and 7 ug/m3, respectively, for elemental carbon [NIOSH method 5040].	
	1b) In the end, the practical effect of this approach in setting the REL for *MWCNT* is minimal as the REL was set above the benchmark excess risk level(s) for MWCNT due to limitations of the test method. It is unclear how NIOSH would have selected the REL if test method sensitivity limits fell between the BMD results for the two studies actually used. For SWCNT and carbon nanofibers (CNF), NIOSH should expand its discussion of why the REL based on two	1b) In addition to the MWCNT subchronic studies, dose-response data are available from several shorter-term studies of SWCNT and other types of MWCNT. These risk estimates are consistent with those from the subchronic studies (Tables A-3 through A-5). Typically, NIOSH would extrapolate below the 10% BMDL to estimate working lifetime exposure associated with lower risk, although	1b) Sensitivity analyses have been added to further evaluate the uncertainties in the risk assessment and the influence of methods and assumptions on the derivation of a health-based REL (Section A.6). Additional discussion has been added concerning the uncertainties in the risk assessment (Section 5.3).

Commenter	Summary of Comments Received	Response	Changes to CIB
Votaw, WilmerHale (cont.)	MWCNT studies is appropriate for these materials and should address the uncertainties associated with that conclusion.	there would be additional uncertainty in these estimates due to the limited animal data and uncertainty about the shape of the dose-response curve beyond the range of the data. Additional information about a health-based REL can be obtained by evaluating the influence of alternative assumptions and methods on the OEL derivation. Despite the variability in the resulting estimates, all analyses support a low mass concentration as 8 hr TWA, as well as the need for developing more sensitive and specific methods to measure exposure to CNT and CNF in the workplace.	
	1c) Similarly, although the draft Bulletin identifies CNT agglomeration state as a relevant physical property that may be important to relative toxicity,[8] and as a complicating factor in intratracheal instillation studies,[9] the draft never resolves how rationally to draw common inferences from studies made with differently agglomerated CNTs.	1c) Please see responses to the previous two comments, which address this comment. That is, the studies in the risk assessment (Appendix A) includes CNT with different particle size, structure, and agglomeration state.	1c) As discussed in the previous two comments.

[8] E.g., draft Bulletin at 18, 29.

[9] E.g., draft Bulletin at 29

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Votaw, WilmerHale (cont.)	1d) A third possible incongruity is the statement in the draft Bulletin that only studies using unground CNT was used in the risk assessment.[10] Grinding CNTs makes them more amenable to some laboratory inhalation exposure techniques, but changes their morphology (e.g., from long to short, from large to small agglomerates), which may affect other relevant properties (e.g., bulk density, AED), which may affect inhalation, deposition and clearance factors. Pauluhn, J. [2010a] used ground (micronized) CNT and Ma-Hock, L. [2009], subjected their samples to a brush aerosol generator which probably affected the agglomerate size.	1d) A priori criteria were selected for the analyses in order to select the most typical animal models and CNT types. It would also be of interest to extend these analyses to include any available dose-response data on the various modifications to CNT (including physical-chemical changes to the surface and structure) which may affect its deposited/retained lung dose and toxicity.	1d) The ground and unground CNT both caused fibrosis (measured by hydroxyproline and soluble collagen), although the dose-response relationship was more apparent for the unground CNT (Figure 4 of Muller et al. 2005]. Additional discussion of the study findings is provided in Section 3.2.2.
	2) The Draft Bulletin Fails to Critically Review Studies. The draft bulletin makes no attempt to critically review the work upon which it draws. A particularly egregious example is repeating the gross speculation that conditions in the World Trade Center disaster may have led to the	2) We agree that the presence of CNT in WTC dust does not mean that this is the etiologic agent of pulmonary dysfunction in first responders. It is likely that inhalation of caustic cement dust and fire smoke dust	2) A new Section 2.2 *Exposure to carbon nanotubes (other sources)* was added to the document citing other references that illustrate the

[10] Draft Bulletin at 99.

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Votaw, WilmerHale (cont.)	growth of CNTs and that these might then be implicated in health problems of those involved. By repeating those "findings," NIOSH will be understood to have evaluated the underlying study and accepted its conclusions. One of the particular values that NIOSH typically brings to the process of considering occupational exposure levels is an evenhanded assessment (typically in a Criteria Document) of the literature and the merit and significance (or not) of past work by others. In the case of the draft Bulletin, this does not appear to have been done, at least in connection with the characterization of the potential hazards. While the analysis in the draft Bulletin has screened out a number of studies from use in the risk assessment, it is not clear to what extent the remaining studies were fully reviewed for expected quality and reliability in addition to more quantitative characteristics.[11]	containing radical species damaged the epithelial lining of the airways and is associated with pulmonary function deficits. This study was deleted from the CIB.	formation of CNT from the burning of natural gas, propane, and other methane-series gases. The purpose of including these references is to show that exposure to CNT can occur from other sources outside of the workplace. All relevant studies published through June 2012 were evaluated for assessing the health risk to CNT and CNF.

[11] E.g., draft Bulletin at 99.

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Votaw, WilmerHale (cont.)	3) The Draft Bulletin Should Expand the Risk Assessment Uncertainty Analysis. The REL is premised in part on a risk assessment identifying the working lifetime exposure concentration to any CNT or CNF that is expected to give a 10% excess risk of developing mild adverse lung changes. As detailed in the appendix, this calculation, while elegant, is premised in part on a great number of assumptions with varying levels of certainty, and varying levels of effect on the outcome(s) of the several BMD analyses. It would be useful to discuss the key assumptions with the greatest uncertainties that most affect the quantitative result(s). This is not to suggest that NIOSH has used assumptions that are not commonly used, only that users need to understand how robust the results are and the extent of uncertainty (e.g., 10 fold uncertainty factors for extrapolating from different types of rats and mice to humans). There is some discussion of uncertainty factors in the Bulletin, but NIOSH's judgments about the *extent* and significance of the uncertainty remains unclear. Presumably a Criteria Document would have addressed the risk assessment uncertainty issue more fully.	3) NIOSH agrees that additional qualitative and quantitative analysis (as feasible) would be useful to evaluate the influence of the various assumptions and methods used in the risk assessment on the REL derivation	3) A detailed sensitivity analysis has been added (Section A.6) which includes several addition tables and alternative animal and human-equivalent dose and risk estimates. Despite the variability in these estimates (which has been quantified in several of these analyses), the various assumptions and methods had little effect on the REL derived from animal dose-response data of early-stage inflammatory and fibrotic lung effects.

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Votaw, WilmerHale (cont.)	4) The Selected Monitoring Method is Subject to Interference. The draft report recommends the use of NIOSH Method 5040 (Elemental Carbon (Diesel Particulate)). As noted in the draft Bulletin, this method can differentiate between elemental carbon (EC) and other particulate matter, but it will not distinguish between CNT and other sources of elemental carbon (e.g., diesel exhaust particulate, combustion products). Accordingly, at least in the early stages in a Method 5040 monitoring program, the monitoring plan should include analysis of positive samples by transmission electron microscopy (modified NIOSH method 7402) to confirm or rule out the presence of CNT or CNF. If necessary, an estimate of CNT mass can be calculated by converting particle count to mass using agglomerate size and bulk density. Establishing typical background EC concentrations may help account for interference but, depending on the circumstance, "background" elemental carbon values may vary widely at a particular location (e.g., unsealed work area proximate to heavy industry or truck traffic). Despite limitations, both of these	4) NIOSH researchers have applied multiple metrics (e.g., Birch et al. 2011, Birch 2011, Evans et al. 2010) to characterize CNF/CNT exposure. However, NIOSH surveillance research may involve exposure assessment methods beyond what is practical for facilities with limited resources. NIOSH is actively recruiting participants for surveillance studies. See response to DECOS-Health Council of the Netherlands, comment 4. Initially, assessments using NIOSH Method 5040 and microscopy will require sufficient measurements to establish background EC for a given workplace, which may vary spatially and temporally. Subsequent monitoring requirements will depend on these initial assessments. Once characterized, a reduced monitoring effort may be possible if the workplace environment is relatively unchanged and background is minimal (e.g., see results in Birch et al. 2011). If so, a relatively simple, low-cost monitoring approach could	4) Section 6.1 and 6.2 have been expanded to provide guidance on optimizing sample collection and how to establish an exposure monitoring program.

Commenter	Summary of Comments Received	Response	Changes to CIB
Votaw, WilmerHale (cont.)	methods are preferable to simple counting – by mass or number – of particulates without any limitation to elemental carbon or CNT as is done in many studies. Maynard [2004]. Idiopathic nano-scale particles from natural and man-made sources are, of course, ubiquitous and plentiful in all uncontrolled environments.	be implemented.	
	5) Uncertain Basis for Suggested Dermal Exposure Controls. The draft Bulletin provides an extended discussion of the evidence supporting concerns for adverse lung affects resulting from the inhalation CNT and CNF in occupational settings and recommends protective measures consistent with those concerns (e.g., administrative controls and respirators where warranted). The draft bulletin also recommends the use of dermal protection (e.g., gloves), but does not identify any of the health concern associated with dermal contact, or evidence supporting it. Indeed, the text cites the absence of dermal response from two different MWCNT based on acute exposure tests. In light of this, any recommendation for dermal protections should be supported by an explanation of why it is warranted and recommended under the circumstances.	5) Section 6.5: NIOSH stated that a potential for dermal exposure exists from the handling of CNT [Maynard et al. 2004] but that data from studies conducted to evaluate the potential health effects from dermal exposure to CNT and CNF were incomplete and thus, no determination could be made regarding the health risk associated with dermal exposure. Until the appropriate research can be conducted to assess the potential health risks from dermal exposure to CNT and CNF, NIOSH made the following recommendation: "Given the limited amount of data on dermal exposure to CNT and CNF, it would be prudent to wear protective clothing and gloves when, • All technical measures to eliminate or control the release of exposures to	5) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Votaw, WilmerHale (cont.)		CNT and CNF have not been successful or, • In emergency situations."	
	6) Medical Surveillance. NIOSH's very specific recommendation for a screening medical surveillance program for workers requires additional explanation.[12] While the draft Bulletin does a creditable job of describing a generic medical screening program, and generic consideration for the design of such a program, NIOSH does not apply those criteria and considerations to the specific case of CNTs and CNFs, and does not explain why, in light of those criteria and considerations, a medical screening program is warranted for CNTs and CNFs and how it should work. This approach to the issue is, as noted above, contrary to the approach typically seen in NIOSH Criteria Documents.[13] Typically, a medical surveillance program may be useful where (a) a health effect endpoint associated with exposure to the target contaminant has been identified; (b) exposure to the target contaminant is known to result in	6) NIOSH has used CIBs to convey medical surveillance and screening recommendations in the past – CIB 60 concerning Nanomaterials was devoted to that topic; CIB 53 (concerning TDE and TDA, 1989) included recommendations for medical monitoring. We agree with the reviewer that there are pros and cons to medical screening and surveillance programs- the factors presented by the reviewer have been considered by NIOSH authors of this document. We also agree that the data concerning health effects and exposure to CNT/CNF are limited. In this document NIOSH attempts to balance the need for direct evidence of health effects among workers that have occurred with a proactive precautionary	6) No revisions required.

[12] Draft Bulletin at 46, 54-57, 134-135.

[13] See Criteria Document discussion at page 2, above.

Commenter	Summary of Comments Received	Response	Changes to CIB
Votaw, WilmerHale (cont.)	one or more distinctive (selective) and objective physical (medical) signs indicative of the disease process or health endpoint of concern; (c) exposures to the target contaminant are known or reasonably believed to be occurring; and are occurring by routes and in doses (considering duration and concentration) that would reasonably be expected to generate the physical sign if exposures were occurring; (d) a surveillance (test) method exists that will detect the physical sign with sufficient selectively and certainty that it will be possible to conclude by evaluation of the surveillance results whether or not significant exposures to the target contaminant are occurring; and (e) the surveillance results can reasonably be expected to be useful and reliable in determining a future course of action in relation to the target contaminant. These are the criteria that NIOSH's recommendation should address in relation to CNT and CNF. When they are not present, a medical screening program may not be warranted. Nonspecific medical testing from unwarranted or poorly designed surveillance programs can have negative consequences such as adverse effects from the tests (e.g., radiation from chest x-rays), creating unnecessary anxiety in workers and employers from false-positive	program to prevent health effects from occurring. Related to the criteria listed (a-e) by the reviewer: (a) and (b) – the CIB sets forth evidence and data that raises concerns for specific health effects in humans – pulmonary fibrosis and cancer; we disagree that exposures known to result in distinctive health effects is a necessary criteria for initiation of medical surveillance or screening; (c) it is evident that exposures by inhalation and skin contact are occurring – we agree that the clinical significance of these exposures is not clear at this time; (d) standard clinical tools to assess likely health effects – for example, in the respiratory system – are recommended. These tests (CXR, spirometry) represent the standard of care and are used in many types of screening and surveillance programs despite the fact that these tests are not necessarily specific; (e) NIOSH feels that it is a prudent secondary health preventive measure to recommend medical screening and surveillance where occupational exposure to CNT/CNF is occurring. The 2009 NIOSH CIB 60 addressed the	

Commenter	Summary of Comments Received	Response	Changes to CIB
Votaw, WilmerHale (cont.)	screening tests, and the lost time and costs of additional diagnostic evaluations.[14] The unexplained recommendation for a screening medical surveillance program at this time is all the more curious because, only two years ago, NIOSH concluded that a screening medical surveillance program was not warranted for CNTs: Key among the criteria for recommending specific medical screening of workers exposed to engineered nanoparticles …[is] whether the disease to be averted is sufficiently common in the worker population to justify routine screening [citations omitted]. For engineered nanoparticles, there is insufficient evidence for a definitive hazard determination…. No chronic inhalation studies of engineered nanoparticles have been conducted to date. The existence of a few short-term inhalation studies on carbon nanotubes … is not adequate to identify what disease endpoints to assess in medical screening. There is also insufficient information available regarding the absolute, relative or population-attributable risks associated with nanoparticle exposures [Citations omitted]. NIOSH has shown that inhalation of SWCNTs cause interstitial	question of medical screening of workers exposed to "engineered nanoparticles" in the absence of sufficient animal or human evidence of an adverse health effect. The current CIB deals specifically with exposure to CNT/CNF in which sufficient toxicological evidence exists demonstrating a risk for respiratory disease. This evidence was used for recommending the establishment of a medical screening and surveillance program for workers exposed to CNT/CNF.	

[14] Current Intelligence Bulletin 60, *Interim Guidance for Medical Screening and Hazard Surveillance for Workers Potentially Exposed to Engineered Nanoparticles,* DHHS (NIOSH) (February 2009) at 7.

Commenter	Summary of Comments Received	Response	Changes to CIB
Votaw, WilmerHale (cont.)	fibrosis [Shvedova et al. 2008]. The problem is that purified SWCNTs are not redox reactive and the interstitial fibrosis is not driven by oxidant generation and inflammation. Therefore, measurement of markers of oxidant stress or inflammation in humans would not be predictive. If interstitial lung disease was considered the health endpoint of concern, monitoring of the carbon monoxide diffusion capacity of the lung could be performed noninvasively. A significant decline in diffusion would indicate a loss of alveolar-capillary gas exchange and suggest early signs of pre-clinical disease. Unfortunately, virtually no published data exist on occupational exposure concentrations for working in SWCNT operations. Consequently, there is too little information available at this time to verify disease endpoints. [15] For these reasons, the draft Bulletin should be revised to address what has changed since NIOSH's last assessment of medical surveillance. It should also include both an explanation of why any CNT or CNF screening medical surveillance program NIOSH recommends is warranted, and present practical program development guidance		

[15] Current Intelligence Bulletin 60 at 61.

Commenter	Summary of Comments Received	Response	Changes to CIB
Votaw, WilmerHale (cont.)	specific to these materials, similar in scope and depth to that typically seen in Criteria Documents. 7) The Assessment of Potential for Exposure Should be Clarified. The studies cited in the draft Bulletin as evidence of potential for CNT handling-related exposure are largely laboratory or R&D operations[16] and are not likely to be representative of realistic, steady-state commercial operations. Because research by its nature comprises a series of one-off and prototype operations, these operations inherently lack the engineering and administrative controls that can be practically developed and applied in a manufacturing setting. On the other hand, small scale laboratory operations, because of their size and limited duration, often can be performed in controlled settings (e.g., fume hoods, glove boxes) that would be impracticable for commercial operations. One important potential exposure scenario the draft Bulletin fails to highlight is the "large-scale research-type" operation, i.e., scaling up volumes without making the transition	7) NIOSH agrees with the commenter that workplace exposure data to CNT and CNF are limited and that most of the exposure data collected at CNT/CNF workplaces are reported as airborne particle count or particle surface area concentrations. The commenter is correct in that the study by Bello et al. 2009 did not specifically identify CNT in collected air samples; however, Lee et al. 2010 did detect the airborne release of MWCNT (page 372). Reference to the Bello et al. 2009 study has been deleted. NIOSH has initiated several research efforts to characterize worker exposures to CNT and CNF using different exposure metrics (respirable mass, particle count, electron microscopy determination of tube dimension and concentration). Research is also being conducted to evaluate the	7) Reported workplace studies were clarified as to whether airborne CNT and CNF were detected. Additional studies [Bello 2010; Birch 2011] have been included in the CIB that identify the airborne release of CNT and CNF, respectively.

[16] See e.g., draft Bulletin at 20-24.

Commenter	Summary of Comments Received	Response	Changes to CIB
Votaw, WilmerHale (cont.)	to the kinds of mature processes susceptible to engineering controls. The discussion in the draft Bulletin of the several exposure studies reviewed should be clearer about which studies detected CNT and which did not. Critical review of several of these sources would support the conclusion that, in many cases, the investigators are observing substrate dust and nothing more. For example, Bello et al. [2009] found that *nanoparticles* were generated by cutting composites containing CNT. However, they also found that there was *no difference* in overall particle release levels, peaks in the size distribution of the particles, or surface area of released particles (including size distribution) between the composites that did and those that did not contain CNT, and, most significantly in this context, no CNTs (either individual or in bundles) were observed in extensive electron microscopy of collected samples. Similarly, it appears that Lee, et al. [2010] similarly found nanoparticles, *but did not find CNTs*. In fact, the cited studies contradict the stated premise that "exposure measurements indicate the potential for worker exposure." It also should be noted that composite parts are desirably molded to final net shape and do not require further cutting or grinding.	effectiveness of various types of engineer control measures.	

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Votaw, WilmerHale (cont.)	8) Bound Materials. To the extent that the draft Bulletin asserts that "many workers" may come in contact with CNTs during their life cycle, it also should be said that this is probably not the case once the CNT are bound to or in a matrix, especially in view of the Bello and Lee references that show that even such aggressive post processing as cutting the composites did not release CNTs. Thus, once bound in a matrix the potential for CNT exposure likely becomes quite remote. This suggests that precautionary control measures should be focused principally on operations handling unbound CNT.	8) Dispersion of unbound CNF/CNT powders during open handling is the greatest concern, but exposure to composite dust also may be a concern if respirable. Some composite operations involve cutting or grinding of the material, releasing insoluble particulate matter. Though there is little evidence of release of matrix-bound CNT/CNF 'fibers' (using asbestos counting rules), inhalation of insoluble particles with embedded CNT/CNF also may be a health concern.	8) No revisions required.

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Cummings, Bayer Material Science	The NIOSH CIB appropriately identifies the need to handle nano-based materials in a safe manner. In fact, we at Bayer Material Science (BMS), as part of our Product Stewardship Program (BayCare®) have published guidelines for the safe handling of Baytubes® entitled, Baytubes® Carbon Nanotubes; Safe Handling Guidelines (BMS, 2009). These guidelines are consistent in many ways with the recommendations offered by NIOSH, particularly those identified in the CIB on pages 8-15. However, while BMS supports many of the principles and recommendations outlined in this CIB, we respectfully offer comment on the document as identified in the following sections.		
	1) One of the critical elements in the derivation of a REL in the CIB is selection of the key studies and the identification and assessment of critical endpoints. As indicated earlier, the subchronic inhalation toxicity studies are considered to represent the key studies for examination of critical endpoints. However, a key flaw in the CIB is not having appropriately defined adversity for the various outcomes reported in the subchronic studies. The CIB notes that early-stage fibrotic and inflammatory lung responses were selected	1) Alveolar interstitial fibrosis can be detected by Sirius red staining of septal collagen [Hubbs et al. 2011]. In SWCNT exposed mice, the septal fibrosis was further confirmed by transmission electron microscopy [Mercer et al. 2008]. Pauluhn [2010a] also reported alveolar interstitial thickening in rats exposed to MWCNT, but distinguished the focal effects observed at 0.4 mg/m^3 from those at higher exposures. Pauluhn [2010a] reported:	1) Section A.2.1.3 of the CIB has been revised to clarify the description of the rat lung responses as reported by Pauluhn [2010a] and the NIOSH interpretation as a benchmark response for risk assessment, as described in this response. Additional evaluation of the influence of pulmonary response endpoint selection and other factors on the REL derivation is

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Cummings, Bayer Material Science (cont.)	and were characterized as lung inflammation, granuloma and interstitial fibrosis. In contrast to the conclusions operative in the CIB, caution against such conclusions for fibrosis is expressed by several investigators studying CNTs. For example, Ellinger-Ziegelbauer and J. Pauluhn (2009) state "*These findings support the hypothesis that the sirius red stained collagen using the Sircol assay likely reflects the exudated, inflammation related collagen rather than the (myo-) fibroblast synthesized septal collagen*" and Ryman-Rasmussen et al. (2009) state "*A caveat is that the fibrosis score relied on trichrome staining, which, although commonly used, could stain other cell matrix components and contribute to the observed pleural wall thickness*." Thus, these investigators are attempting to distinguish their findings from that where significant tissue remodeling occurs with the presence of mature, cross-linked fibroblast-derived collagen. The histopathologic findings described by Pauluhn (2010) are not consistent with pulmonary interstitial fibrosis and do not meet the criteria for "adverse effect" as defined by the USEPA (USEPA-IRIS). The CIB specifically notes on page 103	"Increased interstitial collagen staining occurred at 1.5 and 6 mg/m^3. Focal areas of increased collagen staining were adjacent to sites of increased particle deposition and inflammatory infiltrates (onset at 0.4 mg/m3, see Table 3). Increased septal collagen staining was depicted as equal to interstitial fibrosis (for details, see Fig 12)." The severity level (minimal or greater) persisted or progressed up to 26 weeks after the end of the 13-week inhalation exposure to either 0.4, 1.5, or 6 mg/m^3 [Pauluhn 2010a, Table 3]. The 0.4 mg/m^3 dose group was considered the LOAEL for inflammatory lung effects, while 0.1 mg/m^3 was considered the NOAEL [Pauluhn 2010a]. Pathologists' interpretations may differ as to whether these early-stage responses would be considered adverse or to have the potential to become adverse. NIOSH interpreted the alveolar septal thickening (and associated effects including hypercellularity in the bronchial alveolar junctions) in the 0.4 mg/m^3 and higher dose groups as being	provided in Sections A.6 and 5.3.

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Cummings, Bayer Material Science (cont.)	that "A benchmark dose has been defined as "… a statistical lower confidence limit for the dose corresponding to a specific increase in level of [adverse] health effect over the background level" [Crump 1984]". Thus, in using the benchmark dose model, the CIB has not followed the prescribed input for the model.	adverse changes of relevance to human health risk assessment due to their persistence and consistency with early-stage changes in the development of pulmonary fibrosis. For these reasons, NIOSH selected alveolar septal thickening of minimal or higher grade as the benchmark response for risk assessment and BMD(L) estimation based on the Pauluhn [2010a] study.	
	2) A related limitation to the assessment in the CIB is the use of only incidence data and disregarding the severity of response both as a function of exposure concentration and time. Solely using incidence data led to the input of dichotomous data to the benchmark model and the resultant outcome of a 10% risk being less than the NOAEL determined in the study by Pauluhn (2010). This disregard of severity of response overlooks a key component essential to the determination of an adverse dose-response. Thus, the results of the benchmark analysis of dose-response for the study by Pauluhn (2010), as described in the CIB, are considered inappropriate for derivation of a REL.	2) These NOAEL and BMD estimates are not necessarily inconsistent. A statistical analysis was performed to compare the BMD and NOAEL estimates; the results showed that rat dose-response data on which the NOAEL of 0.1 mg/m^3 is based are also statistically consistent with the BMD model-based estimates (Section A.6.2). The severity of response was already evaluated in the external review draft CIB; working lifetime exposure concentration estimtes (associated with 10% excess risk) were also estimated for the higher severity (grade 2) of rat lung responses (Table A-7).	2) Discussion of the comparison analysis between NOAEL and BMD estimates was added to the CIB (Section A.6.2). Further analyses also show that the use of a NOAEL or BMDL has relatively little effect on the estimation of the working lifetime exposure limit (Sections A.6.2 and A.6.3). Additional discussion of the effect level estimation, including grade 2 or higher severity, was added to Sections 5 and A.6.

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Cummings, Bayer Material Science (cont.)	3) Where sufficient data leads to product specific recommendations of an OEL that diverge from the REL in the CIB, there should be an explicit acknowledgement that allows for acceptance of other product-specific RELs or comparable occupational exposure limits (OEL). The CIB describes experimental evidence that point to differences in toxicologic potency and/or differences in the type of response for different sub-structural materials. Even if the role of specific characteristics of CNTs such as shape, aspect ratio, physical and chemical properties, reactivity, etc that may interact to induce differential response are not clearly understood, it is possible to develop recommended OELs for specific products through product-specific testing. A more thorough understanding of the underlying cause of product-specific effects is more relevant when several subcategories of materials (CNF, SWCNT and MWCNT) with differing characteristics are grouped for the purpose of establishing a common OEL such as the REL proposed in the CIB. Although these materials may display some biologic responses in common such as an inflammatory response in the lung, there	3) NIOSH has stated in the CIB that the REL will be reevaluated as new data become available. Such data might result in different RELs for different types of CNT or CNF. However, the comment is not correct in saying that NIOSH grouped CNF, SWCNT, and MWCNT for the purpose of establishing a common OEL. Each animal study with sufficient dose-response data was used to derive individual BMD(L) estimates (associated with 10% excess risk of pulmonary inflammatory, granulomatous and/or fibrotic responses). Although there was variability in these BMD(L) estimates (up to approximately 2 orders of magnitude), all of these estimates were associated with low mass concentrations (8-hr TWA) over a working lifetime – relative to OELs for other poorly soluble particles and relative to the LOQ of NIOSH method 5040. Thus, the individual animal study data indicate the need to limit exposure to all types of CNT and CNF to low airborne mass concentrations.	3) Discussion of the similarities and differences in the OEL derivation methods and assumptions used by Pauluhn [2010b] and others is discussed in Section 5. Further evaluation and discussion is provided in Section A.6, evaluates the methods and assumptions used to derive the REL. The results were consistent with those in the original analyses and had little effect on the working lifetime REL estimates (Section A.6.3). Clarification is made in the CIB that differences in potency may exist as a result of differnces in physical and chemical characteristics including the effect of functionization of CNT and CNF.

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Cummings, Bayer Material Science (cont.)	are sufficient differences even within a single category of materials (e.g., MWCNT) to warrant consideration of exceptions to a common REL. Thus, where sufficient and relevant toxicological data has been developed to warrant a product-specific recommended OEL and where such a recommendation has been made as in the case of Baytubes® (Pauluhn, 2010; Pauluhn, 2011), the CIB should provide a more specific and detailed justification as to why a product-specific recommended OEL is not acceptable based on scientific grounds, or alternatively explicitly provide for the allowance of product-specific OELs.		
	4) In further support of a product specific recommended OEL for Baytubes®, this product does not meet some of the criteria in the CIB that suggests potential health concerns. A major potential health concern was the prospect of exposures leading to mesothelioma and the CIB attempts to relate three lines of experimental evidence to suggest the plausibility of this possible health threat: migration to the pleura; asbestos-like pathology; and evidence for genotoxicity. The study reporting migration of MWCNT	4) The REL is based on animal dose-response data of pulmonary inflammatory and fibrotic responses. The CIB discusses in Chapters 3 and 4 the animal studies showing that some types of CNT injected into the parietal or peritoneal pleura show asbestos-like responses and that some types of CNT have been shown to migrate from the lungs to the pleural tissue. However, these studies did not provide	4) Revisions were made (in Exec Sum, Sections 3, 4, and 6) to further clarify that some but not all types of CNT have been shown to migrate to the pleura and to be associated with inflammatory responses in the pleural tissue. In addition, recent studies [Mercer et al. 2011; Murphy et al. 2011] have been added to the CIB (Sections 3 and 4). The Mercer et al. [2011]

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Cummings, Bayer Material Science (cont.)	to the pleura did not use Baytubes® and differences in shape (long and thin versus short and coiled) may play a role in movement through various tissues. In addition, the subchronic inhalation toxicity study of Baytubes® (Pauluhn, 2010) did not indicate any effects on the lung pleura; even premonitory indications suggesting a potential progression to mesothelioma (i.e., the key histopathologic landmarks) were not detected in the pleura. Furthermore, to the point of inducing asbestos-like pathology, in addition to the absence of any histopathologic evidence of effects on the pleura, it is noted that the predominant response to Baytubes® in the lungs was an acute inflammatory response with attendant collagen exudation and interstitial thickening. This pattern of response is not consistent with that typically associated with the sequence of events leading to mesothelioma.	dose-response data for mesothelial effects that could be used in quantititative risk assessment to derive an REL.	study showed that the CNT structure influenced its ability to migrate from the lungs to the pleura (short, straight MWCNT fibers migrated but tangled SWCNT fibers did not). The Murphy et al. [2011] study showed that longer fiber-like CNT structures (>5 um in length) injected into the pleura caused inflammation but shorter and tangled structures did not.
	5) Lastly, the study cited as demonstrating evidence of genotoxicity used SWCNT (Sargent, et. al., 2009). It is significant to note that the results of a chromosome aberration test using Chinese Hamster V79 cells (Wirnitzer, et. al., 2009), Ames	5) Baytubes as studied are condensed agglomerates. As such they would not have a morphology reflective of microtubials and using the criteria of Sargent et al, 2009 would not be expected to be genotoxic. It should	5) No revisions required

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Cummings, Bayer Material Science (cont.)	Salmonella reverse mutation assay (Wirnitzer, et. al., 2009), and HGPRT forward mutation using Chinese Hamster V79 cells (BMS, 2010) did not show a mutagenic or clastogenic potential for Baytubes®. In a recent publication by Thurnherr, et. al., (2011), where in vitro-comet assay and -micronucleus assay were performed, Baytubes® didn't display any genotoxic potential. The study by Thurnherr, et al. (2011) also examined other endpoints to compare the response of human pulmonary epithelial cell line A549 and showed marked differences in response between Baytubes® and crocidolite asbestos. The overall weight of evidence from all three lines of inquiry does not indicate a concern for an outcome of mesothelioma from potential exposure of workers to Baytubes®.	be noted the users interest in exploiting the unique physicochemical properties of MWCNT may have to disperse Baytubes prior to use and, if so, may be exposed to smaller structures than were tested in the studies cited by the commenter.	
	6) NIOSH is recommending that a mass-based airborne concentration measurement be used to monitor the workplace for airborne CNT/CNFs. The mass-based measurement technique is one technique/metric commonly proposed. Others include number (i.e., particle counting) and volume (i.e., surface area)	6) A mass-based measurement is a traditional exposure metric. Other metrics have been proposed for nanomaterials, including particle number and surface area. These metrics may have relevance to some materials in controlled atmospheres, such as in animal inhalation studies,	6) Section 6.1 provides additional discussion on how to optimize sample collection using NIOSH Method 5040.

Commenter	Summary of Comments Received	Response	Changes to CIB
Cummings, Bayer Material Science (cont.)	estimates. Each technique presents its own challenge. While we support the use of a mass-based measurement technique the method recommended by NIOSH to measure airborne levels of CNTs/CNFs (NIOSH Method 5040) is not specific for these substances. This method is designed to identify total carbon (TC) with an elemental carbon (EC) exposure marker. Thus, it would be sensitive to all elemental carbon (e.g., soot, diesel exhaust, carbon black, cigarette smoke, etc.). In this regard, an overestimation of the airborne concentration of CNT/CNF is anticipated. There also is some question as to the commercial availability of the thermal-optical analyzer which is integral to the analysis of the airborne sample. Further, high sample volumes are needed to achieve lower limits of detection which is counter to typical CNT/CNF use and handling scenarios that more often are short-term in nature (i.e., 5- to 15-minutes).	but they lack selectivity, a problem for field applications. The reviewer supports a mass-based measurement, but is concerned that NIOSH 5040 is not sufficiently selective. Currently, we know of no alternative approach for quantitative analysis that is broadly applicable to CNT/CNF materials. Possible interferences are discussed in detail, (e.g., soot, diesel exhaust, carbon black) in the CIB and elsewhere, but these may be minimal in many workplaces. In NIOSH surveys, the problem has been low air concentrations, often nondetect (ND). For shorter term sampling, the mass due to background contamination is expected to be ND in many cases. Regarding interferences, cigarette smoke contains very little EC and is not expected to interfere unless there is gross contamination. It is within the employer's discretion to control smoking in the workplace. As discussed, initially, background measurements and microscopy will be required to establish whether there are interference issues. Subsequent	

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Cummings, Bayer Material Science (cont.)		monitoring requirements will be reduced if interferences are found to be negligible and workplace conditions are relatively unchanged. The US EPA has submitted a large number of samples for OC-EC analyses to its contract laboratories for many years. The number of samples submitted for CNT/CNF analysis is expected to be relatively low and should not significantly increase the sample load for existing laboratories (some will welcome the business). The thermal-optical analyzer is commercially available in at least 6 US laboratories (the number outside the US may be more limited). The larger issue may be laboratory expertise. Application of Method 5040 to CNT/CNF requires professional judgment, both in the sample collection and analysis steps. Some laboratories may not be proficient initially. To ensure data quality, it is important that analysts be proficient in the analysis (as specified for EPA methods) and seek expertise when needed. As more data become available, details relevant to this	

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Cummings, Bayer Material Science (cont.)		application (CNT/CNF) will be included as updates to NIOSH Method 5040 and/or in journal publications.	
	7) The suggestion by NIOSH to use other analytical techniques (e.g., TEM, SEM, etc.) when interferents are anticipated is understood, but not practical. In reality, this may be needed in all cases which would be cost prohibitive for most employers. Thus, other consideration should be given to proposed monitoring methods, for example, those that use a "metallic marker" which is present as a trace quantity impurity in CNTs. NIOSH has experience with such methods, where both iron and nickel tracers were used (Maynard, et. al., 2004). This method allowed for the discrimination between the metal containing CNTs and other airborne materials. Note: since metal concentrations can vary with each production batch it is highly recommended to submit a bulk sample with the filter analysis.	7) Initially, microscopy and other methods can establish whether EC monitoring alone is sufficient for monitoring worker exposure. A metal marker may be possible, but if samples are collected with available, respirable dust samplers, the collected mass will likely not be adequate for quantification because of the low metal mass fractions (typically $\leq 1\%$). Further, iron was not a useful indicator of exposure at a CNF manufacturing facility. The major iron source was fine/ultrafine aerosol generated as a production byproduct. As it was not CNF derived, there was no correlation between the iron and CNF concentrations. In cases where a metal is a selective exposure marker, the LOD for ICP/AES likely will not be adequate at low CNT/CNF concentrations (e.g., near the EC LOQ). If a catalyst metal is used as a	7) No revisions required.

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Cummings, Bayer Material Science (cont.)		surrogate measure of exposure, correlation with the CNF/CNT concentrations and adequate detection limits should be verified.	
	8) NIOSH is recommending that engineering controls be installed to control worker exposure to CNT/CNF. Engineering controls are widely recognized as the best means of controlling potential worker exposure. We agree with and support the use of engineering controls such as source enclosures, local exhaust ventilation, and handling of the material in a less air-dispersible form (e.g., as a paste, solution, etc.). Further, as NIOSH has recommended, the exhaust ventilation unit should be properly designed according to recognized principals such as those provided by the American Conference of Governmental Industrial Hygienists (ACGIH, 2010).	8) The commenter agrees with the hierarchy of risk management approaches recommended in the CIB.	8) No revisions required
	9) NIOSH is recommending that formal procedures (e.g., SOPs) be developed to include good work practices, proper	9) Commenter agrees with the hierarchy of risk management approaches recommended in the CIB.	9) No revisions required

Commenter	Summary of Comments Received	Response	Changes to CIB
Cummings, Bayer Material Science (cont.)	selection of PPE, worker training/education, hygienic practices, and clean-up/disposal practices. We agree with and support the recommendation of SOPs to address these considerations. Further, the practices described under 6.3.1 to reduce the potential for exposure during clean-up and disposal (e.g., HEPA-filtered vacuum cleaners, wet wiping techniques, etc.) are recognized "best practices" for these types of materials.		
	10) NIOSH is recommending the use of protective clothing and gloves when "all technical measures to eliminate or control release of exposure to CNT and CNF have not been successful or, in emergency situations." This is considered an industry "best practice" which we believe to be essential to the safe handling of nanomaterials. Further, NIOSH recognizes that the data is limited as to which material type (e.g., latex vs. nitrile vs. cotton) and product garment (e.g., suit vs. apron vs. lab coat) is appropriate in all cases. For example, while an impermeable Level A suit offers a high level of protection, it is the least comfortable to wear and has a low user/worker acceptance. Thus, a balance between protection and user	10) Commenter agrees with recommendations for the selection and use of protective clothing and gloves.	10) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Cummings, Bayer Material Science (cont.)	comfort/acceptance needs to be considered. These factors should be included when conducting a PPE hazard assessment, as required under the OSHA PPE standard, 29CFR 1910.132(d)(1). As part of the assessment CNT/CNF manufacturers and commercial PPE manufacturers should also be consulted to aid in the proper selection of PPE garments.		
	11) NIOSH is recommending the use of respiratory protection "when engineering controls and work practices cannot reduce worker CNT and CNF exposures to below the REL…" or, "…for certain work tasks that place workers at risk of potentially high peak concentrations of CNT and CNF…" We also support the use of applicable respiratory protection (1) when a recognized/representative OEL is/can be exceeded, (2) when CNT/CNF exposure levels are unknown, and (3) during potential high airborne (e.g., peak) concentrations. Of course, when respiratory protection is specified, it must meet the requirements specified in OSHA standard 29CFR 1910.134.	11) The commenter agrees with the decision logic for when respiratory protection should be used by workers.	11) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Cummings, Bayer Material Science (cont.)	12) NIOSH is recommending the implementation of a medical screening and surveillance program for CNT/CNF workers based on their potential for adverse respiratory health effects. This conclusion is based upon limited (and nonspecific) toxicology studies/data which has been extrapolated across a "family" of comparable nanomaterials to support a recommendation for medical surveillance. Primary prevention strategies are based, in significant part, on exposure mitigation via engineering and administrative controls, and the proper use of PPE. Certainly these five elements (i.e., exposure assessment, engineering controls, work practices, personal protective equipment, and respiratory protection) are recognized best practices for nanomaterials safe handling. While it is well understood that medical surveillance protocols are prevention-focused their effectiveness, in secondary prevention, is based upon well-defined and recognized health end point(s) (e.g., specific disease(s), target organs, etc.) which can then be medically monitored for early disease detection. For CNT/CNF's such health end point(s) are not generally recognized nor agreed upon at	12) Although the NIOSH guidance recommends an exam focusing on the respiratory system, an exam by a health care provider is likely to allow the opportunity for evaluation of other symptoms workers may have – judgment would be required by the health care provider concerning work-relatedness of all symptoms noted by the worker. Bayer notes that effective surveillance is based on the specificity of the health endpoint of concern and monitoring for that outcome. The NIOSH guidance recommends standard tools (medical tests) which are useful in assessing respiratory morbidity – the tests used in screening are well-established tests even if they may detect a number of different types of respiratory outcomes. In addition to the use of these standard tests, the NIOSH guidance places some responsibility on the employers' health care provider to use judgment concerning selection of other medical tests (as well as the frequency of the testing). Bayer notes above that there is not sufficient evidence to support the surveillance recommendations. We agree that the human data concerning health	12) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Cummings, Bayer Material Science (cont.)	the present time. Further, by focusing on respiratory effects, it is entirely possible that additional or unexpected health outcomes may be completely overlooked or not recognized, thus sharply limiting the goals of secondary prevention. Thus, the justification for establishing a specific respiratory medical surveillance program, at this time, appears to be preliminary and somewhat discriminatory in its focus. The prevention and detection of CNT/CNF occupational injury and illness is an area of research and understanding which is still in many ways in its infancy. The current recommendations do not appear to be based on sufficient evidence that support its proposed design nor enable more powerful scientific inquiry/study. It may be more fruitful to collect more definitive exposure information which can then be correlated with various health data sources to monitor health and exposure trends, view CNT/CNF worker cohort experience in relationship to explicit risk assessment information, such as a formal registry mechanism would afford. Sources of information include clinical evidence and case reports, diseases registries, epidemiological studies of occupationally exposed workers, national health data resources, etc. Thereafter,	effects is absent and that exposure to CNT/CNF are limited but the animal data are conclusive with regards to adverse respiratory effects (i.e., fibrosis). In this document NIOSH attempts to balance the need for direct evidence of health effects among workers that have occurred with a proactive precautionary program to prevent health effects from occurring. NIOSH feels the toxicological evidence (animal data concerning toxicity presented in the CIB) is such that the recommended screening and surveillance will be a useful tool for workplaces where occupational exposure to CNT/CNF is occurring. Bayer also suggests above methods to correlate exposure data with health effects. Conduct of medical screening over time will allow for just such data analyses to occur, because the necessary health information will be collected. The concept of a formal exposure registry is raised here also -- NIOSH agrees that a registry of exposed workers could be an important tool in improving our knowledge concerning exposures and potential health effects related to occupational exposures to CNT and CNF. Many issues need to	

Commenter	Summary of Comments Received	Response	Changes to CIB
Cummings, Bayer Material Science (cont.)	and with appropriate ongoing analysis and scientific inquiry, it may be possible to make more definitive recommendations concerning effective medical monitoring component(s) of a CNT/CNF medical surveillance program which would directly support disease monitoring and prevention.	addressed in order for this type of exposure registry to be feasible, including issues related to: 1) measurement of exposure and determinations of who is exposed; 2) characterization of the nanomaterial(s) for which the registry would apply (for example, CNT/CNF only); and 3) management of the registry including funding and ownership of data.	

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Materna, California Dept. of Public Health	The California Department of Public Health (CDPH) supports the perspective proposed by NIOSH in the draft Current Intelligence Bulletin, specifically, that until research studies better identify inhalation toxicity from CNT and CNF, "steps should be taken to minimize CNT and CNF exposures of all workers and to implement an occupational health surveillance program that includes elements of hazard and medical surveillance." We also agree with the NIOSH approach to use both medical screening and exposure registries to obtain additional information about health effects and exposures in worker populations. However, the draft Bulletin addresses hazard and medical surveillance only at the level of the employer and in this way misses the opportunity to adopt a public health approach to this potential emerging hazard. Public health surveillance is the ongoing systematic collection, analysis, and interpretation of health data for the purpose of improving safety and health, and dissemination and use of data is a key component.[17,18] We suggest that the aggregation and analysis of these data could		

[17] National Institute for Occupational Safety and Health (NIOSH). NIOSH Safety and Health Topic: Surveillance. Accessed at http://www.cdc.gov/niosh/topics/surveillance February 2011.
[18] Halperin W, Baker EL eds: *Public Health Surveillance*. New York: Van Nostrand Reinhold, 1992.

Commenter	Summary of Comments Received	Response	Changes to CIB
Materna, California Dept. of Public Health (cont.)	support public health follow-up actions at the state or national level. 1) Identification of *workplaces* where CNT and CNF are used is a critical first step in characterizing the potential hazards posed by these products. We suggest that NIOSH identify mechanisms to track workplaces where CNF and CNF materials are handled, and the types, quantities, and uses of these products, in order to identify potentially high-risk worksites or industries where prevention efforts should be directed. 2) The need to collect and aggregate the data from medical surveillance efforts, and to provide some kind of public health analysis/review in order to identify trends across workplaces, should be described and encouraged in the draft Bulletin.	1) NIOSH has several research efforts that focus on identifying workplaces where exposures to CNT and CNF occur. A number of these investigations have been reported in the literature and are cited in the CIB. 2) The NIOSH guidance states "Standardized medical screening data should be periodically aggregated and evaluated to identify patterns of worker health that may be linked to work activities and practices that require additional primary prevention efforts. This analysis should be performed by a qualified health professional or other knowledgeable person to identify patterns of worker health that may be linked to work activities or exposures. Confidentiality of	1) No revisions required. 2) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Materna, California Dept. of Public Health (cont.)		worker's medical records should be enforced in accordance with all applicable regulations and guidelines." The guidance does not take the further step of recommending analysis of trends across workplaces because the mechanism to do that is not clear at this time. NIOSH supports further consideration of exposure registries, the development of which may lead to analysis of medical screening data across workplaces.	
	3) The draft Bulletin contains no recommendations in the event that abnormalities are discovered in the process of medical surveillance. We suggest that NIOSH identify reportable conditions (e.g., chronic lung disease), that medical providers and employers should be encouraged to report to appropriate public health authorities if they identify them in individuals who work with nanomaterials. In addition, the draft Bulletin should remind medical providers to follow state-specific laws related to mandatory reporting of suspected occupational injuries and illnesses.	3) The section on written report of medical findings provides guidance for the health care professional to provide opinions and recommendations to the worker. At this time there is insufficient information to recommend reportable conditions related to CNT/CNF exposure. A reminder to medical providers concerning state specific laws for reporting occupational health effects would likely be of greater impact in a document with a broader audience.	3) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Materna, California Dept. of Public Health (cont.)	4) The utility and importance of establishing exposure registries for workers exposed to nanomaterials has been described previously.[19,20] The recommendations for exposure registries in the draft Bulletin should be expanded to include detailed recommendations for how exposure registries could be established, a list of reportable exposures (or exposure levels) that should be reported to public health authorities, and encouragement for employers to participate.	4) NIOSH agrees that a registry of exposed workers could be an important tool in improving our knowledge concerning exposures and potential health effects related to occupational exposures to CNT and CNF. Many issues need to be addressed in order for this type of exposure registry to be feasible, including issues related to: 1) measurement of exposure and determinations of who is exposed; 2) characterization of the nanomaterial(s) for which the registry would apply (for example, CNT/CNF only); and 3) management of the registry including funding and ownership of data.	4) NIOSH has identified the need for research to determine the feasibility of establishing exposure registries. NIOSH is currently evaluating the workforce exposed to CNT and CNF to determine whether an exposed group of workers can be identified for an epidemiologic study and inclusion in a registry. Section 7 *Research Needs* identifies the need for such studies.

[19] Trout DB, Schulte PA. Medical surveillance, exposure registries, and epidemiologic research for workers exposed to nanomaterials. *Toxicology*. 2010;269:128-135.
[20] Schulte PA, Trout D, Zumwalde RD, Kuempel E, Geraci CL, Castranova V, et al. Options for occupational health surveillance of workers potentially exposed to engineered nanoparticles: State of the science. *J Occup Environ Med*. 2008;50(5):517-526.

Commenter	Summary of Comments Received	Response	Changes to CIB
Kosnett, Univ. of Colorado School of Medicine	In identifying chronic noncancer respiratory effects as a potential hazard associated with the inhalation of engineered carbon nanotubes and carbon nanofibers, the draft CIB has presented a reasonable summary of the scientific literature. While acknowledging the absence of human epidemiological studies pertaining to respiratory endpoints, the CIB summarizes the results of rodent studies of acute to subchronic duration that persuasively document at least two important findings: a) carbon nanomaterials have the potential to induce pulmonary inflammation and fibrosis, and b) they have yielded these effects with a potency equal to and often greater than that of other inhaled particles known to be hazardous (ultrafine carbon black, crystalline silica, and asbestos). While there is some indication that the inflammatory and fibrotic effects induced by short term or subchronic exposure may be persistent, there are no chronic bioassays currently available, and the overall database on that feature is sparse. In Appendix A of the CIB, a complex multi-step analysis is presented to estimate that the human working-lifetime airborne concentration of multi-walled carbon nanotubes associated with a pulmonary benchmark response (ED10) in two subchronic		

Commenter	Summary of Comments Received	Response	Changes to CIB
Kosnett, Univ. of Colorado School of Medicine (cont.)	rat inhalation studies is less than 7 $\mu g/m^3$, the limit of quantification (LOQ) for the measurement method for elemental carbon as an 8 hour TWA (NIOSH method 5040). Therefore, this LOQ for elemental carbon has been proposed at the recommended exposure limit for carbon nanotubes and carbon nanofibers. Although there is acknowledged uncertainty regarding the optimal exposure metric that should be utilized to characterize the risk posed by engineered carbon nanomaterials, NIOSH has understandably focused on a mass-based approach in the draft CIB, because that was nature of the exposure data in the key animal studies. 1) The document appropriately acknowledges that the database used to derive the REL is limited, and that the recommendations in the draft CIB should be subject to re-evaluation 1) The document appropriately acknowledges that the database used to derive the REL is limited, and that the recommendations in the draft CIB should be subject to re-evaluation as additional research become available. Nevertheless, the draft CIB would benefit from a more detailed discussion of the sources and potential magnitude of the uncertainty associated with the REL. A complex multi-	1) Agree that additional analyses and discussion would be helpful to better characterize the variability and uncertainty in these analyses. The new sensitivity analyses in Section A.6 provides additional results to qualitatively and quantitatively describe the uncertainty associated with the REL, including in each of the areas suggested in this comment.	1) A new Section A.6 has been added to provide detailed sensitivity analyses on the influence of the various methods and assumptions used in the risk assessment. The major and minor factors influencing the OEL estimation have been described (Sections A.6 and 5.3).

Commenter	Summary of Comments Received	Response	Changes to CIB
Kosnett, Univ. of Colorado School of Medicine (cont.)	step process has been used to derive the REL, including a) estimation of lung dose from airborne concentration; b) benchmark response (ED10) modeling based on studies with steep dose response curves that contained few (if any) exposures in the low response region, c) interspecies extrapolation, and d) time extrapolation (acute or subchronic to chronic). As such, inclusion of a sensitivity analysis that discusses which step(s) constitute the greatest source of uncertainty would be advisable. In like manner, it would be helpful if NIOSH qualitatively characterized its level of confidence in the REL, perhaps in a manner akin to how EPA characterizes its level of confidence in reference doses or reference concentrations published in IRIS.		
	2) Two particular points are illustrative of issues that would benefit from further discussion of uncertainty. One point concerns the benchmark dose modeling. On page 98, the narrative states, "Comparison of the BMD(L) estimates to the LOAELs or NOAELs provides a check on the estimated and observed responses in the low dose region of the data". In Table	2) The example in this comment is incorrect because it is comparing the animal LOAEL or NOAEL with the human BMD(L) estimates. The correct comparisons (based on the subchronic inhalation studies) are shown in Table A-12. This shows similar effect level estimates – for example, the NOAEL and BMDL	2) Table A-12 added to CIB and provides comparison of the NOAEL, LOAEL, BMD, and BMDL estimates from the subchronic studies in rats. Section A.6.3 provides a comparison of the other assumptions in extrapolating the animal effect levels to

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Kosnett, Univ. of Colorado School of Medicine (cont.)	A-5, the derived BMDL (ED10) for working lifetime exposure to humans range from 0.19 to 1.9 micrograms per cubic meter, values that are two to three orders of magnitude lower than the LOAEL air concentrations reported in the respective subchronic animal studies.	estimates are within a factor of two for grade 1 or higher alveolar septal thickening, and identical for grade 2 or higher (Pauluhn [2010a] study); the NOAEL and BMDL estimates are also similar in the Ma-Hock et al. study (for grade 2 or higher granulomatous inflammation, as no NOAEL was identified for grade 1).	humans over a working lifetime.
	3) What significance should be attached to this comparison? Another point concerns the potential influence of dose rate on the pathological response of the lung in rats and humans. As stated on page 108, the risk assessment approach utilized in the draft CIB assumes "humans and animals would have equal response to an equivalent dose (i.e., mass of CNT per unit surface area of lungs)". However, in the subchronic animal studies, this surface-area adjusted dose was delivered to the alveoli of rats over a 13 week period, whereas in the human extrapolation models, the same surface-area adjusted dose is delivered to human alveoli over a period of 45 years, a 180-fold factor lower dose rate. The draft CIB would benefit from a discussion of what is known about	3) The significance of this comparison is that the BMD(L) estimates appear to be reasonable compared to the NOAEL/LOAEL estimates reported in the studies, and that the effect level selection (NOAEL or BMDL) does not have a large influence on the REL derivation (although these effect levels are interpreted differently, as the BMD(L) estimates are risk-based while the NOAEL/LOAEL estimates are not risk-based). The assumption that the subchronic response is relevant to predicting chronic response to the same dose at a lower dose rate is an important area of uncertainty in this (and any other) risk assessment using subchronic	3) The significance of the effect level estimation has been clarified (i.e., has little influence) in Sections 5.3 and A.6.2. Comparison of the BMD(L) and NOAEL/LOAEL estimates is provided in Table A-12. Section A.6 also provides a quantitative evaluation of the influence of effect level (and other assumptions) on the risk estimates and REL derivation.

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Kosnett, Univ. of Colorado School of Medicine (cont.)	the influence of dose rate on inflammatory or fibrotic responses of alveolar units to particles or fibers of low solubility. What examples exist in the literature that compares results of subchronic rodent exposure to particles or fibers of low solubility to epidemiological studies of pulmonary outcome after chronic human workplace exposure? It should be noted that the foregoing suggestions regarding greater discussion of uncertainty and level of confidence in the proposed REL do not equate to a judgment that the REL itself will require revision, or that it does not represent a prudent, interim approach to the protection of the workforce pending the accumulation of additional research data.	data, which indicates the need for chronic animal bioassay data. Some information suggesting that this assumption is reasonable (discussed in Section 5 and Append A) is that the CNT is slowly cleared in the rat above a relatively low mass lung dose and that the fibrotic lung responses are persistent or progressive after the end of exposure.	
	4) With respect to occupational health management of the workforce, it is suggested that the draft CIB emphasize investment in exposure control measures, exposure assessment efforts, and exposure registries. Because of present uncertainties regarding the utility, predictive value, sensitivity, and specificity of structured medical surveillance (i.e. physical	4) The CIB emphasizes the importance of engineering controls including the use of containment when handling unbound CNT and CNF. NIOSH acknowledges that some residual risk for fibrosis exists at the REL and that efforts should be made to reduce exposures as low as possible below the REL. The recommendations for medical screening	4) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Kosnett, Univ. of Colorado School of Medicine (cont.)	examinations, laboratory tests, and questionnaires) for the nanomaterial workforce, these elements should be encouraged only in the framework of occupational health research.	are warranted given the toxicological evidence of adverse respiratory effects (i.e., fibrosis) observed in animals exposed to CNT and CNF. Medical screening of exposed workers will provide a means to ascertain the health status of workers over time given the residual risk that remains at the REL.	

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Warheit, DuPont Haskell Global Centers	The document represents a good effort and reasonable summary by NIOSH regarding the CNT hazard and exposure literature. The suggested sections/issues that should be reconsidered in a finalized document are detailed below and include the following general comments: ■ Lack of clarity on recommended exposure methodology for monitoring workplace exposures- as evidenced by the inability to reconcile techniques used by other investigators with NIOSH's recommendations to use the 5040 method; and whether the method has relevant applicability and sensitivity to workplace exposure scenarios where there are low CNT or CNF concentrations, e.g., laboratories. ■ A more incisive discussion on the limitations of currently available techniques, and the need to develop better methods for ascertaining the physicochemical characteristics of single walled carbon nanotubes, multiwalled carbon nanotubes, and carbon nanofibers. ■ A reconsideration of the BMD/Risk Assessment Methodology. ■ A reconsideration of NIOSH's decision to include carbon nanofibers in a class with the same hazard potential as SWCNT and		

Commenter	Summary of Comments Received	Response	Changes to CIB
Warheit, DuPont Haskell Global Centers (cont.)	MWCNT – given the paucity of relevant hazard data. Responses to Specific Questions: **A. Is the hazard identification and discussion of health effects for CNT and CNF a full and reasonable reflection of animal studies and other scientific and other scientific evidence in the scientific literature?** The section entitled "Evidence for Potential Adverse Health Effects: - detailed on pages 27-37 represents a reasonable summary of the current toxicology literature on SWCNT and MWCNT studies – with the following exceptions: 1) The Tables located on pages 62-69 were initially difficult to locate and their locations should have been better identified within the text.	1) Agree.	1) Section was reorganized to improve readability.

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Warheit, Dupont Haskell Global Centers (cont.)	2) There is insufficient detailed information on the physicochemical characteristics of the SWCNT or MWCNT test samples described either in the text or provided in the Tables for the various studies outlined in the literature review section. The authors should revise their summary to include these important data.	2) The aim of the toxicology section (Section 3) was to present an overview of the literature on pulmonary effects of SWCNT and MWCNT. Important physical and chemical characteristics of CNT used in the animal studies was described and used as appropriate in the risk analysis [Section 5 and Appendix A].	2) No revisions required
	3) A more incisive, integrated, coherent synthesis/analysis summary section is absent at the end of each of the SWCNT (page 32) and MWCNT (page 37) sections. What is missing are analyses of the studies in the aggregate concomitant with NIOSH's view and discussion of the relevant take-home messages/key learning from these studies, Among other issues, it is recommended that this discussion include the following topics: 1) influence of physicochemical characteristics on documented pulmonary effects (e.g., potential effects of catalysts, fictionalization, surface area, CNT dimensions, agglomeration/aggregation effects); 2) the significance and relevance	3) A) Data thus far suggest the metal contamination does not greatly affect pulmonary response (Lam et al, 2004; Shvedova et al, 2005, 2008). B) Functionalization with COOH decreases the bioactivity of MWCNT (Sager et al, 2011) C) Long MWCNT are more potent after intraperitoneal or intrapleural inject than short MWCNT (Poland et al, 2008; Murphy et al, 2011). D) Mercer et al, 2008 showed the well dispersed SWCNT were 4 X more fibrogenic than poorly dispersed SWCNT. E) Mercer et al showed that SWCNT are more fibrogenic on a mass basis than MWCNT.	3) No revisions required

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Warheit, DuPont Haskell Global Centers (cont.)	of intraperitoneal injection study results; 3) the potential significance of inhaled CNT particulate translocation from airspace to supleural regions; 4) the relevance of various routes of pulmonary administration, i.e., inhalation exposures vs. intratracheal instillation/pharyngeal aspiration administration – as they relate to the results of the toxicity studies.	However, considering that risk still exists at the proposed REL due to level of detection, these potency differences would not significantly affect the REL. Discussion of IP injection studies, translocation to the pleura, and the relevance of IT and aspiration to inhalation is beyond the scope of the document.	
	4) In the Executive Summary on page 4 – the CIB documents that "SWCNT can cause genotoxicity and abnormal chromosome number due to interference with mitosis (cell division" – Sargent *et al.*, 2009). Additional clarification is needed to inform the reader that positive *in vitro* genotoxicity studies with nanomaterials are not uncommon, but require validation using *in vivo* assays (see Landsiedel et al., 2009; Warheit and Donner, 2010 references).	4) Agree. Long term (1 year post inhalation) studies with MWCNT are being conducted by NIOSH. Data won't be available for a year.	4) Since the genotoxic data were not part of the risk assessment, no revisions required.
	5) The hazard database for carbon nanofibers is severely limited – i.e., a single nasopharyngeal aspiration-based lung toxicity study in mice (Kisin et al., 2010). As a consequence, the paucity of CNF toxicity data does not warrant NIOSH's	5) The 2010 draft CIB cited the CNF toxicity study conducted by Kisin et al. in which the results of the study were submitted for publication. The final published manuscript entitled *Factoring in agglomeration of*	5) The REL is based on an assessment of risk for CNT. The similarities in respiratory health outcomes observed in mice exposed to CNF [Murray et al. 2012] warrants

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Warheit, DuPont Haskell Global Centers (cont.)	conclusion that CNF have the same hazard profile as CNT. Therefore, it is premature and inappropriate to set a REL for CNFs at the same exposure levels as recommended for SWCNT and MWCNT. **B. Is the risk assessment and dosimetric modeling methods used in this document appropriate and relevant?** 1) NIOSH estimates of the lung burden based on alveolar deposition are questionable and the calculations are not clearly justified.	*carbon nanotubes and nanofibers for better prediction of their toxicity versus asbestos* was authored by Murray et al. and published in Part Fibre Toxicol 9:10, 2012. The DeLorme et al. [2012] 90-day inhalation study with rats exposed to CNF was also added. 1) The commenter does not provide any basis for this statement. Actually, the Nov 2010 draft CIB explains the rationale for providing estimates for either the deposited or the retained lung burden (Appendix A; Section 5). These estimates are supported by animal data showing greater retention of CNT at lung doses greater than a relatively low mass burden. The use of the deposited and retained lung dose estimates from spherical particle models is supported by the lung deposition models which have been developed based on the deposition efficiency in the respiratory tract predicted by the airborne particle size distribution data (e.g., MMAD and GSD) [ICRP	the application of the REL for controlling occupational exposure to CNF. 1) An analysis was added to compare the cobalt tracer-based estimates of MWCNT in rat lungs to those estimated from the MPPD rat models (Section A.1.6.2).

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Warheit, DuPont Haskell Global Centers (cont.)		1994; CIIT and RIVM 2007; ARA 2011]. Moreover, rat lung burden estimates from on the cobalt-tracer based measurement [Pauluhn 2010a] were generally between the deposited and retained dose estimates in MPPD 2.0 (Section A.6.1.2).	
	2) The BMD estimates and corresponding risk assessment data calculations should be predicated on the results of the two 90-day inhalation studies and not based on the studies utilizing nonphysiological routes of exposure (i.e., intratracheal instillation or pharyngeal aspiration administration).	2) NIOSH has provided BMD and risk estimates using the dose-response data in the subchronic (91-d) inhalation studies of two types of MWCNT, and for various types of SWCNT or MWCNT based on short-term inhalation, intratracheal instillation, or pharyngeal aspiration. These BMD(L) estimates are similar (Tables A-3 through A-5. In addition, Shvedova et al. [2008] showed that the lung responses were qualitatively similar in rats exposed to SWCNT by either pharyngeal aspiration or inhalation. The fibrotic and lung response was actually greater for the inhaled SWCNT compared to an estimated equivalent SWCNT lung dose by pharyngeal aspirated [Shvedova et al. 2008] –	2) The document was checked for opportunities to clarify or better communicate this information which is already in the CIB (especially in Appendix A and Section 5).

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Warheit, DuPont Haskell Global Centers (cont.)		which does not suggest a bolus effect for a single dose (vs. the same dose delivered at a lower and more physiological dose rate). It may be that there was greater agglomeration in the aspirated dose, as more dispersed CNT structures were associated with greater fibrotic response [Mercer et al. 2011].	
	3) The calculations formulated in this CIB should not be based upon BMD estimates and BMD models but rather should be conducted using pulmonary toxicity effect levels, such as sustained lung inflammation endpoints.	3) A comparison of the BMD(L) and LOAEL/NOAEL effect levels showed these estimates were similar and had little influence on the working lifetime REL derivation (Section A.6.3 and 5.3).	3) As part of the sensitivity analyses of the methods and assumptions used to derive the REL, the NOAEL and LOAEL effect levels reported in the subchronic inhalation studies [Ma-Hock et al. 2009; Pauluhn 2010a] were used as alternative effect level estimates to derive human-equivalent working lifetime exposure estimates and evaluate the effect of various assumptions in extrapolating the animal dose to humans (Section A.6.3).

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Warheit, DuPont Haskell Global Centers (cont.)	**C. Are the sampling and analytical methods adequate to measure worker exposure to carbon nanotubes and nanofibers?**		
	1) One can appreciate the difficulties in measuring exposures to CNT and CNF in the diverse workplace. However, the proposed NIOSH method of measuring elemental carbon (NIOSH Method 5040) leaves much to be desired and should be reconsidered as a methodology for the general public. The method was initially developed as a diesel particulate mining procedure. The method is designed to measure Elemental Carbon, but does not appear to be sufficiently sensitive to delineate background carbon or organic carbon contributions from an accurate measurement of CNTs in the workplace; or measure effectively exposures scenarios of low CNT or CNF concentrations. In addition, the methodology appears to be qualitative and rather nonspecific, and would likely produce an overestimation of CNT/CNF exposures. The results would be an indication of total carbon exposure,	1) See previous response regarding availability of laboratories. Elemental carbon is the analyte, not total carbon. The method provides a quantitative measure of particulate carbon, speciated as OC and EC.	1) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Warheit, DuPont Haskell Global Centers (cont.)	ignoring the physiochemical properties that better correlate with the toxicity of several of the individual CNT/CNF materials. This methodology appears to have several in-field sampling and downstream sample analysis limitations and clearly has not been validated in any manner to provide confidence in the accuracy of any obtained results. Moreover, in addition to the limitations in accuracy, there appear to be very few laboratories available in the US that can conduct accurate analyses of the submitted quartz filters (NIOSH 5040 App. C). Beyond the availability of analytical laboratories, the significant expense and timing for producing verifiable analyses for one or more samples at various sampling time periods would likely be impractical. 2) Another major troubling issue involves lack of consideration of the appropriate dose metrics for measuring CNT/CNF exposures, In this regard, there appears to be a disconnect between NIOSH recommendations for the LOQ 5040 methodology and the majority of publications cited in the Exposure Assessment literature review of the CIB document (i.e., pages 19 – 25). For	2) None of the direct-reading methods listed are selective, quantitative, nor suitable for exposure monitoring. A similar approach was used by NIOSH, but aerosol instruments such as a CPC were indicators of byproduct emissions (Evans et al. 2010; Birch et al. 2011, Birch 2011). NIOSH researchers continue to apply multiple methods for workplace assessments, including direct-	2) No revisions required.

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Warheit, DuPont Haskell Global Centers (cont.)	example, in the studies conducted by Han *et al.*, and Lee *et al.*, the investigators measured a variety of exposure endpoints in MWCNT workplaces, including particle number, composition, aspect ratio and gravimetric concentrations, using both personal and area monitoring strategies. Some of the equipment utilized in these studies included the following devices: SMPS, long and short DMAs, CPCs, gravimetric analyses/dust monitors, portable aethalometers, SEM and TEM EDAX methodologies. In the NIOSH study reported by Methner *et al.* on characterization of worker exposure to carbon nanofibers during polymer composite laboratory operations, NIOSH utilized a variety of methodologies to assess workplace exposures (general area exposure concentrations – but not representative breathing zone concentrations). The methodologies used in those studies included 1) filter-based samples (NIOSH 5040- "NIOSH 5040 was evaluated for diesel particulate matter (DPM) but is has application to other carbonaceous materials"); 2) SKC Button Aerosol Sampler; 3) Real time instrumentation – CPC; an aerosol photometer; a diffusion charger; and an electrical low	reading and filter-based methods. Microscopy is confirmatory, but not quantitative. A method to quantify CNT/CNF concentrations by microscopy is under investigation. Most workplace studies where there was a potential for exposure to CNT and CNF a variety of different instruments were used to measure the airborne release of nanoparticles including CNT/CNF. The instruments used to measure exposure were non-specific for CNT/CNF but provided general information (e.g., particle count concentrations) that could be used for assessing the adequacy of exposure control measures. NIOSH is recommending the collection of respirable mass samples using Method 5040 (elemental carbon) for quantifying worker exposures to CNT/CNF. A respirable mass concentration (elemental carbon) of CNT and CNF was selected as the exposure metric since this was the metric used in evaluating the dose-response relationship for adverse respiratory effects in CNT exposed animals. NIOSH acknowledges that other exposure metrics (e.g.,	

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Warheit, DuPont Haskell Global Centers (cont.)	pressure impactor; 4) transmission electron microscopy; 5) ventilation assessment – the ventilation system was evaluated using "smoke tubes".	concentration of CNT/CNF by dimension) may eventually be more appropriate pending the results from ongoing animal research.	
	3) Accordingly, the recommendations made by NIOSH in the Executive Summary of the CIB to use solely the NIOSH 5040 Method for measuring CNTs in the workplace appears to be confusing, inadequate and imprecise. Aerosol technology instrumentation is expensive and the more NIOSH can do to establish a methodology, with a high confidence level of relevancy, the better for organizations to manage the economics of the exposure control strategy.	3) We agree that an inexpensive, simplified monitoring approach is needed, but all methods have limitations. NIOSH applied a variety of methods in its initial and subsequent surveys, but the direct-reading instruments employed were useful as relative indicators of emissions and air quality, not CNT/CNF monitoring (Evans et al. 2010, Birch et al. 2011). NIOSH is not recommending EC as a single analyte, rather its use as a quantitative exposure marker. NIOSH acknowledges method (5040) limitations, and these are clearly stated in the CIB, and welcomes input on alternative methods. NIOSH scientists continue to investigate methods to improve exposure assessment and will update findings as new information becomes available. Meanwhile, NIOSH is	3) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Warheit, DuPont Haskell Global Centers (cont.)		disseminating important information regarding the potential dangers of CNT/CNF.	
	4) The exposure assessment section of the CIB would be substantially improved by inclusion by the authors of a critical analysis (strengths and weaknesses) of 1) all of the studies noted in the literature review section of the document; and 2) an evaluation of the current best practices for measuring worker exposures to CNTs and immediate areas for development of integrated exposure assessment techniques that can be validated. **Included in this discussion on exposure assessment methodologies, NIOSH should address some of the following questions:**	4) As discussed, NIOSH researchers have applied multiple methods to characterize exposures to CNT/CNF. Regarding exposure assessment, the weaknesses of direct-reading methods are the many potential interferences and their qualitative nature.	4) No revisions required.
	1) What are the best dose metrics to utilize in measuring CNT/CNF exposures?	1) See previous response. There is still no consensus on this issue, but NIOSH will continue to monitor mass concentrations as well as other exposure metrics. The respirable mass of CNT and CNF were chosen as the best dose metric for evaluating	1) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Warheit, DuPont Haskell Global Centers (cont.)		the risk of pulmonary fibrosis. The respirable mass concentration of CNT was the dose metric used in animal studies and was the metric used in the risk assessment analysis.	
	2) Can aerosolized CNT particle numbers in the workplace be accurately measured or even in aerosol generation/inhalation toxicology studies from which valuable hazard data is obtained for formulating risk estimates?	2) CNT/CNF aerosol mass concentrations can be accurately measured in inhalation toxicology studies. It is not yet known if particle number concentrations can be accurately quantified. This is currently under investigation.	2) No revisions required.
	3) Can CNT/CNF dimensions such as length and diameter distributions be accurately measured in the occupational setting or in inhalation toxicity studies?	3) Asbestos measurements (length and diameter) have not been reproducible between laboratories. NIOSH is investigating a method to count CNT 'structures', but NIOSH scientists anticipate the same problems. The measurement of CNT/CNF dimensions might be accomplished using electron microscopy techniques; however, to obtain meaningful results there will need to be established a set of criteria on how to size tubes that are agglomerated, found in bundles or	3) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Warheit, DuPont Haskell Global Centers (cont.)		tangled. Ideally, the criteria should incorporate dimensional specifications (length, diameter, aspect ratio) that are closely linked to the toxicological data. Unfortunately, information on the relationship between CNT size and adverse effects in the lung are missing.	
	4) Can CNT/CNF surface area measurements be accurately measured in the occupational setting or in inhalation toxicity studies?	4) The specific surface area (SSA) for bulk materials can be accurately measured, but the instrumentation is not field portable. Field portable, direct-reading instruments for 'active' surface area (ASA) are available, but they generally do not agree with SSA results and have other limitations. Further, SSA measurement is a problem in the field due to lack of specificity. Ultrafine particles (high surface area) are ubiquitous and interfere with field measurement. The surface area of CNT/CNF can probably be determined in a controlled environment such as in animal studies where discrete amounts of CNT or CNF are administered. In most animal studies some specification data on size exists	4) No revisions required

Commenter	Summary of Comments Received	Response	Changes to CIB
Warheit, DuPont Haskell Global Centers (cont.)		which can be used to calculate surface area if instrument surface-area measurement data can't be obtained during the generation of exposures for inhalation studies. Work place surface area exposure measurements for CNT/CNF pose a greater problem due to the lack of instrument specificity for distinguishing CNT/CNF from other airborne contaminants	
	5) What is the role of CNT/CNF-based metal catalysts and how do they factor into the measurement schemes?	5) See previous discussion on catalysts.	5) No revisions required.
	6) Are the same recommended exposure assessment methods (NIOSH 5040) to be used for SWCNT, MWCNT, CNF? – what are the advantages or limitations for each – Is the nonspecific methodology recommended by NIOSH – suitable for each Carbon Nano-type structure, or surface-coated CNT or CNF?	6) Yes, our research indicates that a wide variety of materials can be analyzed (Birch, in preparation). As part of the analytical protocol, a bulk sample of the material should be analyzed to determine whether a given material may pose an analysis problem. For example, Mitsui 7 MWCNT is more refractory than most materials and requires a longer heating period and higher final temperature (in He/O_2) to oxidize. In contrast, some materials may be	6) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Warheit, DuPont Haskell Global Centers (cont.)		partially evolved during the maximum temperature in helium. Analysis of a bulk sample will guide the analyst in adjusting the analysis conditions accordingly (see CIB for details). Also, in some cases, a manual OC-EC split may be required. NIOSH (Dr. Birch) is collaborating with Sunset Laboratory and a contract laboratory to provide technical expertise and conduct inter-laboratory comparisons.	
	7) Could surface area metric analyses provide a distinguishing feature between the accurate measurements of SWCNTs, MWCNT, CNF and "background elemental carbon"?	7) Unlikely. Field instruments measure "active" surface area, which differs from specific surface area based on gas adsorption (i.e., classic BET analysis), depending on particle size. Further, they lack selectivity, are more responsive to ultrafine aerosols, and their response is particle-size dependent. Studies by NIOSH researchers did not find these instruments to be useful indicators of CNT/CNF. (Evans et al. 2010)	7) No revisions required.

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Warheit, DuPont Haskell Global Centers (cont.)	8) How does particulate agglomeration/aggregation behavior impact the measurement of CNTs in the workplace and for inhalation toxicity studies for which the crucial hazard data is obtained?	8) The particle size and structure affect its aerodynamic properties, and therefore air sampling. Agglomeration increases particle size. Depending on the size distribution, the air concentration measured using air samplers that collect different particle size fractions can differ significantly. This was the case for CNFs (Birch *et al.*, 2011). NIOSH has recommended collection of a respirable dust fraction based on the animal toxicological evidence in which effects were observed in the small airways. Based on published workplace CNT exposure data, most agglomerations of CNT appear to be respirable in size. If all of the particles (e.g., CNT, CNF) are respirable, a total or 'inhalable' dust sampler may give comparable results.	8) No revisions required.
	9) In summary, the NIOSH CIB needs to provide a significantly improved summary and candid analysis of the current methodology status on the accuracy of CNT and CNF measurements in the	9) NIOSH investigators conducted extensive air monitoring at a facility that manufactures and processes CNF [Evans et al. 2010; Birch et al. 2011; Birch 2011]. Personal	9) Section 6 of the CIB has been revised to provide more guidance on the sampling and analysis of CNT and CNF.

Commenter	Summary of Comments Received	Response	Changes to CIB
Warheit, DuPont Haskell Global Centers (cont.)	workplace, which are diverse. NIOSH also needs to critically evaluate the current strengths and limitations associated with their recommended 5040 – elemental carbon procedure (e.g., technological, dosemetric, background, availability of analysis (only 3 Labs in the country can process these samples?), expense, etc. By virtue of the recommendation of a suggested REL of 7 $\mu g/m^3$ – NIOSH provides a greater incentive and generates a sense of urgency for developing an accurate and reproducible method that can be validated by multiple independent investigators and should require a round-robin experimental approach for verification purposes. The current recommended technique of NIOSH 5040 procedures appears only to be a temporary "placeholder" while awaiting development of methodologies with greater precision and efficacy.	breathing zone and area samples were collected. Total, thoracic, and respirable dust samples were included. The relative percent difference (RPD) and RSD (%) for repeat analyses of samples collected in different areas of the facility are reported in the CIB (Table 1 of Appendix C). In three areas, samples were collected with paired samplers. The RPD was determined by analyzing either two punches from the same filter (duplicates) or one punch from two different filters (paired samplers). The RSD was determined by analyzing one filter in triplicate. The precision for the EC results ranged from about 3% to 14% except for one paired respirable sample, where the RPD was about 22%. Spatial variation is a likely explanation for the higher variability as the other two paired-sampler sets did not have higher variability. The RPDs for these two are about 8% and 13%, comparable to results for multiple punches from the same filter. In addition to the CNF survey, NIOSH	

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Warheit, DuPont Haskell Global Centers (cont.)		researchers have applied NIOSH 5040 to multiple surveys on CNT/CNF over the last year. A paper (Dahm et al.) summarizing these findings has been published in the Annals of Occupational Hygiene (09/23/11). Inter-laboratory comparison and other quality assurance data are being collected. Whether or not NIOSH 5040 is a "temporary placeholder" depends on the availability of alternative methods. NIOSH will continue to examine other methods, but all have limitations (e.g., poor selectivity, precision and accuracy; lack of calibration standards). NIOSH researchers have employed TEM to confirm airborne CNT/CNF since the first survey conducted and are currently investigating its potential for quantitative assessments. However, given the poor inter-laboratory agreement that has been found for asbestos counts, developing a quantitative TEM-based method will be challenging. While TEM has the advantage of being confirmatory, precision and accuracy have been a problem for measuring asbestos. Reproducibility for CNT/CNF is expected to be worse, given the variety	

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Warheit, DuPont Haskell Global Centers (cont.)		of complex particle structures. A draft ASTM method was reviewed by NIOSH scientists in 2011; however, several procedural issues remain including criteria for categorizing and counting the many complex structures found in workplaces that produce/use CNT/CNF. Further, even if the different types of structures are sorted and counted adequately, there currently is no basis (e.g., aspect ratio for asbestos fibers) for weighting their potential toxicity. NIOSH 5040 has been used for OC-EC measurement in occupational and environmental settings for many years. Numerous inter-laboratory comparisons on EC methods (5040 and others) have been conducted over the years. The method was evaluated using multiple types of particulate carbon (e.g., ground coals of different ranks, diesel particulate matter, urban dust, CNTs, buckyballs, carbon blacks, etc.) and organic compounds. NIOSH researchers are collecting quality assurance data for CNT/CNF measurements. Analysis of a CNT/CNF material itself is not a challenging measurement—even different methods show good agreement	

Commenter	Summary of Comments Received	Response	Changes to CIB
Warheit, DuPont Haskell Global Centers (cont.)		for this type of sample (i.e., EC with no pyrolyzable OC). The challenge for OC-EC methods has been complex carbonaceous aerosols that contain pyrolyzable materials that carbonize. Even with these types of samples, TC determined by different methods has shown good agreement; rather it is the "split" between OC and EC that has been variable. Though OC-EC methods are "operational", NIOSH 5040 is well documented, reproducible, and accurate in the analysis of TC. It also has been demonstrated to be more accurate than other methods in determining EC content of complex samples. NIOSH researchers continue to evaluate air samplers for CNT/CNF, but this relates to the desire for a high-flow respirable sampler, not the analysis itself. EPA has applied thermal-optical analysis for its NAAQS (national ambient air quality standards) and STN air monitoring networks for years. It is unlikely that the number of CNT/CNF samples will add much to the current sample load for the existing laboratories.	

Commenter	Summary of Comments Received	Response	Changes to CIB
Warheit, DuPont Haskell Global Centers (cont.)		We anticipate a learning curve for some laboratories. Laboratories with little or no experience with the analysis will need to come up to speed if used. This is a common issue. There are quite a few instruments at US universities that can perform the analysis, but the existing commercial labs should be sufficient. Outside the US, there are instruments at multiple Institutes and universities (e.g., in Spain, Sweden, Italy, Belgium, Australia, Hong Kong, and China), though the number of commercial labs may be more limited.	
	10) The proposed methodology recommended by NIOSH still raises many fundamental questions. How to deal systematically with background elemental carbon interference – based upon time of day, incidents outside the measurement area – e.g., diesel trucks outside, mechanized devices inside the occupational setting, worker (normal human contributions) density within a given sample area? How to delineate between "elemental carbon" vs. true CNT-based exposures? How to better describe/characterize the CNT or CNF-material characteristics to which workers	10) See previous responses on EC background and other complementary monitoring metrics.	10) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Warheit, DuPont Haskell Global Centers (cont.)	are exposed (e.g., surface area, CNT – particle dimension distributions such as length/diameters, particle numbers)?		

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Pauluhn, Bayer Healthcare Pharmaceutical	The CIB is a comprehensive and state-of-the-art review of the current literature. The interpretation of data is sound taking into account that the focus of the CIB is to derive a "PAN-CNT REL". By default, such approach must be ultimately conservative in order to address all possible pathomechanisms. The uncertainty involved in the derivation of OELs from substance-specific data is likely to be markedly reduced, especially in the presence of PBPK-based study design, verification of lung dosimetry by empirical data, and a mechanism-based target organ dose-effect analysis. In such cases; any product-specific OEL should supersede the generic more conservative REL. There are yet no internationally harmonized or regulatory binding testing guidelines for poorly soluble micronsized or nanosized particles; however the more recent OECD#GD39 gives advice what type of minimal testing standard is necessary to produce meaningful data for quantitative risk characterization. 1) Overwhelming published evidence appears to support a stratified approach which categorizes toxicology findings from repeated exposure inhalation studies in	1) This comment describes the rat lung responses associated with the overloading of lung clearance of poorly soluble particles (discussed	1) The document was checked for opportunities to clarify or better communicate this information (especially in

Commenter	Summary of Comments Received	Response	Changes to CIB
Pauluhn, Bayer Healthcare Pharmaceutical (cont.)	terms of 'below, in the range of, and markedly exceeding particle lung overload'. Any OEL or REL derivation should focus on the primary response to particles at the lower end of the dose-response curve rather than to the secondary response(s) at higher cumulative doses at overload conditions. For reversible findings, an ordinal approach should be given preference to an 'all or nothing' approach. Suffice it to say, reversibility is tightly linked to the extent of lung overload (see below) and associated kinetic variables of particle clearance.	further comment 2). The NIOSH risk assessment did focus on the lower end of the dose-response curve (e.g., dose associated with 10% excess risk). The animal lung responses used in the risk assessment were not reversible in a subchronic study (up to 6 months post-exposure) [Pauluhn 2010a], and were persistent or progressive in the short-term studies (up to 56 days post-exposure) [Shvedova et al. 2005, 2011; Mercer et al. 2011].	Appendix A and Section 5).
	2) Many studies presented in the CIB do not have the depth of validation or even that level of GLP compliance that have OECD-compliant testing methods. Most of the research-based publications utilize single bolus pharyngeal or intratracheal regimens. Single administration studies have limited validity to simulate the outcomes of repeated long-term inhalation exposure studies or even the recurrent chronic exposure occurring at the workplace. In the absence of data showing the particle morphology of the deposited and retained	2) Agree that the animal data are limited and that the subchronic inhalation studies may generally be considered to provide the currently best available data for human health risk assessment (as discussed in the CIB, Sections 5.1, A.2.1, and A.4). However, a similar dose-response relationship was seen at an equivalent estimated mass dose of MWCNT whether delivered in a single day or subchronic inhalation exposure	2) Checked the CIB for opportunities to clarify or better communicate this information. Mention of needed research for positive and negative benchmark (reference) particles in future studies of CNTs (Section 6). Added a comparison of the cobalt tracer-based MWCNT lung burden estimates to the MPPD

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Pauluhn, Bayer Healthcare Pharmaceutical (cont.)	material in the lung over a time period that would be long enough to cover at least one or multiples of the physiological clearance half-time of approximately 60 days, research-based studies cannot necessarily provide that type of information required for quantitative risk characterization. One of the major shortcomings of the alternative dosing protocols is that kinetic data on lung burdens are rarely available and adequate positive and negative benchmark dusts (micronsized vs. nano sized reference dusts) are often missing to demonstrate the diagnostic/prognostic power of the devised protocol. In the absence of such data, it appears to be difficult to attribute findings to specific nano- or micron-size particle characteristics. Retained lung dose may be contingent on numerous methodological variables. Many effect-focused data lack actual measurements of lung burdens. In none of the cited toxicity studies the proposed NIOSH 5040 method was used for measurements of either airborne concentrations or lung burden measurements. Before promulgating NIOSH 5040 as the mandated analytical method, one would have wished to see empirical data from controlled inhalation studies to better judge its benefits and	[Ellinger-Ziegelbauer and Pauluhn 2009; Pauluhn 2010a] (Section A.2.1.2). In addition, Shvedova et al. [2008] showed that the lung responses were qualitatively similar when administered by inhalation or pharyngeal aspiration (PA), and the inhaled dose was four-fold higher than the estimated equivalent PA mass dose. The BMD(L) estimates were also consistent (i.e., relatively low mass concentrations) based on either the subchronic and short-term studies (Section A.3.2; Table A-3 through A-5). Agree that use of positive and negative benchmark dusts would improve the utility of the animal studies for risk assessment, and that this is a research need. A comparison of the cobalt-tracer based estimates of MWCNT lung burden in Ellinger-Ziegelbauer and Pauluhn [2009] and Pauluhn [2010a] to the MPPD model-based estimates shows that the cobalt-tracer estimates were generally between the MPPD 2.0 model-based estimates of deposited and retained lung dose, which is consistent with the finding of reduced clearance	model-based estimates (Section A.6.1.2).

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Pauluhn, Bayer Healthcare Pharmaceutical (cont.)	limitations of this method relative to other methods.	(overloading) at relatively low mass lung burdens [Pauluhn 2010a]. Agree that it would be informative to use NIOSH method 5040 to measure airborne concentrations in the toxicology studies, and this work is underway at NIOSH. Point of clarification: NIOSH develops recommendations, not promulgated standards.	
	3) The CIB does not attempt to appropriately categorize the various types of CNTs. Some types (short, thin and tangled) have been shown to be thermodynamically present in an assembled, coiled structure while the more rigid CNTs may be present as agglomerates of thick/long tubes which may liberate isolated tubes with fiber-like structures under certain circumstances. Their surface properties can make them hydrophilic or lipophilic and surface/matrix bound residual impurities of catalysts may potentially exert modified local toxicities and clearance/translocation kinetics. The critical mode of toxic action of each subtype may differ from one category of CNTs to another.	3) Toxicology study findings of the different types of CNTs are discussed in Chapter 3, and various types of CNTs are included in the risk assessment (Appendix A). The risk estimates were based on the early-stage lung effects (inflammation, granuloma, fibrosis), whereas the intraperitoneal injection studies (showing differences in mesothelial effects from different CNT structures) are useful for hazard assessment but of limited utility for quantitative risk assessment given uncertainties in the translocation of CNT from the lungs to the pleural or peritoneal tissue.	3) Clarified the data basis for the REL. Added the recent studies (published since the Nov 2010 external review draft CIB) on lung responses related to CNT structure (Chapter 3). Expanded the discussion of the role CNT physical-chemical properties on the lung responses (Section A.4.2).

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Pauluhn, Bayer Healthcare Pharmaceutical (cont.)	4) The basic concept of risk assessment is to articulate the likely mode of action decisive for the outcome of short-term (acute) and long-term (subchronic + postexposure period) inhalation studies and why CNTs are considered to elicit a different toxic potency than other types of biopersistent poorly soluble particles. So far, the scientific community has not yet unanimously agreed which metric of dose is causal for the most critical effect observed. Nonetheless, prevailing evidence supports the mechanistic concept of volumetric particle lung overload (Morrow's overload hypothesis). This concept describes the dynamic decrease in clearance with increasing fractional particle load of the lung. Thus, the changes in lung clearance is not necessarily a substance-specific property, it may solely be related to the accumulated or administered 'particle volume dose'-dependent decreased clearance. Therefore, the conclusions drawn in regard to the regression and persistence should be related to the degree as to which a non-physiological pulmonary overload has been attained or exceeded. Accordingly, a more thorough understanding of the	4) Agree that evaluating the evidence for the biological mode of action is part of hazard and risk assessment (described in Sections 3 and A.1). As stated in the comment, overloading of rat lung clearance of MWCNT was observed in a subchronic inhalation study [Pauluhn 2010a], and was related to the volumetric particle burden [Pauuluhn 2010b. 2011]. Other studies have shown that particle surface area was related to overloading and dose-response to various poorly soluble particles [Tran et al. 2000], including CNT [Nakanishi 2011]. Human lung clearance is underestimated by a simple first-order clearance model as in the rat at low doses (discussed in Sections 5.2 and A.6.3.2). To the extent that the data support different OELs for various types of CNT, then NIOSH would consider recommending more than one OEL. However, BMD(L) estimates based on the subchronic and short-term studies in rats and mice exposed to various types of CNT (by IT,PA, or inhalation) are all associated with estimated risk of	4) Section A.6.3 provides an evaluation of the influence of alternative methods and assumptions on the estimation of the human-equivalent concentration, including those based on the overloading hypothesis, as described in Pauluhn [2010b].

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Pauluhn, Bayer Healthcare Pharmaceutical (cont.)	underlying cause of product-specific effects appears to be more relevant when several subcategories of materials (CNF, SWCNT and MWCNT, including their subcategories) with differing characteristics are grouped for the purpose of establishing a common or generic OEL such as the REL proposed in the CIB. Therefore, whenever sufficient and adequate product-specific data are available, any product-specific data-based recommendation of an OEL should be given preference to the generic REL.	early-stage lung effects at relatively low mass concentrations in animals and in humans over a working lifetime (Table A-3 through A-5). Similar working lifetime concentrations were estimated based on NOAELs or LOAELs reported in subchronic studies, including using different risk assessment methods and assumptions (Section A.6.3). These 8-hr TWA estimates are near or below the LOQ for the measurement method [NIOSH method 5040].	
	5) When using the concept of the Human Equivalent Concentration it is important to recognize the sequence of events taking place in the lung. Dosimetry considerations need to distinguish target organ sub-compartments where the deposition and accumulation of particles occur and what specific type of toxicity ensues. Using the alveolar surface area as the denominator to adjust the retained dose may be a valid approach for soluble particles with short half-times; however, for essentially insoluble particles this approach does not necessarily reflect the dominating pathway	5) Agree that dosimetry in the lung target subcompartments is relevant to the estimation of the human equivalent lung dose. Evidence suggests that the particle dose to either the alveolar macrophages [Morrow 1988; Muhle et al. 1991; Pauluhn et al. 2010a,b; 2011] or to the alveolar epithelial cell surface [Tran et al. 2001; Oberdorster et al. 1994; Donaldson et al. 2008] is associated with the rat lung responses, including pulmonary inflammation, to poorly soluble particles.	5) Section A.6.3 describes the quantitative influence of normalizing the animal lung dose on the interspecies differences in either the alveolar lung surface area or the alveolar macrophage cell volume.

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Pauluhn, Bayer Healthcare Pharmaceutical (cont.)	of particle clearance taking place in the lung. A wealth of published information provides ample evidence that the lung burden-dependent recruitment of inflammatory cells, not the particle as such, orchestrates the severity of disease and is causal for the terminal outcome.		
	6) Pulmonary fibrosis to the histopathologist is typified by deposition of collagen in excessive amounts (in diffuse or nodular form) or abnormal deposition in an incorrect location (pleural, peribronchial, intra-alveolar) which results in disruption of the normal lung architecture. The biochemist regards pulmonary fibrosis as increase in total lung collagen as assessed from measurements of hydroxyproline. Both definitions are very simplistic, especially at disease stages where acute inflammation prevails. The latter produces a marked increase in soluble intra-alveolar collagen and fibrin perambulating the septal interstitium. Following lung injury, fibroblasts proliferate, differentiate into myofibroblasts expressing α-smooth muscle actin and migrate towards the	6) Alveolar interstitial fibrosis can be detected by Sirius red staining of septal collagen [Hubbs et al. 2011]. In SWCNT exposed mice, the septal fibrosis has been further confirmed by transmission electron microscopy [Mercer et al. 2008]. Pauluhn [2010a] also reported alveolar interstitial thickening in rats exposed to MWCNT, but distinguished the focal effects observed at 0.4 mg/m^3 from those at higher exposures. Pauluhn [2010a] reported: "Increased interstitial collagen staining occurred at 1.5 and 6 mg/m^3. Focal areas of increased collagen staining were adjacent to sites of increased particle deposition and inflammatory infiltrates (onset at 0.4	6) The CIB has been revised (Section A.2.1.3) to clarify the description of the rat lung responses as reported by Pauluhn [2010a] and the benchmark response as used by NIOSH in the risk assessment. Evaluation of the influence of the pulmonary response and other factors on the REL derivation is provided in Sections A.6.2 and 5.3; comparison of BMD(L) estimates by severity level are shown in Tables A-5 and A-6.

Commenter	Summary of Comments Received	Response	Changes to CIB
Pauluhn, Bayer Healthcare Pharmaceutical (cont.)	fibrinous exudate inside the alveolar airspace or perivascular space. In the absence of any (myo)fibroblasts proliferation and secretion of cross-linked collagen types or fibrosing alveolitis, the term 'fibrosis' as perceived irreversible lesion, should be used cautiously, especially when exudative acute inflammation is still ongoing. The various stages of fibrotic changes are generally described in an ordinal manner. Lower grades may be reversible, higher not. When using ordinal data for any type of quantitative risk assessment, one would have expected to see generalized definitions of the severity categories applied equally by all pathologists involved with lung pathology. In none of the studies cited, the more quantitative scoring according to Ashcroft was used. As long such harmonized guidance is not defined in even in the current OECD Series of Testing and Assessment No. 125 "Guidance Document on Histopathology for Inhalation Toxicity Studies, supporting TG412 and TG413", histopathology findings the CIB notes that early-stage fibrotic and inflammatory lung responses were selected and were characterized as lung inflammation, granuloma and	mg/m3, see Table 3). Increased septal collagen staining was depicted as equal to interstitial fibrosis (for details, see Fig 12)." The severity level (minimal or greater) persisted or progressed up to 26 weeks after the end of the 13-week inhalation exposure to either 0.4, 1.5, or 6 mg/m^3 [Pauluhn 2010a, Table 3]. The 0.4 mg/m^3 dose group was considered the LOAEL for inflammatory lung effects, while 0.1 mg/m^3 was considered the NOAEL [Pauluhn 2010a]. Pathologists' interpretations may differ as to whether these early-stage responses would be considered adverse or to have the potential to become adverse. NIOSH interpreted the alveolar septal thickening (and associated effects including hypercellularity in the bronchial alveolar junctions) in the 0.4 mg/m^3 and higher dose groups as being adverse changes of relevance to human health risk assessment due to their persistence and consistency with early-stage changes in the development of pulmonary fibrosis. For these reasons, NIOSH selected	

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Pauluhn, Bayer Healthcare Pharmaceutical (cont.)	interstitial fibrosis.	alveolar septal thickening of minimal or higher grade as the benchmark response for risk assessment and BMD(L) estimation based on the Pauluhn [2010a] study.	
	7) In cases where the opinion reflected in the CIB is at variance from that of the scientific investigator one would have wished to see a clear rationale for doing so.	7) Agree that it would be helpful to provide additional information concerning various possible interpretations of the rat lung effects and benchmark responses used in the risk assessment .	7) As mentioned in previous response, the CIB has been revised to clarify the rat lung responses as reported by Pauluhn [2010a] and the benchmark response as used by NIOSH in the risk assessment (Section A.2.1.3). The influence of the pulmonary response severity on the BMD(L) estimates is shown in Tables A-5 and A-6, and discussed further in Sections A.6.2 and 5.3.

Commenter	Summary of Comments Received	Response	Changes to CIB
Hollenbeck, Oak Ridge National Lab	1) A one-size fits all REL for carbon nanotubes (CNTs) and carbon nanofibers (CNFs) should not be considered the best approach as there is available information regarding varying levels of toxicity for CNTs involving different catalysts resulting in a wide range of functionalization structures. The level and type of functionalization for CNTs and CNFs can obviously play a significant role on the level of toxicity in various biological systems. A more reasonable approach, from the standpoint of safety conservatism without being overburdening from a regulatory standpoint, would be to apply the established asbestos air standard to CNTs and CNFs. The British Standards Institute has adopted a CNT standard similar to the asbestos standard which validates this line of reasoning. This approach would seem to be more biologically plausible as well.	1) In response to the first part of this comment, the REL was not derived a priori as a single value for all CNT. Instead, the risk assessment based on subchronic and short-term studies of several types of MWCNT and SWCNT resulted in low mass concentrations (8-hr TWA) over a working lifetime (Tables A-3 through A-6; Table A-13). In response to the second part of the comment, the CIB recommends research to develop more sensitive measures of exposure to CNT; however, currently there are no standard methods for counting CNT structures, which can be quite heterogeneous. Currently, there are also insufficient dose-response data based on CNT structure type and count for quantitative risk assessment. For these reasons, the REL is based on respirable mass concentration.	1) The document was checked for opportunities to clarify this information.

Commenter	Summary of Comments Received	Response	Changes to CIB
Hollenbeck, Oak Ridge National Lab (cont.)	2) The asbestos standard would be more protective than the NIOSH recommended REL of 7 μg/m3 elemental carbon.	2) This may be true, depending on the CNT structures and the extent to which they are asbestos-like in form and biological response. Since CNT can occur in heterogeneous forms, the proportion which elicits asbestos-like responses may differ. For example, Murphy et al. [2011] reported that CNT with a higher proportion of longer, straighter structures elicited inflammatory responses consistent with asbestos in intra-peritoneal injection studies in rats, whereas the shorter, tangled CNT structures did not induce inflammation at the same dose (5 ug/rat).	2) Revised research recommendations to include: "Improve the sensitivity and precision of … methods for measuring airborne concentrations of CNT and CNF, including those based on metrics that may be more closely associated with the potential adverse effects (e.g., electron microscopy-based CNT or CNF structure counts)" (Section 7.1).
	3) In terms of a safety factor approach, using the 7 ug/m^3/mass of 0.25 um x 5 um fibers as an upper limit, as diameters became smaller (presumed increase in toxicity) the	3) This comment appears to be describing the greater toxicity expected for a given mass of CNT with smaller diameters compared to CNT with larger diameters. There is	3) Research needs were revised to include was electron microscopy structure counts (see response to previous comment).

Commenter	Summary of Comments Received	Response	Changes to CIB
Hollenbeck, Oak Ridge National Lab (cont.)	safety factor would increase; while a mass based REL would not change with changes in particle size.	some evidence for this concept based on analogy to asbestos [e.g., Stayner et al. 2008]. However, there is little quantitative evidence for CNT, which can be highly heterogeneous in structure. Also, standard electron microscopy counting methods have not yet been developed for CNT.	
	4) Mass measurement does not correspond adequately with anticipation of potential health outcomes regarding exposure to CNTs and CNFs. It may be appropriate for a specific form of CNT/CNF where mass can be related to particle concentration or surface area but on the whole it would be better served to base measurement on particle counts and/or fiber counting methods. Available toxicity data appears to favor a surface area criterion over a mass criterion or a number concentration with specific dimensions i.e., the asbestos standard presuming a similar toxicological etiology to asbestos.	4) Neither number concentration nor surface area are adequately selective for exposure monitoring. Fiber counting methods may not be adequately protective if large respirable agglomerates are counted with equal weight as single fibers. The animal dose-response data provide association between the airborne mass concentration (or estimated lung dose) and early stage inflammatory and fibrotic lung effects, and these data were used in a quantitative risk assessment to estimate the human-equivalent working lifetime exposures (Appendix A). The surface area, volume, or number of CNT particles	4) The research recommendation to develop more sensitive and specific measurement methods has been revised (see previous two comments).

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Hollenbeck, Oak Ridge National Lab (cont.)		may be a better descriptor across a range of particle sizes but toxicology data and workplace measurement methods based on these metrics are limited at this time.	
	5) There are numerous analytical methods established for determining asbestos counts in air that could be applied to CNTs in air (NIOSH 7402, ASTM 06281-06. OSP 10312: 1995).	5) Available animal data are incomplete at this time to establish a dose-response relationship between CNT or CNF count/dimension and adverse respiratory effects. If CNT and CNF count is determined to be a better metric then criteria will need to be developed on how CNT/CNF should be counted and sized. Electron microscopy methods exist for counting various types of fibers but criteria will need to be developed that are specific to the size characteristics found to be associated with the toxicological effect.	5) No revisions required.
	6) Count and size data could be subsequently used to derive estimates of surface area. This potential would be lacking with gravimetric exposure data, which would therefore be of limited use for retrospective	6) Agree that data are needed on exposure or dose metrics other than mass.	6) Section 7 already discusses the need for research on dose metrics and measurement methods for metrics other than mass of CNT.

Commenter	Summary of Comments Received	Response	Changes to CIB
Hollenbeck, Oak Ridge National Lab (cont.)	epidemiology. 7) For CNT forms of lesser anticipated toxicity, i.e., non-doped SWCNTs the fiber count approach for fiber glass could be applied which again addresses size while relaxing the stringency of control. 8) Any exposure limit recommendations should address short-term exposure periods as certain workplaces (i.e., research and development) are task based and do not handle CNTs and CNFs on what would be considered an 8-hour work schedule. The higher sample volumes as required by the method are inappropriate for these types of short duration tasks.	7) The biological and other data basis for this assumption is not clear. It does not make use of the available dose-response data on CNT but makes assumed analogies with other materials in the absence of any comparative data. 8) The sample volume required depends on the mass concentration. NIOSH is not proposing a short-term exposure limit at this time. See CIB for revised detection limits. Short-term exposure limits are typically derived to prevent 'acute' adverse effects; the animal toxicological data indicated that exposure to CNT and CNF pose a chronic respiratory hazard. The commenter is correct in that most CNT/CNF job tasks that have been reported to date appear to be short-term. NIOSH recognizes that to collect a sufficient amount of sample during these short-term tasks that a larger volume of air will need to be collected for personal samples. The CIB was revised to address this issue.	7) No revisions required. 8) Section 6.1.1 *Exposure monitoring program* was added to the CIB to provide guidance on optimizing sample collection so that appropriate determinations of exposure concentrations could be made.

Commenter	Summary of Comments Received	Response	Changes to CIB
Hollenbeck Oak Ridge National Lab (cont.)	9) The information available through other recommended exposure standards such as Bayer Baytubes ® is based on specific knowledge of a specific CNT form. This approach is advantageous and should be studied by NIOSH in further detail and adopted as appropriate.	9) The dose-response data from the Pauluhn [2010a] study are included in this risk assessment, and a quantitative comparison of other approaches has been provided (Section A.6).	9) Additional discussion and quantitative comparison of the effect of the different methods and assumptions including those in Pauluhn [2010b] have been provided in Section A.6.3
	10) NIOSH has historically provided many useful logic flow and/or decision tree diagrams to assist health hazard evaluators and in this case this would be very useful in providing more standardized measurement methods for CNTs and CNFs.	10) Additional guidance provided.	10) Section 6.1.1 *CNT and CNF measurement* was added to the CIB to provide guidance on the sampling and analysis of CNT and CNF.
	11) Development of an accurate REL should be based on more specific information and a discussion on other applicable analytical	11) NIOSH researchers have applied multiple methods to characterize worker exposure. Determining metals in bulk materials is useful, but	11) Other analytical methods are discussed that can supplement the use of Method 5040 for exposure characterization.

Commenter	Summary of Comments Received	Response	Changes to CIB
Hollenbeck, Oak Ridge National Lab (cont.)	methods including microscopy (i.e., TEM, AFM, etc.) and elemental analysis (i.e., metals) should be in this dialogue.	at low CNF/CNT concentrations, the levels are too low for practical application. Typical metal contents of CNFs/CNTs are 1% or less, and there may be interference problems (e.g., catalyst byproducts generated during synthesis). See previous discussion on exposure metrics.	

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Gallet, Producers Association of Carbon Nanotubes in Europe (PACTE)	PACTE supports NIOSH's effort to develop a recommended exposure limit (REL). Such guidelines contribute to the responsible development of carbon nanotubes (CNTs) technology, which will in turn lead to better acceptance by regulators, industrial users, and consumers.		
	1) PACTE believes that the CIB would be enhanced significantly by a discussion of the fact that not all CNTs have the same characteristics with respect to purity, length, and other features that are known to influence hazard potential. PACTE appreciates that NIOSH selected an REL that is within current analytical capabilities, such that the approach can actually be implemented. However, as NIOSH notes in the draft CIB, the proposed REL may require adjustment as alternative or improved methods become available.	1) The CNT CIB describes in several places the differences in CNT structures observed in the workplace and in animal studies (especially Exec Sum, Chapters 3, 4, 5, and Appendix A), and this discussion has been revised to include new studies published since the external review draft (Nov 2010). The CIB also states that NIOSH will reevaluate the CNT REL as new data become available.	1) More recently published studies showing differences in animal lung response have been added [Murphy et al. 2011; Mercer et al. 2011] (Chapter 3 and Appendix A).
	2) CNTs are treated in the document in a very undifferentiated manner and no attempt is made to correlate the effects described with certain physico-chemical characteristics. Differences in CNTs morphology and physico-chemical features might indeed	2) The evidence on the influence of the physico-chemical properties of CNTs on animal lung responses has been described in the CIB. In the risk assessment, the CNT were not grouped; rather, individual	2) Additional studies and discussion of physical-chemical factors has been added to Chapter 3 and Appendix A.

Commenter	Summary of Comments Received	Response	Changes to CIB
Gallet, Producers Association of Carbon nanotubes in Europe (PACTE)(cont.)	modulate their toxicity and some CNTs types may be much more innocuous than others. In addition, even though the range of effects is quite large, some of them may in part depend on experimental protocols and/or interferences with test systems used leading to various artifacts. The consequence of grouping all CNTs together is that the worst adverse effects found for one specific type of CNTs are assigned to the whole class. For this reason, the proposed REL may not be appropriate for all CNTs. NIOSH should acknowledge that CNTs produced by different manufacturers may have different properties and characteristics that lend themselves to more sensitive and specific detection and quantification approaches. There may be instances in which individual manufacturers have the ability to set their own health-protective REL based on hazard assessment specific to their material, and the CIB should incorporate such flexibility.	benchmark dose and risk estimates were derived for each of the individual animal studies of CNT with sufficient dose-response data (Appendix A). The derivation of a single REL results from the consistently low mass concentration estimates over all the studies, regardless of the type of CNT (although there were differences across the various studies by approx two orders of magnitude within a low mass dose region relative to the LOQ of method 5040).	
	3) For some specific CNT types a number of long-term studies are available that are suitable to derive an OEL (Pauluhn (2010), Ma-Hock (2009)). The NIOSH recommendation should point to the	3) The Pauluhn [2010a] and Ma-Hock et al. [2009] studies are subchronic (vs long-term) inhalation studies. NIOSH did use dose-response data from these studies in the quantitative	3) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Gallet, Producers Association of Carbon Nanotubes in Europe (PACTE)(cont.)	possibility of derivatisation of a product-specific OEL when sufficient information for a specific CNT-type is available.	risk assessment and REL derivation (Appendix A and Section 5). The CIB already notes that the REL may be reevaluated as new data become available.	
	4) Specific endpoints (such as fibrosis and granulomas) should be discussed in more details in the context of study designs and test materials. Otherwise it may lead to the misrepresentation that all CNTs produce irreversible fibrotic and granulomatous lesions irrespective of the route of exposure, the exposure concentration or the exposure duration.	4) Additional discussion has been added on the pulmonary responses used in the risk assessment, including alveolar septal thickening and fibrosis (Section A.2.1.3) and more recent studies on evidence on the role of CNT structure (individual vs. more agglomerated) have been added (e.g., Mercer et al. [2011]).	4) Discussion on interpretation of the fibrotic response has been revised (Section A.2.1.3)..
	5) No definition is given as to how 'fibrosis' is characterized. The term is used in an inconsistent manner across the document as well as in the literature quoted. Due to the unspecificity of the marker a correct wording in many cases may be inflammatory collagen and not fibrosis. Indeed inflammatory fibrosis and granulomatous findings should be discussed in the context of high loading and may be consistent with overload related phenomena. Specifically in some	5) Fibrosis can be detected by Sirius red staining of the interstitial (septal) collagen (Section A.2.13). Interstitial thickening with fibrosis has been demonstrated by Sirius red staining of lungs from mice exposed to SWCNT or MWCNT [Shvedova et al. 2005, 2008; Mercer et al. 2011], and fibrosis was confirmed by transmission electron microscopy in SWCNT exposed mice [Mercer et al. 2008]. Pauluhn [2010a] also reported	5) Discussion on the detection and interpretation of fibrosis has been clarified (Section A.2.1.3), and the findings of alveolar septal thickening and fibrosis have been more clearly described. .

Commenter	Summary of Comments Received	Response	Changes to CIB
Gallet, Producers Association of Carbon nanotubes in Europe (PACTE)(cont.)	publications indications are given that inflammatory collagen cannot systematically be equated to fibrosis and that some histopathological markers are not specific to fibrosis. For example in Ellinger-Ziegelbauer et al (2009) "*These findings support the hypothesis that the 115anoma red stained collagen using the Sircol assay likely reflects the exudated, inflammation related collagen rather than the (myo-) fibroblast synthesized septal collagen*" or in Ryman-Rasmussen et al. (2009) "*A caveat is that the fibrosis score relied on trichrome staining, which, although commonly used, could stain other cell matrix components and contribute to the observed pleural wall thickness*". Page 28: The reference to Lam et al. (2004) is inappropriate as the authors mentioned that: "At the doses used in the present study, no fibrosis was observed in the lung."	alveolar interstitial thickening in rats exposed to MWCNT, but distinguished the focal effects observed at 0.4 mg/m3 from those at higher exposures. This has been clarified in Section A.2.1.3 and throughout the document.	
	6) For CNT no report of penetration can be found in the literature (Crosera, 2009). The literature references quoted in the CIB on dermal penetration deal with fullerene and quantum dots (Rouse 2007 and Ryman-Rasmussen 2006). It would be preferable to assess the potential for penetration from the	6) The commenter is correct in that no dermal penetration data for CNT and CNF have been reported in the literature. NIOSH believes that it is prudent to recommend dermal protection of workers exposed to CNT and CNF until results from appropriately designed	6) The CIB currently states in Section 6.5 *Personal protective clothing:* "Given the limited amount of data on dermal exposure to CNT and CNF, it would be prudent to wear protective clothing and

Commenter	Summary of Comments Received	Response	Changes to CIB
Gallet, Producers Association of Carbon Nanotubes in Europe (PACTE) (cont.)	available data on dermal toxicity and dermal 116 nanomaterials (e.g. MWCNT Baytubes dermal acute toxicity LD50>2000mg/kg; no 116 nanomaterials). In our view there is no evidence for any significant dermal penetration of CNT.	studies have been completed. Specific guidance is given on when the use of dermal protection might be warranted.	gloves when: - All technical measures to eliminate or control the release of exposure to CNT and CNF have not been successful or, - In emergency situations."
	7) PACTE appreciates that NIOSH utilized a specific method (NIOSH 5040, *Diesel Particulate Matter*) for measuring exposure. However, it is important to recognize that 5040 has several limitations in the context of carbon nanomaterials, one of the most critical of which is that it not specific for CNTs and will be sensitive to all elemental carbons (such as soot, diesel exhaust gas or cigarette smoke). This may lead to an overestimation of the real concentration of CNTs in the air. Other possible methods should be listed, for example the use of a metallic marker	7) Problems with metallic markers are discussed above. Cigarette smoke contains a very low EC fraction and is not expected to interfere unless concentrations are very high. Further, employers may restrict workplace smoking. Background EC is a limitation that becomes significant when CNF/CNT levels are low. Careful background assessments are necessary to establish whether potential background interferences are an issue. See previous discussion.	7) Additional explanation on the limitations of Method 5040 and how to optimize sample collection and analysis are provided in Section 6.1.

Commenter	Summary of Comments Received	Response	Changes to CIB
Gallet, Producers Association of Carbon Nanotubes in Europe (PACTE) (cont.)	presents as impurity in the CNTs in traces quantity as described for CNTs in Maynard et al. (2004).		

Commenter	Summary of Comments Received	Response	Changes to CIB
Ono-Ogasawra, Japan National Institute of Occupational Safety and Health	I appreciate your challenging and tough work. I learned a lot from the document. My concern is about exposure measurement of CNTs, although it is not directly related to risk assessment of CNTs. One of the difficult problems relating to CNT is a lack of exposure assessment method. To connect the hazard data and the exposure data, some metric is needed, but in the present status, only gravimetric mass and amount of chemicals included in the nanomaterial can do. I trust that carbon analysis by using thermal-optical method like NIOSH 5040 is a useful tool to assess the CNT exposure. Though the detection limit of carbon analysis is not enough to analyze sub-microgram per cubic meter level of CNTs, we can acquire some information of CNT exposure by this method. I have two questions about sampling for this analysis:		
	1) Even if you want to know full-shift exposure, sampling has to be conducted only when the work possibly generating the CNT aerosols is done. Longer sampling duration may make the background concentration of carbon higher. Sampling duration and assessment of background concentration of carbon in each work	1) Careful background assessments are necessary, and this point is stressed in the CIB. NIOSH and others have traditionally expressed exposure standards as 8-hour TWAs. In addition, short-term exposure limits (STELs) sometimes apply, but NIOSH is not proposing a STEL for	1) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB _ _
Ono-Ogasawra, Japan National Institute of Occupational Safety and Health (cont.)	environment is very important.	CNT/CNF since the health effects are probably chronic in nature and not acute. Collecting an air sample over 8-hours in cases where the actual exposure occurs over a much shorter period both increases the environmental background contribution to the sample and obscures the actual exposure concentration during the task. If a worker performs a task repeatedly, and if it is clear that exposure occurs almost exclusively during the task, monitoring the task multiple times gives a more accurate measure of the average air concentration during that task. A background sample collected over a much shorter period will be non-detect at typical environmental background levels. If the background concentration is relatively stable, a longer term (e.g. 6 hours or more) can be collected to obtain enough mass to determine the ambient concentration, but subtracting this from a result for a full-shift sample overcorrects for background if the exposure occurred over a much	

Commenter	Summary of Comments Received	Response	Changes to CIB
Ono-Ogasawra, Japan National Institute of Occupational Safety and Health (cont.)		shorter period. NIOSH researchers applied a task-monitoring approach to monitor one task (bagging small amounts of CNF) during their study at a CNF facility (Birch et al 2011, Birch 2011, Evans 2010), but this is not always possible, depending on the task. For example, in the CNF study, a worker was asked to repeat a bagging task so adequate mass could be collected. In our study, a photometer was useful for identifying CNF plumes (i.e., high concentrations) generated during manual handling. In cases where longer-term samples were collected, the photometer indicated that the bulk of the mass was sampled during a much shorter period. Estimates of the CNF air concentrations during these episodic releases can be estimated by knowing the period (air volume) over which the bulk of the mass was collected (if the sample EC mass is adequate for quantification).	

Commenter	Summary of Comments Received	Response	Changes to CIB
Ono-Ogasawra, Japan National Institute of Occupational Safety and Health (cont.)	2) Usually most of CNTs suspend in the air as aggregates/agglomerates. What is your opinion about the sampling of size separated sampling. My opinion is that sampling should be conducted for PM4, because we do not have enough information on the behavior of agglomerated CNTs. For safe side, CNT in respirable size or greater is better to be monitored.	2) NIOSH researchers collected three size fractions (total, thoracic, and respirable) in their study at a CNF facility (Birch et al 2011, Birch 2011, Evans 2010) for this very reason. NIOSH has proposed sampling a respirable fraction based on animal toxicological data in which adverse effects were observed in the small airways of animals. NIOSH researchers will continue to collect size distribution data and different size fractions in field investigation studies to better understand the exposure and ultimately any associated health risks. For initial workplace surveys, it would be prudent to determine the particle size distribution and collect different size fractions to establish whether there are substantial differences between them (as was done by NIOSH researchers). Collecting such data may be useful should future research indicate that a different exposure metric might be warranted for establishing an occupational exposure limit.	2) No revisions required.

Comment [jad41]: If the commenter is correct that most CNTs suspend in the air as agglomerates, why are we recommending sampling for the respirable fraction? I think this needs to be better answered here and in the CIB.

Comment [jad42]: typo

Comment [jad43]: If the size distribution is found not to be in the respirable range, should the employer then apply the thoracic or inhalable fraction to the REL?

Commenter	Summary of Comments Received	Response	Changes to CIB
Masahide Hayashi, Nanotechnology Business Creation Initiative, Japan	1) NIOSH prefers not to use expressions that imply CNT is harmful. No scientific evidence exists that would indicate CNTs are harmful. The reports by Poland et al. (2008) and Takagi et al. (2008) point out the possibility that CNTs may cause acute mesothelial inflammation or induce mesothelioma similar to asbestos exposure. The studies were, however, conducted by administering MWCNTs into the abdominal cavity, which is absolutely impossible as a path for human exposure. Therefore, the studies by Poland and Takagi should be regarded as simply reference information on the potential risk of mesothelioma. None of the past studies on MWCNT inhalation exposure and intratracheal injection tests have reported even a single case of mesothelioma induced by administered MWCNTs.	1) The scientific evidence presented in the document focuses on the risk of developing pulmonary fibrosis based on subchronic and short-term animal inhalation studies with CNT. While animal IP data suggest that the dimensional characteristics of CNT (tube length and diameter) may pose a risk of mesothelioma, the document recognizes that additional research is needed to determine whether exposure to CNT poses a cancer risk.	1) No revisions required.
	2) Expressions that limit the use of CNTs are harmful. The radical expression is detrimental to CNT-based product applications and technological developments expected to	2) Part of the hierarchy of control for potentially hazardous materials is the replacement of substances with a non-hazardous or less hazardous substance. We acknowledge that the manufacturing and use of CNT and	2) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Masahide Hayashi, Nanotechnology Business Creation Initiative, Japan (cont.)	help alleviate global environmental problems. Such product applications and technological developments include reductions in other hazardous substance emissions, improvements in energy efficiency, and reductions in product weight. For all of above reasons, we request the deletion of the sentence "When possible, substitute a nonhazardous or less hazardous material for CNT and CNF when feasible" in the third item of Section 1. Recommendation for Employers.	CNF is for a specific commercial use and thus can't easily be substituted with a different material. However, there is some indication that a change in surface chemistry and/or the functionalization of the tube can alter the potential toxicity of the CNT or CNF while not affecting its properties needed for its specific commercial application. Additional research is needed to confirm these preliminary findings.	

Commenter	Summary of Comments Received	Response	Changes to CIB
Takuya Igarashi, National Institute of Advanced Industrial Science and Technology (AIST)	***On behalf of*** Dr. Junko NAKANISHI, the Project Leader of NEDO project "Research and Development of Nanoparticle Characterisation Methods" (P06041), and ***on behalf of*** colleagues in the Research Institute of Science for Safety and Sustainability within the National Institute of Advanced Industrial Science and Technology (AIST) of Japan, ***on*** February 18, 2011, Takuya IGARASHI would like to submit the following comments ***on*** your November 2010 Draft of "NIOSH Current Intelligence Bulletin - Occupational Exposure to Carbon Nanotubes and Nanofibers", ***together with*** two PDF files of our Interim Report issued on October 16, 2009 for your immediate reference: 1) ***First of all***, it is our regret that the CIB authors in NIOSH made the same misinterpretation as the authors of "Report of Project Six: Preliminary Outline of the Paper on Critical Issues on Risk Assessment", ENV/CHEM/NANO(2010)12 dated 1 July 2010, a document for the 7th Meeting of OECD/WPMN held on 7-9 July 2010, more specifically its Footnote 4 of Page 13. This footnote was to argue that "the proposed	1) Section 5.2 has been revised to correct this information.	1) The CIB text and reference list have been revised as requested.

Commenter	Summary of Comments Received	Response	Changes to CIB
Takuya Igarashi, National Institute of Advanced Industrial Science and Technology (AIST)(cont.)	OEL of 0.21 mg/m^3 is 10 times higher than calculated based on the information provided", which was just a misunderstanding resulting from not considering the deposition fraction (DF) of CNT on the lungs, whose value was assumed to be 0.1 (10%). As for "Calculation of deposition into lung", the questioned interim report for CNT [Nakanishi J (ed) 2009] did refer to the sister interim report for titanium dioxide (TiO_2) [Nakanishi J (ed) 2009b], as simply noting that "Based on the same method and parameters as in the TiO2 risk assessment document"*, where the equation DOSE = (C × RMV × T × DF)/BW was clearly given**. *: See Line 23, Page 30 of "Nakanishi J (ed) [2009]. Risk Assessment of Manufactured Nanomaterials: Carbon Nanotubes (CNTs). NEDO project "Research and Development of Nanoparticle Characterisation Methods" (P06041). Interim report issued on October 16, 2009. **: See Line 7, Page 26 of Nakanishi J (ed) [2009b]. Risk Assessment of Manufactured Nanomaterials: Titanium Dioxide (TiO_2). NEDO project "Research and Development of Nanoparticle Characterisation Methods" (P06041). Interim report issued on October 16, 2009.		

Commenter	Summary of Comments Received	Response	Changes to CIB
Takuya Igaraski, National Institute of Advanced Industrial Science and Technology (AIST)(cont.)	2) ***In addition***, we would prefer the way of making reference such as [Nakanishi (ed) 2009], instead of [Kobayashi et al. 2009] and instead of [Kobayaski et al. 2009] which is misspelled. ***Below*** you will find a complete set of detailed comments.	2) The reference has been corrected.	2) The citation was changed to read Nakanishi (ed) 2009. In addition, the Nakanishi 2011 reference has been added.
	3) **Lines 5-7, Page 43, regarding NEDO/AIST and Kobayashi et al.** "proposed in a report by the Japanese New Energy and Industrial Technology Development Organization (NEDO) [Kobayashi et al. 2009]." **should read** "proposed in a report by the National Institute of Advanced Industrial Science and Technology (AIST) of Japan [Nakanishi (ed) 2009], which was supported by the New Energy and Industrial Technology Development Organization (NEDO) of Japan."	3) The revision has been made as requested.	3) The CIB (Section 5) has been revised accordingly.
	4) **Lines 9-10, Page 43, regarding calculation of the equivalent rat lung dose rate** "The equivalent rat lung dose rate was calculated to be 6.0 µg/kg/day [Kobayashi et al. 2009]." **should read** "The equivalent rat lung dose rate was calculated to be 6.0	4) The revision has been made as requested	4) The CIB (Section 5) has been revised accordingly.

Commenter	Summary of Comments Received	Response	Changes to CIB
Takuya Igarashi, National Institute of Advanced Industrial Science and Technology (AIST)(cont.)	µg/kg/day [Nakanishi (ed) 2009, Nakanishi (ed) 2009b]." **Explanation**: The calculation in Section 4.2 of Nakanishi (ed) [2009] was based on the same method and parameters as in Section 3.3 of Nakanishi (ed) [2009b], particularly in Subsection titled "Conversion into the amount deposited on the lungs" in Page 26.		
	5) **Line 10, Page 43, regarding an uncertainty factor** "an uncertainty factor of 2 for individual difference" **should read** "an uncertainty factor of 2 for extrapolation of exposure period". **Explanation**: Re-check Lines 26-27, Page 30 of Nakanishi J (ed) [2009], which said "× UF concerning extrapolation of exposure period: 2".	5) This revision has been made as requested.	5) The CIB (Section 5) has been revised accordingly.
	6) **Lines 14-17, Page 43, regarding the deposition fraction of CNT on the lungs** "From this information, NIOSH calculates that 3.0 µg/kg/day in a 70 kg worker would result in a total daily dose of 210 µg. Assuming that a worker inhales 10 m^3 of air in an 8-hr day [ICRP 1994], this total daily dose would be attained at an 8-hr TWA	6) The deletion has been made and the section has been revised to clarify and to correctly describe the methods and assumptions used in the OEL derivation for MWCNT in the Nakanishi (ed) [2009b], which was updated in the Nakanishi [2011] report.	6) The CIB (Section 5) has been revised as indicated.

Commenter	Summary of Comments Received	Response	Changes to CIB
Takuya Igarashi, National Institute of Advanced Industrial Science and Technology (AIST)(cont.)	concentration of 0.021 mg/m^3 (i.e., 21 μg/m^3)." **should be deleted completely.** **Explanation**: These two sentences are just of a misunderstanding resulting from not considering the deposition fraction (DF) of CNT on the lungs, whose value was assumed to be 0.1 (10%). As for "Calculation of deposition into lung", the questioned interim report for CNT [Nakanishi J (ed) 2009] did refer to the sister interim report for titanium dioxide (TiO_2) [Nakanishi J (ed) 2009b], as simply noting that "Based on the same method and parameters as in the TiO2 risk assessment document"*, where the equation DOSE = (C × RMV × T × DF)/BW was clearly given**. *: See Line 23, Page 30 of "Nakanishi J (ed) [2009]. Risk Assessment of Manufactured Nanomaterials: Carbon Nanotubes (CNTs). NEDO project "Research and Development of Nanoparticle Characterisation Methods" (P06041). Interim report issued on October 16, 2009. **: See Line 7, Page 26 of Nakanishi J (ed) [2009b]. Risk Assessment of Manufactured Nanomaterials: Titanium Dioxide (TiO_2). NEDO project "Research and Development of Nanoparticle Characterisation Methods" (P06041). Interim report issued on October 16, 2009.		

Commenter	Summary of Comments Received	Response	Changes to CIB
Takuya Igarashi, National Institute of Advanced Industrial Science and Technology (AIST)(cont.)	7) **Lines 12-15, Page 44** "In Kobayashi et al. [2009], the normalization of lung dose from rat to human based on equivalent dose per unit body weight does not account for species-specific differences in inhalation rate, lung surface area, or particle size-specific lung deposition fractions." **should read** "In Nakanishi (ed) [2009], the normalization of lung dose from rat to human based on equivalent dose per unit body weight does not account for lung surface area or particle size-specific lung deposition fractions." **Explanation**: The calculation in Section 4.2 of Nakanishi (ed) [2009] was based on the same method and parameters as in Section 3.3 of Nakanishi (ed) [2009b], particularly in Subsection titled "Conversion into the amount deposited on the lungs" in Page 26, where you will find, at least, sufficient consideration for species-specific differences in inhalation rate.	7) This revision has been made as requested.	7) The CIB (Section 5) has been revised accordingly.
	8) **Line 8, Page 45, regarding Kobayashi et al.** "Kobayaski et al. 2009" **should read** "Nakanishi (ed) 2009"	8) This revision has been made as requested.	8) The reference citation has been corrected.

Commenter	Summary of Comments Received	Response	Changes to CIB
Takuya Igarashi, National Institute of Advanced Industrial Science and Technology (AIST)(cont.)	9) **Lines 11-15, Page 45, regarding the NIOSH's recalculation** "The currently proposed OELs for CNT range from 2.5 to 50 μg/m^3 (8-hr TWA concentration) [Nanocyl 2009; Kobayashi et al. 2009; Pauluhn 2010b], including the NIOSH REL of 7 μg/m^3. These CNT OELs are considerably lower than the current U.S. OELs for graphite or carbon black (approximately 2.5 to 5 mg/m^3), by a factor of 100 to 1000." **should read** "The currently proposed OELs for CNT range from 2.5 to 210 μg/m^3 (8-hr TWA concentration) [Nanocyl 2009; Pauluhn 2010b; Nakanishi (ed) 2009], including the NIOSH REL of 7 μg/m^3. These CNT OELs are considerably lower than the current U.S. OELs for graphite or carbon black (approximately 2.5 to 5 mg/m^3), by a factor of 10 to 1000." **Explanation**: Use our original OEL of 210 μg/m^3.	9) This correction has been made for the OEL derived in Nakanishi (ed) [2009], and as updated in Nakanishi [2011].	9) The CIB (Section 5) has been revised accordingly.
	10) **Column 1, Row 3, Table4, Page 70, regarding Kobayashi et al.** "Kobayashi et al. 2009" **should read** "Nakanishi (ed) 2009".	10) This revision has been made as requested.	10) The CIB (Section 5) has been revised accordingly and in the reference citation.

Commenter	Summary of Comments Received	Response	Changes to CIB
Takuya Igarashi, National Institute of Advanced Industrial Science and Technology (AIST)(cont.)	11) **Lines 7-9, Column 3, Row 3, Table4, Page 70, regarding deposition fraction on lungs:** "Human lung deposition of MWCNT calculated from rat data and an" **should read** "The deposition fraction of MWCNT on the lungs, whose value was assumed to be 0.1, and an"	11) This revision has been made as requested	11) Table 4 has been revised accordingly.
	12) **Note, Table 4, Page 70, regarding the NIOSH's recalculation** **This note should be deleted completely.** Explanation: NIOSH's recalculation is ten times lower than the OEL of 0.21 mg/m^3 reported by Nakanishi (ed) 2009. The recalculation is of just a misunderstanding resulting from not considering the deposition fraction (DF) of CNT on the lungs, whose value was assumed to be 0.1 (10%). As for "Calculation of deposition into lung", the questioned interim report for CNT [Nakanishi J (ed) 2009] did refer to the sister interim report for titanium dioxide (TiO_2) [Nakanishi J (ed) 2009b], as simply noting that "Based on the same method and parameters as in the TiO2 risk assessment document"*, where the equation DOSE = (C × RMV × T × DF)/BW was clearly	12) The CIB has been revised to clarify and correct this description of the method used to derived the OEL value in the Nakanishi (ed) [2009] report, and as updated in the Nakanishi [2011] report.	12) These revisions have been made in Section 5 of the CIB.

Commenter	Summary of Comments Received	Response	Changes to CIB
Takuya Igarashi, National Institute of Advanced Industrial Science and Technology (AIST)(cont.)	given**. *: See Line 23, Page 30 of "Nakanishi J (ed) (2009). Risk Assessment of Manufactured Nanomaterials: Carbon Nanotubes (CNTs). NEDO project "Research and Development of Nanoparticle Characterisation Methods" (P06041). Interim report issued on October 16, 2009. **: See Line 7, Page 26 of Nakanishi J (ed) (2009b). Risk Assessment of Manufactured Nanomaterials: Titanium Dioxide (TiO_2). NEDO project "Research and Development of Nanoparticle Characterisation Methods" (P06041). Interim report issued on October 16, 2009. 13) **Lines 3-5, Page 83, regarding Kobayashi et al.** "Kobayaski N, Kishimoto A, Ogura I, Gamo M [2009]. Risk Assessment of Manufactured Nanomaterials: Carbon Nanotubes (CNTs). Interim report issued on October 16, 2009. Executive Summary. Ed. Nakanishi J." **should read** "Nakanishi J (ed) [2009]. Risk Assessment of Manufactured Nanomaterials: Carbon Nanotubes (CNTs). NEDO project "Research and Development of Nanoparticle Characterisation Methods" (P06041). Interim report issued on October 16, 2009. [http://www.aist-riss.jp/main/modules/product/nano_rad.html]" and	13) These revisions have been made in Chapter 5 of the CIB.	13) The reference citation has been revised.

Commenter	Summary of Comments Received	Response	Changes to CIB
Takuya Igarashi, National Institute of Advanced Industrial Science and Technology (AIST)(cont.)	14) **<u>Add the following new reference:</u>** "Nakanishi J (ed) [2009b]. Risk Assessment of Manufactured Nanomaterials: Titanium Dioxide (TiO2). NEDO project "Research and Development of Nanoparticle Characterisation Methods" (P06041). Interim report issued on October 16, 2009. [http://www.aist-riss.jp/main/modules/product/nano_rad.html]".	14) This reference citation has been added as requested.	14) Reference citation has been added.

Commenter	Summary of Comments Received	Response	Changes to CIB
Casuccio, RJ Lee Group	The need of standards for nanomaterials is critical. NIOSH has made a bold attempt to propose health standards for CNT/CNF at a time when the toxicology data is limited and often based on a poor understanding of the tested materials. But it is counterproductive for NIOSH to propose a single mass-based REL for the heterogeneous group of CNT/CNF.		
	1) The proposed method (NIOSH 5040) is not specific to CNT/CNF. This method has distinct limitations and is not standard practice in most analytical laboratories. The EC/OC method has been used for many years in air quality speciation studies. However, it has also been the subject of debate. It should also be noted that in air quality studies, samples are typically collected for longer sampling periods (24-hours) and at higher flow rates (18 L/min).	1) Air quality studies collect samples at high flow rates because of the low air concentrations of the analytes of interest. NIOSH 5040 and other methods have been used for years and continue to be applied. There is no controversy regarding the ability of different OC-EC methods to accurately quantify total carbon; disagreement has been in the split between OC and EC. This discrepancy is mainly caused by sample components that carbonize during the analysis, forming 'char' that can cause positive bias if no correction is made. Relative to methods without char correction, NIOSH 5040 is less subject to positive bias. Further, if a sample does form char, it is obvious and can	1) Section 6 of the CIB provides more detail on the use of Method 5040.

Commenter	Summary of Comments Received	Response	Changes to CIB
Casuccio, RJ Lee Group (cont.)		be noted in an analytical report. If pyrolyzable materials are absent, even different methods show good agreement. NIOSH Method 5040 is well characterized and has performed well in multiple interlaboratory comparisons. It is reproducible and being applied internationally. It may not be "mainstream", and it is subject to the interferences noted, but 5040 is a useful tool for measurement of particulate carbon, and there are a sufficient number of laboratories available (see previous response). The method may be even more appropriate for CNT/CNF than for diesel particulate matter (DPM), the analyte for which it was developed, because typical CNT/CNF are almost exclusively EC, while the EC fraction of DPM is quite variable. Detailed information and references on NIOSH 5040 are provided in the CIB.	
	2) Currently the majority of CNT/CNF work in the USA is related to short-term "task-based" (i.e., less than 8-hour). An 8-hour	2) Based on limited workplace exposure data collected in research laboratories and pilot production facilities, the job	2) Section 6.1.*1 Exposure monitoring program* was added to the document to

Commenter	Summary of Comments Received	Response	Changes to CIB
Casuccio, RJ Lee Group (cont.)	TWA will not be appropriate for short-term task-based work. NIOSH should provide guidance on a short-term exposure limit to address the way work is conducted in research and many production facilities.	tasks in which exposures to CNT and CNF are likely to occur are short-term. However, the potential for worker exposure may increase significantly once these nanomaterials are introduced into commercial application. The assessment of risk based on animal data was used to estimate risk over a working lifetime (40-45 years). These estimates of risk are best expressed as a time-weighed exposure over a workshift (8-hrs). Short-term exposure limits (less than 8-hrs have historically been used to address acute health effects (e.g., irritation).	provide guidance on optimizing the collection of airborne samples during periods of short-term exposure to CNT and CNF.
	3) NIOSH is recommending a REL of 7 µg/m3 of elemental carbon (EC) as an 8-hr TWA respirable mass airborne concentration, and they state "excess risk of adverse lung effects is predicted below this level". However, NIOSH does not provide a basis for this statement. Furthermore, NIOSH does not state what part of the population the REL will protect. In general this is not the process that has been followed in protecting workers by standard setting. Standards or RELs are set to protect	3) Additional analysis has been added to the CIB to describe the risk associated with exposure to CNT. A sensitivity analysis has been performed so that risks can be compared using alternative risk assessment approaches. The commenter is incorrect in stating that 'standards or RELs' are set to protect a known percentage of workers; knowing the population potentially exposed is important	3) Additional analysis of risk added to Appendix A and Section 5.

Commenter	Summary of Comments Received	Response	Changes to CIB
Casuccio, RJ Lee Group (cont.)	a known percentage of workers from a known hazard. NIOSH must provide better dose-response information.	for hazard characterization so that appropriate risk management strategies can be recommended.	
	4) NIOSH proposes a mass-based standard, but mass measurements for CNT/CNF may not correlate well with health outcomes. A mass-based standard might be appropriate for a single type of CNT/CNF, where mass has been related to particle surface area or particle counts, or where the material of interest can be related more closely to health outcomes fitting a dose-response relationship. Health protection for fibrous materials has classically been done using the established counting methods.	4) The mass-based exposure or lung dose in the animal studies does correlate with the lung responses. These studies were used in the risk assessment and REL development (Appendix A and Section 5). Established counting rules for the many complex structures in CNT/CNF have not been established nor has the appropriate chronic studies. Particle surface area varies considerably for these materials, thus a single dose-response relationship would not hold across all materials. NIOSH researchers are investigating a 'structure' count method, but based on years of asbestos fiber counting, poor inter-laboratory agreement is expected to be an issue (See previous comments).	4) No specific changes made but evaluated document for opportunities to clarify this information.
	5) NIOSH is vague in the ancillary testing that should be considered to better describe the CNT/CNF materials. NIOSH could help	5) Additional guidance on exposure monitoring and analysis has been added to Section 6 of the CIB	5) Sections 6.1.1 *Exposure monitoring program* and 6.1.2 *CNT and CNF measurement*

Commenter	Summary of Comments Received	Response	Changes to CIB
Casuccio, RJ Lee Group (cont.)	industry by providing a detailed flow diagram and logic decision tree (e.g., see draft NIOSH TiO2 Guidance Document flow chart) to guide standardized test methods for ensuring that CNT/CNF is well described.		were added to the CIB to provide guidance on developing a sampling strategy and optimizing sample collection and analysis
	6) Where another country has already set a standard, NIOSH should address how the standard(s) should be compared with respect to the proposed NIOSH REL. The BSI standard is analogous to the asbestos standard (NIOSH has compared CNT/CNF to asbestos).	6) NIOSH acknowledges the need to evaluate alternative dose metrics and more sensitive and specific measurement methods including fiber-based electron microscopy counting methods (Exec Sum, Sections 5, 6, 7, and Appendix A). NIOSH believes its assessment of risk for CNT and CNF best reflects the results of animal research data in which exposure to CNT and CNF caused pulmonary fibrosis. The dose-response relationship from this research was best described as the mass of CNT and CNF and thus provided the best scientific data for risk assessment analysis. If results	6) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Casuccio, RJ Lee Group (cont.)		from ongoing research indicate a better dose metric for describing adverse lung effects, NIOSH will reevaluate the basis for its REL.	
	7) NIOSH has taken an extremely diverse group of materials and simplified a method for quantification of exposure that offers questionable protection and at the same time may be overly conservative for materials that are intentionally made safer (such as those intended for use in medical treatment.) This approach inhibits development of safer alternatives and removes one of the most useful control approaches of substitution.	7) In contrast to this statement, NIOSH actually developed individual benchmark dose and risk estimates based on the individual animal studies of various types of CNT. All of these individual study estimates resulted in low mass concentrations over a working lifetime. In contrast to the statement that the NIOSH REL inhibits development of safer alternatives, the standardized BMD risk assessment methodology that NIOSH used to derive the CNT REL may enhance the development of safer alternatives because it provides a standardized approach on which to evaluate the relative toxicity. Additional standardization in study design and response endpoints are also needed to adequately compare various CNT.	7) The sensitivity analyses in the new section A.6 further evaluate the role of various methods and assumptions on the REL derivation.

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Casuccio, RJ Lee Group (cont.)	8) There is sufficient knowledge to know that tubes without catalyst are of lesser cytotoxicity than those that are associated with cadmium, cobalt, nickel, etc. catalyst particles. NIOSH should use this knowledge to set a more appropriate set of RELs for differing types of CNT/CNF.	8) The REL is based on benchmark dose and risk estimates for both purified and unpurified CNT with various types and amounts of metal catalysts (Appendix A). Low airborne mass concentrations over a working lifetime are predicted from the dose-response data of all CNT evaluated, including the purified CNT (Tables A-3 through A-5). The Nov 2010 draft CIB discusses the available data on the influence of metal content on the toxicity of CNT in the animal studies (Executive Summary, Sections 3, 4, 5, and Appendix A).	8) No specific changes to the sections on the influence of metal catalyst on the lung responses. Recent studies by Mercer et al. [2011] and Murphy et al. [2011], showing differences in lung responses based on CNT structure, have been added to the CIB (Sections 3, 4, and Appendix A).

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Baker, ICU Environmental, Health and Safety –a Total Safety Company	I have a concern that the recommended NIOSH method 5040 for elemental carbon may not be the best choice in all situations. For example, we looked at using NIOSH 5040 for a workplace exposure assessment for the decommissioning of a CNT manufacturing pilot plant, but elected to go with a modified NIOSH 7500 XRD method for synthetic graphite because elemental carbon would have been ubiquitous in the petroleum refinery pilot plant environment for that project. The same may be true where propane powered lift trucks or other combustion processes are involved.	As mentioned in previous responses to comments, diesel vehicles may be an issue, especially older ones, but propane-powered lifts are not expected to contribute much EC. Each workplace must be evaluated to determine whether environmental background is an issue. Regarding XRD, in our work, we found it to be useful for examining material purity (amorphous C peaks were less intense and broader, and metal impurities were seen as small peaks), but we had difficulties with quantification. NIOSH would be glad to consider any data and method information (e.g., sample holder, calibration, LOD, interferences).	No revisions required.

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Landsiedel, BASF Product Safety-Experimental Toxicology and Ecology	**Is the hazard identification and discussion of health effects for CNT and CNF a full and reasonable reflection of the animal studies and other scientific evidence in the scientific literature?** 1) NIOSH combined the data from several studies with different CNT and very few with CNF, using different airway exposure techniques. NIOSH has used all available and relevant toxicological studies and interpreted the individual toxicological data correctly. The extrapolation of rodent data to a human-equivalent dose assumed, however, that responses to lung burdens are equal in rodents and humans. This, however, ignores higher susceptibility of rodents due to overload of their lung clearance. NIOSH has grouped the data to draw general conclusions on all CNT and CNF materials. Yet, different substances showed – in part - very different effects and therefore do not justify a common assessment. Likewise, materials in inhalation studies may well cause effects different from effects found by direct administration to the lung (intratracheal	1) Actually, NIOSH did not combine the data from several studies of different CNTs, but calculated individual benchmark dose and estimates based on the individual study dose-response data. The benchmark doses are at or below the doses causing overloading of lung clearance in the rat [Pauluhn 2010a,b]. In addition, humans have long-term retention of a proportion of the deposited lung dose even at relatively low mass lung doses which would be below overloading doses in the rat [Kuempel et al. 2000, 2001a; Kuempel and Tran 2002; Gregoratto et al. 2010, 2011]. All of the CNT evaluated resulted in low mass working lifetime exposure concentrations relative to other poorly soluble particles and to the LOQ of the measurement method [NIOSH method 5040].	1) Section A.6.3 provides an evaluation on the influence of various methods and assumptions on the estimation of the human-equivalent CNT concentration; the influence of different estimates of long-term particle retention rates in rat and human lungs is included in this evaluation.

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Landsiedel, BASF Product Safety-Experimental Toxicology and Ecology (cont.)	instillation and oropharyngeal aspiration). Remarkably, NIOSH did not differentiate fiber-specific effects and general effects of (glomerular) particles in the lung.	Shvedova et al. [2008] showed similar lung responses in mice to SWCNT by inhalation or pharyngeal aspiration. NIOSH noted the research need for dose-response data and sampling and analytical methods (including electron microsopy standard procedures) for CNT fiber-like structures.	
	Is the risk assessment and dosimetric modeling methods used in this document appropriate and relevant? 2) NIOSH has used the benchmark dose approach for the risk assessment; this is an appropriate model for these data. With the exception of studies using single dose only. NIOSH selected an estimate of lung burden rather than airborne concentrations as a dosimetry. By taking this approach it was possible to include the data from studies with direct administration to the lung (intratracheal instillation and oropharyngeal aspiration) along with data from inhalation	2) Lung burden (measured or estimated) is used in risk assessment to normalize the critical effect dose in animal lungs to an equivalent lung dose estimate in humans. Even if exposure concentration is used to estimate the BMD based on modeling the exposure-response data, an estimate of deposited (or retained) lung dose is needed to extrapolate the critical dose estimates from animals to humans.	2) Section A.6.1.2 provides an evaluation of the model-based lung dose estimates with cobalt tracer-based estimates of MWCNT in rats.

Commenter	Summary of Comments Received	Response	Changes to CIB
Landsiedel, BASF Product Safety-Experimental Toxicology and Ecology (cont.)	studies. Deposited lung burden is, however, calculated based on a model validated for spherical particles and may thus be inaccurate. Moreover, for carbonaceous material, the lung burden is not measured but merely calculated from the airborne concentrations. Therefore it is a data transformation through an unvalidated model which may add to the uncertainty of the dosimetry. Furthermore, the dosimetry does not adequately consider size distributions, heavy metal (catalyst) contents and, agglomeration states of the administered material.	To evaluate the uncertainty in the lung dose estimates, both deposited lung dose (no CNT clearance) and retained dose (assuming normal clearance based on spherical particle models) estimates were used in deriving BMD(L)s (Tables A-5 and A-6). These estimates provide bounds on the possible lung clearance rate kinetics for CNT. An evaluation of cobalt tracer-based measurements of MWCNT with that predicted from a rat lung dosimetry model (MPPD 2.0) showed that the measured lung burden was between that expected from deposited and retained lung burdens (Section A.6.1.2), which supports this bounding approach to lung dose estimation given the absence of a validated model for CNT. The dosimetry actually does consider the size distribution data; that is, the MMAD (GSD) reported for CNT were used as input in the dosimetry models to predict lung deposited dose. The metal catalyst particles would be included in those MMAD (GSD) data, and the agglomeration	

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Landsiedel, BASF Product Safety-Experimental Toxicology and Ecology (cont.)		state would be accounted for in the MMAD (GSD) data as well. However, the influence of these factors on the lung clearance of CNT materials is not known.	
	Is the use of respirable mass as a dose metric appropriate for estimating worker risks from inhalation to CNT and CNF?		
	3) NIOSH uses mass as a dose metric, which is a pragmatic approach. Basically, mass concentration can be converted into other metrics such as total fiber number concentration or total surface area concentration. An accurate conversion can, however, not be accomplished as assumptions have to be made for the length and diameter of a reference fibre and any information on the fibre size distribution is not possible.	3) NIOSH agrees that the heterogeneous structures of CNT limit the reliability of any CNT structure count estimates based on mass concentration and assumptions about standard (uniform) CNT dimensions. The need for research to develop more sensitive and specific dose metrics, including for possible cancer responses, has been described in Section 7.	3) The research recommendation to develop more sensitive measurement methods was revised to include CNT structure counts by electron microscopy (Section 7.1).

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Landsiedel, BASF Product Safety-Experimental Toxicology and Ecology (cont.)	**Are the sampling and analytical methods adequate to measure worker exposure to carbon nanotubes and nanofibers?** 4) NIOSH refers to the measurement method (5040), which was developed to measure diesel particulate matter as elemental carbon. The method is not validated for CNT or CNF. The method is disturbed by any confounding emission source releasing carbonaceous material. The distinction from the aerosol background concentration is thus cumbersome and not possible without additional sampling followed by subsequent, appropriate off-line analysis, as for example electron microscopy. However, morphological information is required to provide evidence of CNT release rather than exposure to the aerosol background. It is recommended to consider to (additionally) assess CNT by their catalyst content using metal or metal oxide residues as a tracer. This may be more specific and	4) See previous response on issues with metal surrogates (low metal content and possible lack of correlation with CNT/CNF mass, depending on metal and process). Initial assessments will require careful evaluation of EC background. Method 5040 is validated for EC measurement, which is what CNT and CNF are. In comparison, it is more appropriate for CNT/CNF assessment than for diesel particulate matter (DPM), which has variable EC content (e.g., 10-70%).	4) No revisions required.

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Landsiedel, BASF Product Safety-Experimental Toxicology and Ecology (cont.)	may also yield lower LOQs. **Are there additional relevant studies or methods that NIOSH should consider in developing the REL for CNT and CNF?** 5) NIOSH based its CIB on the LOQ of the best-available analytical methods. Calculated lung burdens were used to derive human equivalent doses. Both approaches are somewhat imperfect. Instead, no-observed-effect concentrations from inhalation studies present an alternative directly utilizing airborne concentrations and biological effects.	5) Agree that further evaluation of alternative methods and assumptions may be useful to examine the influence on the REL derivation.	5) NOAEL and LOAEL estimates are included in an evaluation of the influence of alternative methods and assumptions on the REL (Section A.6).

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West, American Chemistry Council	The Nanotechnology Panel of the American Chemistry Council (ACC) is pleased to offer comments on the National Institute for Occupational Safety and Health's (NIOSH) draft Current Intelligence Bulletin (CIB) *Occupational Exposure to Carbon Nanotubes and Nanofibers* (NIOSH Docket Number: NIOSH 161-A). The Panel supports the responsible development of nanotechnology and appreciates the considerable effort NIOSH has invested in the draft CIB. We have identified what we believe to be several important areas for improvement and clarification, and we urge NIOSH to consider our comments in the development of the final CIB.		
	1) The Panel supports NIOSH's effort to develop a recommended exposure limit (REL). Such guidelines contribute to the responsible development of carbon nanotube and nanofiber (CNT/F) technology, which will in turn lead to better acceptance by regulators, industrial users, and consumers. The Panel appreciates that NIOSH utilized a specific method (NIOSH 5040, *Diesel Particulate Matter*) for measuring exposure. However, it is important to recognize that 5040 has	1) As explained in previous responses, careful assessment of the environmental background is necessary to establish whether EC interferences are an issue in a given workplace. Soot from diesel engines and amorphous carbon are potential interferences, but cigarette smoke is mostly OC. NIOSH has routinely collected background samples and has applied electron microscopy to address this issue. See previous	1) Additional guidance has been added to Section 6 on the sampling and analysis of CNT and CNF.

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)	several limitations in the context of carbon nanomaterials, one of the most critical of which is that it cannot differentiate among different forms of particulate carbon that may be present in the work place. Method 5040 is designed to identify total carbon (TC) with an elemental carbon (EC) exposure marker. Thus, it would be sensitive to all elemental carbon (*e.g.*, soot, diesel exhaust, carbon black, cigarette smoke, etc.). During the February 3 public meeting to discuss and obtain comments on the draft CIB, NIOSH indicated that typical environmental background levels of EC are in the range of 0.5 $\mu g/m^3$, and thus any workplace exposure levels above the proposed REL could be attributed to CNT/F. However, other sources (*e.g.*, diesel particulate matter) may be present in the workplace and can contribute to EC measurements at or above the proposed REL, leading to overestimation of CNT/F presence.	comments on EC background.	
	2) While NIOSH recognizes this possibility, its referral to emission assessment guidance that suggests the use of direct-reading, real-time instrumentation to collect both pre- and post-process background samples, in addition to collection of "at source" filter-based air	2) See previous responses on environmental background. See also several papers by NIOSH researchers that are published or soon will be: Evans et al. 2010, Birch et al. 2011 (in press), and Dahm et al. 2011 [all	2) Guidance on sampling and analysis has been added to Section 6 of the CIB.

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)	samples for TEM/SEM and mass analysis, would be cost prohibitive and impractical for most employers. Thus, consideration should be given to proposed product-specific monitoring methods, for example those that use a "metallic marker" which is present as a trace quantity impurity in CNTs. Given that 5040 is not specific for type of EC, the CIB would be more useful if it included a discussion of key considerations in background monitoring, expected background levels, and approaches to differentiating sources of background particles from what might be reliably attributed to CNT/F. Any data NIOSH collected through real-time monitoring during the development of the draft CIB should be included in the CIB. Users will find such information extremely helpful.	cited in the CIB].	
	3) The Panel appreciates that NIOSH selected an REL that is within current analytical capabilities, such that the approach can actually be implemented. However, as NIOSH notes in the draft CIB, the proposed REL may require adjustment as alternative or improved methods become available. A more appropriate approach might be one that is more closely related metrically to measurements used to understand human	3) Results of animal research studies (inhalation, IP) with CNT indicate that adverse respiratory effects may be related to its physical (dimension) and chemical (durability) characteristics and that these characteristics are similar to that of asbestos. At this time there are no animal dose-response data that use CNT dimensions/concentration as the exposure metric for evaluating a	3) The discussion of possible health concerns (e.g., pulmonary cancer, mesothelioma) from exposure to CNT and CNF was expanded in Section 4 *Conclusions-Hazard and*

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)	health risks from CNT/F (*i.e.*, a fiber-based approach). The CIB acknowledges this issue in the Executive Summary. The Panel realizes that such an approach may not be available at this time, but we believe that the CIB could be strengthened with additional discussion around this issue, particularly its implications for the quantitative risk assessment and the recommended REL. 1 Page 7: "These data indicate that exposure metrics other than airborne mass concentration (*e.g.*, number concentration of CNT or CNF structures of specified dimensions) may be a better predictor of certain lung diseases (*e.g.*, fibrosis)." 2 See for example Tabet, L. et al. 2011. *Coating carbon nanotubes with a polystyrene-based polymer protects against pulmonary toxicity.* Particle and Fiber Toxicology 8:3.	biological response.	*Exposure Assessment*
	4) The Panel also believes that the CIB would be enhanced significantly by a discussion of the fact that not all CNT/F have the same characteristics with respect to purity, length, and other features that are known to influence hazard potential. Indeed, CNT/F can vary significantly in terms of their shape, size, structure, agglomeration state,	4) This information is already included in the CIB in several places. For example, in Chapter 1, a paragraph describes the types of CNT and CNF, including: "There is no single type of carbon nanotube. They may differ in shape, dimension, physical characteristics, surface coatings,	4) The recently published describing differences in response in lung and pleural tissue responses have been added to the

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)	physical-chemical properties, surface treatment, and functionalization. For this reason, the proposed REL may not be appropriate for all CNT/F. NIOSH should also acknowledge that CNT/F produced by different manufacturers may have different properties and characteristics that lend themselves to more sensitive and specific detection and quantification approaches.	chemical composition ('raw' CNT, which contain residual metal catalysts vs. 'purified' CNT, from which most of the metal catalysts have been removed) or surface functionalization. ..." The document describes the evidence that CNT containing certain metals (nickel, 26%) [Lam et al. 2004] and higher metal content (17.7% vs. 0.2% iron) are more cytotoxic in vitro and in vivo [Shvedova et al. 2003, 2008]. However, in experimental animal studies both unpurified and purified (low metal content) CNT are associated with early-onset and persistent pulmonary fibrosis and other adverse lung effects [Lam et al. 2004; Shvedova et al. 2005; 2008]. The study by Poland et al. [2008] is also cited, which shows that longer, fiber-like CNT structures elicit an inflammatory response after intraperitoneal injection, whereas shorter or more tangled structures do not at the same dose. Mercer et al. [2008] showed that more disperse CNT produced greater interstitial fibrosis, whereas the agglomerated CNT produced granulomas. All of	revised CIB [Mercer et al. 2011; Murphy et al. 2011]. The document has been reviewed for opportunities to better communicate this information concerning the role of CNT physical-chemical properties on the toxicity of CNT and the influence on the REL.

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)		these studies are cited in the CIB (including in Sections 3 and 4). Yet, the studies with sufficient dose-response data to identify or estimate effect levels for inflammation or fibrosis in animals and to extrapolate those doses to humans have shown that all CNTs studied thus far are associated with low mass concentrations over a working lifetime relative to OELs for other poorly soluble particles and relative to the LOQ for the analytical method to measure airoborne CNT [NIOSH method 5040].	
	5) There may be instances in which individual manufacturers have the ability to set their own health-protective REL based on hazard assessment specific to their material, and the CIB should incorporate such flexibility.	5) The CIB provides a reasonable assessment of the risk based on available toxicity data. Similar methods can be used by others should they chose to develop their own in-house OEL based on new data.	5) No revisions required.
	6) The issue of CNT/F variability has significant implications for the way NIOSH approached its risk assessment. NIOSH used a benchmark dose (BMD) estimate to evaluate dose-response, combining data	6) This comment is not correct. Data from several studies were not combined in the risk assessment. Instead, BMD(L) estimates were derived from the dose-response data	6) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)	from several studies. Doing so was an appropriate strategy given the disparity in the exposure concentrations. However, for the endpoint or biological metric, NIOSH selected an estimate of lung burden rather than a common biological endpoint such as inflammation. The assumed value of this approach was to allow NIOSH to include data from other studies that utilize routes of administration that directly enter the lung (*e.g.*, intratracheal instillation and oropharyngeal aspiration). Such an approach presents several issues that NIOSH or other regulatory bodies should weigh carefully:	of the individual animal studies (Appendix A). Also, NIOSH did not use an estimate of lung burden for the endpoint or biological metric. Instead, the administered lung burden (IT or PA studies) or estimated deposited or retained lung burden (inhalation studies) was the dose, and the reported pulmonary inflammatory or fibrotic lung responses were the biological response endpoints used in the risk assessment.	
	7) Lung burden is overestimated. Alveolar deposition fraction of 0.01 was estimated from a study using a single exposure concentration.[3] Furthermore, traditional values for deposition were used based on spherical particles. However, this approach may be incorrect. Modeling and experimental data demonstrate that alveolar deposition of particles less than 100 nm decreases as the size decreases to 1 nm.[4] Unless large agglomerates are expected, a lower lung deposition may be	7) This comment is not supported by the information available. NIOSH estimated the alveolar deposition faction of the inhaled CNT from the data on the airborne particle size distribution (MMAD and GSD) reported in the studies, using a spherical particle based lung dosimetry model (MPPD; CIIT and RIVM 2007] in the absence of a CNT-specific model. The model may underestimate lung burden given the reduced clearance of CNT compared	7) No specific changes concerning the deposition fraction estimates (as these were based on the measured MMAD and GSD) (Table A-2). Concerning evaluation of estimated lung doses, analyses were added in

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)	appropriate.	to low mass doses of other poorly soluble particles [Pauluhn 2010a,b; 2011], although NIOSH bounded the estimate with deposited (no clearance) and retained (normal clearance based on spherical particle estimates). Concerning alveolar deposition of structures from 1-100 nm, this likely had little influence on the deposition estimates since the reported MMADs of the CNT were in the 1-4 μm size range (Table A-2), which is well-predicted by the lung dosimetry models for spherical particles (although there is uncertainty in how shape may influence the deposition of the nonspherical CNT structures).	Section A.6.1.2 to compare the MPPD model-based lung dose estimates with those based on cobalt-tracer data in Pauluhn [2010a] and Ellinger-Ziegelbauer and Pauluhn [2009]. These analyses showed that the cobalt-tracer based CNT lung dose estimates were numerically between the estimated deposited and retained dose estimates from MPPD 2.0 [CIIT and RIVM 2007]. This is consistent with slower CNT clearance at low mass lung doses relative to other

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)			poorly soluble particles [Pauluhn 2010a,b].
	8) Lung burden produces dose-response curves that are not easily extrapolated. In fact, Figure A-1 for the two inhalation studies demonstrates that few lung doses are in the linear portion of the response curve. Rather, it would appear that the lung burden curves reflect only the unique responses of the rat (*i.e*, lung overload). Using airborne concentration and a continuous variable such as neutrophil number might better demonstrate a linear response along the entire dose response curve and be more amenable to BMD calculations. Such an approach was used by others with better results.[5]	8) Section A.2.1 discusses the limitations in the animal dose-response data, including the generally limited number of dose groups and the dose spacing. NIOSH selected the granulomatous inflammation, focal septal thickening, and fibrotic responses because these responses were observed to be persistent or progressive in the studies which included post-exposure observations. In contrast, the neutrophilic inflammation response was observed in some of the studies to decline after the end of exposure while the fibrosis persisted or progressed [Shvedova et al. 2005, 2008; Pauluhn 2010a], suggesting that neutrophilic inflammation may not be the best indicator of long-term lung response to CNT. Concerning rat lung overload, this response was observed at lower mass doses of CNT compared to other poorly soluble particles [Pauluhn 2010a,b], which	8) Section A.6 show that the BMD(L) estimates based on subchronic dose-response data are similar to the LOAEL and NOAEL estimates from those studies (Table A-12), and thus the use of BMDL estimates vs. NOAEL or LOAEL estimates had little influence on the REL.

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)		are relevant to equivalent workplace exposures and estimated lung doses. Studies in mice showed similar dose-response relationship to those in rats (Tables A-1 and A-3 through A-5).	
	9) Inclusion of data from studies using direct administration methods such as intratracheal instillation or pharyngeal aspiration is questionable. These methods intentionally bypass nasal deposition, which could be significant for particles less than 100 nm. Furthermore, while pulmonary distribution may be even across the lung lobes, this may not reflect airborne exposure. Making matters worse, one study used a single dose level, making calculation of a BMD impossible[6]	9) Concerning nasal deposition, it was lung responses that were being evaluated, and also the airborne CNT particles are larger than 100 nm (Table A-2). Concerning lung response by route of administration, a study comparing the rat lung responses from PA or inhalation showed qualitatively similar responses by both routes of administration [Shvedova et al. 2008]. The response from inhalation was approx. 4x greater for an estimated equivalent lung dose to that administered by PA, which is opposite from the findings expected for a bolus dose (e.g., with high dose IT). The reasons may be that the PA dose was a relatively low mass dose	9) No specific changes were made as this information is already explained in Appendix A.

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)		and was reasonably well distributed in the lungs [Shvedova et al. 2008]; also, the inhaled dose may have been more disperse, which has been shown to increase the interstitial fibrotic response [Mercer et al. 2008]. Moreover, the BMD(L) estimates based on the PA or IT doses were similar to those based on the subchronic inhalation studies (Tables A-3 through A-5). Finally, the single dose study was actually an inhalation exposure, and this study was included because it is the only inhalation data available for SWCNT; it is not impossible to calculate a BMD based on a single dose, although it does assume a linear dose-response relationship.	
	10) Extrapolation to a human-equivalent dose does not consider rodent-specific phenomenon that are not relevant for humans (*i.e.*, lung overload). In the extrapolation of effects in the rat to effects in humans, NIOSH assumes that equal responses to equivalent doses are expected.	10) As noted in the CIB (Appendix A), there is uncertainty in the assumption that humans will have an equal response to an estimated equivalent lung burden. However, by estimating the equivalent lung dose, the differences in rat and human	10) Section A.6 examines the influence of the methods and assumptions used in the NIOSH risk assessment,

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)	However, clearance mechanisms in the rat are more easily overloaded than in humans.[7] Thus, the effects in rats, especially those at high dose levels, clearly overestimate the effects in humans. Despite the fact that these weaknesses in the risk assessment were acknowledged in Section A.4.4, Strengths and Limitations, NIOSH seems to have given them insufficient weight. The Panel feels strongly that there is a need to explore these issues in more depth. Given the differences in occupational exposure levels (OEL) cited in Schulte et al., 2010[8] the Panel strongly recommends that instead of forging ahead on the basis of the current risk assessment, NIOSH would do better to convene a work group of parties whose OEL values were reported in the Schulte et al. paper to attempt to reach consensus on the appropriate approach, given the vast differences in the characteristics of commercially available CNT/F.	clearance kinetics are taken into account (uncertainty in these estimates is also discussed). This comment is not correct in suggesting that the rat dose levels are excessively high (by causing overloading) and therefore not relevant to humans. For example, the LOAEL in the subchronic inhalation studies was 0.1 mg/m^3 [Ma-Hock et al. 2009] or 0.4 mg/m^3 [Pauluhn 2010a], which are much lower than, for example, than the current graphite PEL of 5 mg/m^3. Also, the highest doses in the subchronic inhalation studies were 2.5 mg/m^3 [Ma-Hock et al. 2009] and 6 mg/m^3 [Pauluhn 2010a] – which are much lower than the doses associated with overloading to other poorly soluble particles (e.g., 100 mg/m^3 has been suggested as the MTD for studies of inhaled particles [Lewis et al. 1989]) – and which are relevant to permissible workplace exposures. The statement concerning rat and human lung clearance mechanisms is not entirely correct. Several studies in humans have shown that at low	including alternative estimates of human-equivalent dose based on interspecies normalization of CNT dose per alveolar macrophage cell volume (according to overload). This resulted in a factor of ~4 difference relative to the original alveolar surface area adjustment, but still resulted in low mass concentration (8-hr) TWA estimates over a working lifetime (e.g., relative to the LOQ of the measurement method) [NIOSH method 5040].

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)		mass lung doses, humans have greater retention than predicted from first-order clearance models (i.e., as predicted in rats at doses below overloading). See Section A.6.3 for a discussion of these studies.	
	11) While the Panel recognizes that Section 6, Recommendations, largely follows the traditional occupational hygiene hierarchy, we are concerned by NIOSH's recommendation to "substitute a non-hazardous or less hazardous material for CNT and CNF when feasible" (page 9). While we agree that the potential hazards of a material should be considered when evaluating that material for use, the nature and costs of CNT/F are such that substitution is not likely. Also, the statement implies that CNT/F can never be handled or used safely, regardless of risk management controls and protections. We request that NIOSH deleted it from the CIB. The Panel understands that the evaluation of potential risks from CNT/F is a matter of ongoing research, and the Panel sponsors and participates in such research. The Panel fully supports best practices to minimize exposures, implement risk management controls, and provide	11) Part of the hierarchy of control for potentially hazardous materials is the replacement of that substance with a non-hazardous or less hazardous substance. We acknowledge that the manufacturing and use of CNT and CNF is typically for a specific commercial application and thus can't easily be substituted with a different material. However, there are some indications that changes to the surface chemistry, size, and/or the functionalization of the CNT/CNF may alter its potential toxicity while not affecting its potential commercial application. Additional research is needed to confirm these preliminary findings.	11) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
West, American Chemistry Council (cont.)	appropriate guidance to manufacturers and users of CNT/F. We believe that potential risks can be managed effectively with the current state of knowledge, even while hazard and exposure evaluation continues.[9]		
	12) Finally, the Panel strongly recommends greater clarity and specificity around the types of personal protective equipment that should be used to limit exposure. Including more detail would significantly improve the practical utility of the CIB. It is our understanding that during the February 3 public meeting, NIOSH staff referenced practices in the pharmaceutical and cosmetic industries. Examples from those industries should be described in more detail if in fact NIOSH believes them to be best practices.	12) Guidance on the selection of clothing and gloves reflects the absence of appropriate research data on the potential dermal penetration of CNT and CNF. The selection of respiratory protection is consistent with both the NIOSH and OSHA requirements for selecting a respirator based on workplace concentrations of CNT and CNF	12) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA) Feitshans	**NIOSH must assert its statutory obligation to define and recommend measures that protect people from occupational exposure to "Recognized Hazards", consistent with international scientific consensus regarding emerging risks from Carbon Nanotubes (CNT) and Nanofibers:** 1) NIOSH has been timid in its assertion of the justification for the use of its powers regarding nanotechnology. Instead, NIOSH must be bold in its assertion of this statutory mission once the agency has discovered that there remain logical and clear risks to human health from the implementation of a new generation of technology, and concluded that although potentially very important through its diligent research and ongoing discourse with stakeholders, private sector partners and peer organizations in Europe, the United Kingdom, and international governance around the world. NIOSH has failed to so state in its Current Intelligence Bulletin, and has left the Preface blank in the draft that was provided to ISRA [suggested text for use by NIOSH in the ISRA submission].	1) NIOSH states its responsibility under the Occupational Safety and Health Act of 1970 [Public Law 91-596].	1) A Foreword was added to the CIB stating NIOSH authority under the Occupational Safety and Health Act to assure safe and healthful working conditions for every working person.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	**NIOSH Has the Statutory Obligation to Go Beyond Existing Data in Order to Generate New Research Protecting Public Health:** 1) It is not possible to understate the importance of medical surveillance in this context. Basic sound occupational medicine and industrial hygiene practices such as but not limited to: screening and sound, on-going and accessible medical care services for workers who face a variety of unquantified risks from novel nanotechnology exposures take on greater importance in light of uncertainty. Although it may be premature for NIOSH to recommend specific procedures for occupational exposure, in reality that baseline data must be collected and that infrastructure for such precautions must be encouraged to develop alongside the research and development of industrial and pharmaceutical applications of nanotechnology. To emphasize this statement, ISRA wishes to note that defining internationally accepted components of basic occupational health services for medical surveillance and future epidemiological studies typically should be	1) NIOSH agrees with the commenter's assessment.	1) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	considered as one of the top priorities for precautionary programs. In addition to any existing programs for worker health as may be created by the employer in compliance with existing occupational health and safety laws, it is recommended that people who have an occupational exposure to carbon nanotubes and nanofibers have regular screenings at least once a year, using the most recent accepted best practices to confirm the status of lung function after exposure to nanomaterials. **Synthesizing Precautionary Concerns with New Data Requires a Flexible Framework, In Partnership with Industry, Multinational Corporations, Foreign Governments, Research Institutions and Stakeholders from Novel Branches of Civil Society:** 1) ISRA endorses the approach suggested by Murashov and Howard, which offers an admixture of an array of ways to manage risk. Their six-prong approach to the management of occupational health risks in emerging technologies combines: qualitative risk assessment; the ability to adapt strategies and refine requirements; an appropriate level of precaution; global	1) NIOSH agrees with the commenter's recommendations on providing an array of risk management measures. The document provides many examples of minimizing the risk of exposure to CNT/CNF which are consistent with the hierarchy of control measures.	1) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	applicability; the ability to elicit voluntary cooperation by companies; and stakeholder involvement. This means creating new methods for risk communication; new paradigms for the awareness of risk; new concepts of the right to know and the implications for all society from exposure to workplace toxins-- for all people regardless of business size. **Specific comments regarding proposed language from NIOSH:** 1) Medical Screening and Surveillance The evidence summarized in this document leads to the conclusion that workers occupationally exposed to CNT and CNF may be at risk of adverse respiratory effects. These workers may benefit from inclusion in a medical screening program recommended as a prudent means to help protect their health" Comment: This is a platitude, not law. Any worker benefits once they have been included in a screening program! In addition to any existing programs for worker health as may be created by the employer in compliance with existing occupational health and safety laws, it is	1) NIOSH agrees with the commenter. Criteria are provided for the medical screening of workers potentially exposed to CNT and CNF.	1) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	recommended that people who have an occupational exposure to carbon nanotubes and nanofibers have regular screenings at least once a year, using the most recent accepted best practices to confirm the status of lung function after exposure to nanomaterials. **ISRA proposes the following language:**		
	1) Staff in charge of the medical surveillance program should be qualified in occupational medicine, or a certified public health specialist, who has dedicated at least thirty (30) hours per year of professional time to becoming conversant in the emerging risks to workers from nanotechnology and any or all attendant adverse health effects.	1) The suggested language does not add substantively to the information in the CIB, and "most recent accepted best practices" is likely to be text interpreted in different ways by different people.	1) No revisions required.
	2) Defining internationally accepted components of basic occupational health services for medical surveillance and future epidemiological studies typically should be considered as one of the top priorities for precautionary programs. In addition to any existing programs for worker health as may be created by the employer in compliance	2) Agree. Specific guidance is given on the medical screening of workers potentially exposed to CNT and CNF.	2) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	with existing occupational health and safety laws, it is recommended that people who have an occupational exposure to carbon nanotubes and nanofibers have regular screenings at least once a year, using the most recent accepted best practices to confirm the status of lung function after exposure to nanomaterials. 3) All secondary exposures of children (via worker exposures leading to offspring exposure or potentially intergenerational effects) should be identified and monitored. The epigenetics of environmental contaminants are currently of scientific interest and this area may expand to include effects in those exposed to CNTs/CNFs and other nanomaterials. Rationale In addition to the fact that staff must have very precisely specialized training in order to design and implement effective programs, the requirement of at least thirty hours per year for such development will provide an incentive that fosters new training programs that will integrate research into fieldwork.	3) Although the authors agree that the topic of "take home toxins" is important, we are currently challenged with understanding workplace exposures. A better understanding of CNT/CNF exposure assessment will be needed prior to monitoring children or others who may be secondarily exposed to these substances. Recommendations are given in the CIB for workers to shower and change clothing before leaving work; this practice is intended to eliminate "take-home contamination".	3) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	**The existing text makes sense when collecting baseline data but in the case of nanotechnology has no specific relevance:** A chest X-ray (All chest X-ray images should be interpreted by a NIOSH-certified B Reader using the standard International Classification of Radiographs of Pneumoconiosis [ILO 2000 or the most recent equivalent].) **ISRA proposes the following language:** 1) Until such time as NIOSH announces the approval or certification of nano-specific instruments that are reliable and replicable tests to measure the impact of CNTs on the individual worker, the medical surveillance program should make good faith efforts to capture accepted baseline data including but not limited to NIOSH-certified B Reader using the standard International Classification of Radiographs of Pneumoconiosis [ILO 2000 or the most recent equivalent], Rationale Without baseline data, it will not be possible to understand the long term impact of occupational exposure to carbon nanotubes. Such data cannot, however,	1) Changes to the requirements for CXR interpretation were suggested by another reviewer (see above); we agree that organ systems beyond the lungs may be target organs of concern after occupational exposure to CNT/CNF, however, clinical interpretation and classification of X-ray images may be required and should be conducted by a NIOSH-certified B reader using the standard International Classification of Radiographs of Pneumoconioses (ILO 2011 or the most recent equivalent) are recommended.	1) Clarification is provided on the interpretation of Chest X-rays.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	serve to replace more refined instruments once they will have been developed and approved or certified by NIOSH. Furthermore, lung function may prove to be less important than recent evidence about spleen and liver accumulation of nanomaterials and the pseudo-allergic response of mammals to nanomaterials is emerging as a potentially important facet of nano-exposures. Liver function measurements, spleen accumulation measurements and appropriate biomarkers of exposure may be conducted (e.g. serum levels thereof), according to Dr Michaela Kendall, University of Exeter [cited in response from ISRA] **Program oversight** Oversight of the medical surveillance program should be assigned to a qualified health care professional who is informed and knowledgeable about potential workplace exposures, routes of exposure, and potential health effects related to CNT and CNF. 1) *Comment: This is a platitude, not law.* Any worker benefits once they have been included in a screening program Furthermore, there is nothing new added to	1) See comment and response above.	1) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	the discourse to note that a qualified professional is aware of basic precepts of occupational medicine, NIOSH should suggest something precise regarding carbon black or MWCNTs or SWCNTS and recommend experts with expertise in this area. **Periodic evaluation of data and screening program** NIOSH wrote: "Confidentiality of worker's medical records should be enforced in accordance with all applicable regulations and guidelines" 1) ISRA Comment: Unfortunately this is a gross understatement of the employer obligations under a host of existing laws beyond the scope of OSH Act, but relevant in USA workplaces all the same. Even though NIOSH is not the enforcer, it behooves NIOSH to remind employers that there exist a host of fines and penalties under parallel USA law protecting individuals regarding their confidential medical information, even when such information is generated by the employer. Two such statutes leap to mind: The Americans With	1) The suggested changes go beyond the scope of the CIB.	1) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	Disabilites Act and the Health Insurance Portability and Accountability Act. Both laws have very severe penalties for any breach of patient confidentiality, even if such information is generated by an employer at the employer's own worksite. ISRA proposes the following language: Confidentiality of medical Information is governed by a wide variety of laws, including but not limited to: the Americans With Disabilities Act (ADA) and the Health Insurance Portability and Accountability Act (HIPAA). Each of these laws carry major penalties for violation of confidentiality, and therefore a prudent employer should consult with counsel before designing and implementing a medical program that plans to release information to third parties including release of information to staff within the employer's enterprise. **Worker training** This section eroneously omits description of worker rights under OSH act and International law. This section also neglects the needs of vulnerable populations, such as but not limited to workers of reproductive age and capability who may be sensitive to		

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	teratogenic or cytogenetic aspects of nanofibers, older workers who be sensitized due to cumulative or synergistic effects of exposure to nanomaterials across their lifetime, and subpopulations not discovered thusfar, who may develop particular sensitization to some but not all types of nanofibers and nanomaterials.		
	1) ISRA proposes the following language: Worker training programs must comply with existing law. Therefore, in addition to discussion of the best practices for the safe handling of carbon nanotubes, nanofibers and nanomaterials containing CNTs and CNFs, and a description of the possible long-term and acute health effects, each session of worker training, in order to be considered adequate, must include a review of the key elements of worker rights to information and to follow-up those rights under the OSHA Hazard Communication Standard (29 CFR 1900.1200), relevant USA statutes such as but not limited to the EPA Nanoscale Materials Stewardship Program and international treaties and agreements such as but not limited to	1) Additional guidance has been added on worker training and education.	1) Section 6.3 *Worker education and training* was added to the CIB and specifies that worker training and education should be consistent with the OSHA Hazard Communication standard and the Hazardous Waste Operation and Emergency Response standard.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	Globally Harmonized System of Classification and Labelling of Chemicals (GHS). **Recommendations for workers •** 1) NIOSH wrote this entire section in the second- person. There is no grammatical reason for this shift in tense there is nothing to suggest that only workers should participate in this section or that workers are not affected by other sections. NIOSH should write the entire list of recommendations in the same tense. Regarding substantive rights of workers under law that cannot be changed by NIOSH; see the discussion of worker rights and obligations that are settled law under OSH Act and several additional USA and international regulatory regimes, in DESIGNING AN EFFECTIVE OSHA COMPLIANCE PROGRAM (Westlaw). **ISRA proposes the following language:** 1) Workers have rights and duties. The right to be provided information about the hazards, safe handling and use of dangerous materials and have access to working safety equipment free of charge. Dr Kendall of ISRA an expert in nanoparticle exposure and nanotoxicology from the European	1) The sections entitled Recommendations for Employers and Recommendations for Workers are written in the same tense. 1) Chapter 6 *Recommendations* clearly defines the responsibility of the employer in providing a safe workplace as described in the Occupational Safety and Health Act. A responsibility of the employer is to inform all workers of the potential	1) No revisions required. 1) Section 6.3 *Worker education and training* was added to the document to emphasize the importance of

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	Centre of Environment and Human Health (University of Exeter, UK) recommends the following approach: Vulnerable groups such as pregnant women, the elderly and others identified in the literature should be informed of the potential hazard. The right to be involved in the management and supervision of OSH measures at the workplace includes the right to be organized in a representative group that can select delegates to OSH committees; the right to regularly scheduled updates concerning information and training on hazards/risks associated to their work and the measures to prevent them; The right to be offered protection against retaliation or untoward consequences when they take action to implement those measures; The right to refuse hazardous work in case of imminent serious danger to their health and life, without retaliation.	hazards in the workplace and to provide the necessary training and education to workers so that they are able to recognize those hazards and be able to appropriately use all safety measures.	establishing an education and training program for workers.
	2) Workers must: • Follow safety and health rules when using protective equipment; Participate in safety and health training and awareness-raising activities; Cooperate with their employer to implement safety and health measures; Inform to their direct supervisor if they withdraw from an imminent and	2) The recommendations given in the Executive Summary and Section 6 define the responsibilities of workers as they pertain to workplace safety and health.	2) Section 6 *Recommendations* was expanded and provides additional guidance to employers and workers on their

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	serious danger to their health and life, and the reasons for it. **Current exposure measurement methods and challenges in measuring workplace exposures to carbon nanotubes and nanofibers;** NIOSH wrote: [21] "Given the low density and small diameters of individual CNT and CNF structures, a mass-based sampling method may not be sufficiently sensitive to detect all CNT and CNF structures in the air at low mass concentrations. Thus, research is needed to determine the most sensitive dose metrics for estimating various health risks of exposures to CNT and CNF and to develop sampling and analytical methods corresponding to those metrics. CNT are widely accepted to be durable due to the process they undergo during synthesis in which contaminating catalytic metals are frequently removed either by high temperature vaporization or acid treatment. Neither treatment is found to significantly alter the physical structure of CNT. "		responsibility to ensure a safe and healthful workplace.

[21] **Draft Document for Public Review and Comment** NIOSH Current Intelligence Bulletin: *Occupational Exposure to Carbon Nanotubes and Nanofibers* [PDF - 804KB] Docket Number NIOSH-161-A subject to hearing for public comments, February 3, 2011 9:00am—4:00pm Millennium Hotel Cincinnati, 150 West 5th Street, Cincinnati, OH 45202

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	1) Dr. Michaela Kendall an expert in nanoparticle exposure and nanotoxicology from the European Centre of Environment and Human Health (University of Exeter, UK) recommends the following approach: Workplace exposure measurement, by either stationary or personal measurement techniques, is a crucial part of worker protection and critical in the case of CNTs/CNFs. Mass based measurements will not suffice for nanomaterials and this is explained variously in the literature. In the absence of a viable real-time worksite-based detection/measurement technique capable of such measurement (clearly a scientific challenge today), we recommend NIOSH identify and publish a detailed viable CNT/CNF detection and quantification method for workplaces, whereby a workplace must install/implement such a method on worksites with potential CNT/CNF exposures within 60 days of the NIOSH notice.	1) As noted in response to comments from other reviewers, the dose-response relationship observed in animal studies was based on the respirable mass of CNT and CNF administered to animals. This dose metric was the best available data for conducting a quantitative risk analysis and the development of an occupational exposure limit. NIOSH acknowledges that the monitoring of workplace exposures to CNT and CNF should also incorporate the collection of airborne samples for electron microscopy analysis in which tube/fiber count can be performed to determine a tube/fiber concentration. These data may prove to be useful should ongoing animal research demonstrate that a tube/fiber concentration to be a better dose metric of adverse respiratory effects.	1) No revisions required.
	2) Dr. Kendall recommends a long-term, possibly low volume gaseous collection method which deposits CNT/CNFs onto a	2) As noted in the response to the previous comment, NIOSH acknowledges that a dose metric	2) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	substrate which may be followed by a microscopic counting procedure (preferably TEM [transmission electron microscopy] or AFM [atomic force microscopy]), with parallels to the asbestos fiber identification method. If such a method cannot be identified or the scientific community do not reach consensus on an accepted method, a desk-based risk and hazard assessment of each CNT/CNF should be conducted which in particular focuses on the length of the CNT/CNF and propensity of the particular CNT/CNF of interest to occur as single fibers or small agglomerates that are capable of lung penetration. Workers/workplaces must be monitored where long CNT/CNFs with propensity to disperse as single fibers are prevalent. Worker protection from CNT/CNF exposure must be carefully considered and this may include respirators, gloves, clothing, emergency clean-up facilities, etc, depending on the classification of the CNT/CNF type.	similar to that used for asbestos and other hazardous fibers might be more protective of adverse health effects. Currently, dose response data from animal studies are lacking for developing an occupational exposure limit based on a tube/fiber concentration. Risk management recommendations are given in the CIB for protecting workers from exposure to CNT and CNF.	
	3) By contrast, the Swiss government-based insurance agency, Suva defined in the 2011-OEL edition guidance values for carbon nano-tubes and -fibres that correspond to those for asbestos (definition	3) See response to previous comment. Data are currently lacking on developing a REL based on a tube/fiber concentration.	3) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	of fibre dimensions concerned and also concentration). I.e. it does not provide a mass-limit for all CNT (NIOSH), but a number limit for those believed to be the most hazardous.[22] The SUVA approach assumes that CNTs and CNFs that have the same dimensions as hazardous asbestos fibers pose a similar risk as asbestos. Shorter CNTs and CNFs are not treated differently than normal particles. The mechanistic idea of CNTs and CNFs being similar to asbestos is supported by animal experiments. The problem is that for the animal studies, the fibres were prepared to be "nicely individualized". However, in real world situations, CNTs are very often big bundles consisting of dozens to hundreds of fibres with a diameter of a few micrometers. This poses a problem on how to count them. Research only started about how to correctly count fibers contained in these bundles and how easily fibers can be		

[22] https://wwwepp1.suva.ch/webshop/4D/4D212E53C9BB06F0E10080000A630358.pdf Aufgrund der aktuellen Datenlage können folgende Richtwerte formuliert werden: ..Kohlenstoffnanoröhrchen und -fasern (Länge über 5 µm, Durchmesser weniger als 3 µm, Länge - zu Durchmesser - Verhältnis von über 3:1): 0.01 Fasern/ml; dieser Wert entspricht dem Grenzwert für lungengängige Asbestfasern.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	released from these bundles in-vivo over many years. The NIOSH publication has the strength that it proposes an overall strategy for an initial guidance towards healthy working conditions until fully validated sampling and analytical methods are developed *(page 8 NIOSH doc)*. The recommendations provide a comprehensive guidance to employers and workers. However, it does not address the question of dimension of CNTs and CNFs. This might be considered as a weakness because in worst-case situations (as outlined above), workers' health might be at risk even though all recommendations were followed.		
	4) In conclusion, the NIOSH and the Suva approaches each raise methodological questions. The challenge that might reduce the applicability of the NIOSH approach is that one REL would apply to all CNTs, i.e. both, relatively short ones and long ones with similar dimensions as asbestos. By contrast, the challenge of the SUVA approach is that there is no validated sampling method for CNTs and CNFs and that the risk of short CNT/CNFs are not at all addressed by their guidance values.	4) See response to previous comments. Precise dimensions of CNT and CNF that might pose a respiratory hazard are lacking. In fact, different dimensions may be related to different health outcomes (e.g., lung cancer, mesothelioma, fibrosis). Also, it appears from the animal studies that agglomerated CNT plays a role in the development of fibrosis. While there are similarities in the physical characteristics of CNT/CNF and	4) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Feitshans, International Safety Resources Association (ISRA)(cont.)	ISRA therefore recommends that NIOSH include the CNT and CNF dimensions into the recommendations. One possible approach could be to ask for regular visualization and documentation of airborne particle samples in situations where CNTs and CNFs of critical dimensions are being handled, and to propose increased vigilance if they are found to become airborne independent of whether this is in the form of individual fibers or as bundles.	asbestos, results from some *in vitro* and *in vivo* studies indicate differences in their toxicity potential.	

Commenter	Summary of Comments Received	Response	Changes to CIB
Lippy, The Lippy Group	I would like to congratulate NIOSH for taking the lead among federal agencies in trying to quantify the health risks posed by carbon nanotubes and nanofibers and set a Recommended Exposure Limit. Having had the opportunity to follow the efforts of the NEHI working group of federal agencies, I have been impressed with the commitment to focus the research on the health implications of engineered nanoparticles where the most pressing questions still exist. Unfortunately, there are many remaining. This NIOSH Current Intelligence Bulletin is comprehensive and extremely well written. It stands as a major addition to the international literature on the health and safety risks posed to workers by carbon nanotubes and nanofibers. Not only is the research strong, but the entire NIOSH nanotechnology team is readily accessible to others in the field, starting with Dr. Charles Geraci. I would make the following recommendations on strengthening the document:		

Commenter	Summary of Comments Received	Response	Changes to CIB
Lippy, The Lippy Group (cont.)	1) Provide more consideration of workers other than those directly involved in manufacturing the nanotubes or incorporating them into products. There are many construction workers who will be handling products that contain nanotubes that currently don't need any labeling. The presence of these materials in the waste stream will expose many other workers.	1) Although reported workplace exposure data for CNT and CNF have been limited to laboratory and pilot manufacturing facilities, NIOSH acknowledges that exposure can occur during the life cycle of these materials. The recommendations given in the CIB pertain to all workers who have the potential to be exposed to CNT or CNF.	1) No revisions required.
	2) Consider adding stronger conditional language about the limitation of using a mass-based REL. The current document correctly points out that the TEM/SEM counting protocols for carbon nanotubes are not sufficiently standardized, but the limitations to a mass-based approached argues for more clearly identifying the preference for a counting protocol. One is under develop by ASTM. The great fear is that a mass-based REL will remain due to regulatory inertia.	2) NIOSH has attempted to describe the limitations of using a respirable mass REL for CNT and CNF. Sample collection for electron microscopy analysis for tube/fiber count and concentration is also recommended.	2) No revisions required.
	3) Give worker training more focus. Currently, the current language and location within the section on medical	3) The CIB has been revised to emphasize the importance of worker education and training.	3) Section 6.3 *Worker education and training* has

Commenter	Summary of Comments Received	Response	Changes to CIB
Lippy, The Lippy Group (cont.)	surveillance, it feels like an older NIOSH Criteria document. Kristen Kulinowski and I have created a guidance of training workers through the National Institute of Environmental Health Sciences that has gotten excellent and substantial review by NIOSH. It should at least be noted.		been added to the CIB. Requirements specified in the OSHA Hazard Communication standard and the Hazardous Waste Operation and Emergency Response standard are recommended. The guidance described by Kulinowski and Lippy [2010] are also recommended.
	4) More strongly address the woeful nature of Material Safety Data Sheets for carbon nanotubes.	4) Recommendation added to CIB on what information should be included in an MSDS for CNT and CNF	4) Executive Summary and Chapter 6 *Recommendations* contain language stating that information contained in the CIB should be used in preparing

Commenter	Summary of Comments Received	Response	Changes to CIB
Lippy, The Lippy Group (cont.)	5) Consider adding warning language to all nanomaterials so workers understand what is there.	5) Recommendations for labeling added.	an MSDS 5) Recommendation was added to follow the OSHA Hazard Communication Standard which requires specific education and training of workers including requirements for the labeling of materials and posting of warning signs regarding the hazard potential of the material.

Commenter	Summary of Comments Received	Response	Changes to CIB
Challis, Canadian Auto Worker's Union Local Environment Representative	Excellent document! I agree with the recommendations except for 7ug/m^3. Exposure limits should be set at 0. History has demonstrated that this is the only acceptable way of protecting workers and their families.		
	1) Also the recommendations appear to be aimed at production workers [those that manufacture] however there are thousands of other workers that could be exposed to CNTs through added value manufacturing, repair and recovery and disposal. Education of the work force is then necessary to prevent unintended exposure.	1) Most of the reported workplace exposure data pertains to laboratory and pilot manufacturing facilities. The CIB states that the potential for exposure exists throughout the life cycle of the material. The recommendations contained in the CIB apply to all workers potentially exposed to CNT and CNF.	1) No revisions required.
	2) The next question to be asked is what effect/affect will CNTs have on the consumer? History tells us that consumers were adversely affected by asbestos. Today's knowledge and experience lays open the possibility of legal claims on manufactures and governments and everyone involved in setting exposure limits. Just because 7ug/m^3 is the lowest detectable amount does not justify that being the recommended exposure level. This document recognizes that damage does	2) NIOSH is recommending a lower REL in the final version of the CIB due to improvement in the ability to measure airborne concentrations to CNT and CNF. These improvements in sampling and analysis are described in the CIB. With a lower REL the residual risk at the REL for developing fibrosis over a working lifetime has been reduced. With other risk management practices recommended (e.g., PPE, medical	2) A lower REL for CNT and CNF is incorporated into the CIB along with recommendations (6.1 *Exposure assessment*) on how to optimize the evaluation of worker exposures.

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Challis, Canadian Auto Worker's Union Local Environment Representative (cont.)	occur at that exposure level but workers are expected to survive past their expected work life. How healthy will they be after retirement? How will their health impact their family?	surveillance/monitoring) the risk for developing fibrosis should be minimal.	
	3) History also demonstrated that 0 exposure led manufacturers to a higher efficiency and thus a higher profit when they reduced their employee's exposure to PVC to 0! Easy, readily attainable, lowest detectable are escape and excuse words that should never be used when discussing worker or even consumer health.	3) A recommendation is made that airborne exposures should be reduced as low as possible below the REL. This recommendation reflects the fact that some residual risk exists at the REL. In some workplaces this might result in zero exposure whereas other workplaces might not be able to eliminate exposure.	3) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Goldberg, Aerospace Industries Association (AIA)	AIA believes that industry and government should be guided by the best available science and established medical practice that provides the most effective opportunity to protect human health based on actionable data. In the absence of data, AIA recommends developing policies that are protective of human health but that do not stifle the development of materials and technologies that may revolutionize industries and create great economic benefit to the United States. It is in this context that AIA offers the following comments. **<u>Medical Screening and Surveillance</u>** 1) In the draft document, NIOSH recommends B-reading of films for a pneumoconiosis that has not been identified and does not exist in a clinical sense to date. AIA believes a more effective approach would be to require a Board Certified Radiologist or Pulmonologist review the films, since they are trained to recognize findings of lung disease of many types. This would	1) We agree with this point of requiring a review of X-ray images by a board certified radiologist or pulmonologist. However, there may be a bases for having the images evaluated by a NIOSH-certified B reader.	1) Revisions to Section 6.7.3 *Screening elements* and in the Executive Summary. Revised wording: "All baseline chest X-ray images

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Goldberg, Aerospace Industries Association (AIA) (cont.)	allow for recognition of subtle findings that might not be specified in any known occupational lung disease/pneumoconiosis.		should be clinically interpreted by a board eligible/certified radiologist or other physician with appropriate expertise, such as a board eligible/certified pulmonologist. Periodic follow up chest X-rays may be considered, but there is currently insufficient evidence to evaluate effectiveness. However, if periodic follow up is obtained, clinical interpretation and classification of the images by a NIOSH-certified B reader using the standard

Commenter	Summary of Comments Received	Response	Changes to CIB
Goldberg, Aerospace Industries Association (AIA) (cont.)			International Classification of Radiographs of Pneumoconioses (ILO 2011 or the most recent equivalent) are recommended".
	2) Since there is not a recognized human disease from carbon nanotube (CNT) or carbon nanofiber (CNF) exposure, there is no rationale for comparing films from workers exposed to CNT/CNF with the ILO guidelines and films. There is no evidence that these guidelines and films will be beneficial in distinguishing lung disease resulting from CNT/CNF exposure.	2) See above comment and response on the same issue.	2) Revisions made to Section 6.7.3.
	3) Finally, the ILO/B-reader requirement places additional burden on employers to find radiology facilities that do not use digital radiography. This may be a challenge since most facilities are switching to digital radiography. Allowing employers to send employees for digital radiography	3) See earlier comment and response on evaluating chest X-ray images and when the images should be evaluated by a NIOSH-certified B reader.	3) Revisions made to Section 6.7.3.

Commenter	Summary of Comments Received	Response	Changes to CIB
Goldberg, Aerospace Industries Association (AIA) (cont.)	will promote compliance with this guidance, while requiring B-reading of film x-rays will not. **<u>Sampling Methodology</u>** AIA believes that the NIOSH recommendation to establish a 7µg/m^3 REL based on NIOSH Method 5040 suffers from two significant shortcomings.		
	1) First, Method 5040 is not specific for CNT or CNF, but rather is a test for elemental carbon. Depending on this method alone will result in an overestimation of exposure. The discrepancy between CNT/CNF and measured elemental carbon cannot be estimated, but instead will vary according to the materials, tasks and the general operating conditions in which the tasks are performed.	1) See previous responses on potential interferences and background assessments. Method 5040 is a useful screening tool, especially in combination with electron microscopy.	1) Section 6 .1 provides additional guidance on sampling and analysis of CNT and CNF.
	2) Also, NIOSH indicates *7ug/m^3* is at the upper Limit of Quantitation (LOQ). However, LOQ is dependent on a number of factors such as sample volume, filter size and sample portion analyzed. NIOSH suggests that the following sample volumes based on flow rate and sample period are	2) The LOD and LOQ depend on filter size and flow rate as described in the revised CIB. Method 5040 has been optimized so that it's now possible to obtain an LOQ of 1 µg/m^3.	2) Section 6.1 provides additional guidance on sampling and analysis of CNT and CNF.

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Goldberg, Aerospace Industries Association (AIA) (cont.)	necessary to quantify the elemental carbon that is used as a surrogate for CNT/CNF. Examples of sampling periods and flow rates (Lpm= liters per minute) required for collection of recommended air volumes (green area below) are listed in the following table:		
	3) If the tasks of interest are less than four hours at the typical sampling flow rate of 2 liters per minute, it will be unlikely that the an accurate exposure assessment would be possible. At four liters per minute, a task would have to take place for at least 2 hours in order to obtain a useful sample.	3) The time required for a sample loading at the mass LOQ depends entirely on the air concentration (i.e., filter mass loading). The table in the CIB simply provides examples.	3) Section 6.1 provides additional guidance on the sampling and analysis of CNT and CNF.
	<u>Recommended Exposure Limit (REL)</u> 1) The animal studies used to derive the REL suffer from significant limitations. As NIOSH points out in Section 5 page 41 "There remains some uncertainty in extrapolating respiratory effects observed in short-term or subchronic animal studies to the potential for causing chronic respiratory effects in humans. Based on currently available data, it is difficult to assess the	1) NIOSH agrees that there is uncertainty in extrapolating the animal short-term or subchronic studies to estimate risk in humans. However, suchronic inhalation studies are typically used in risk assessment in the absence of chronic studies. The findings from the short-term studies were consistent with	1) No specific changes were made in response to this comment. However, additional references on the workplace assessment of

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Goldberg, Aerospace Industries Association (AIA) (cont.)	relative potency of the various types of CNT and CNF because there has been limited systematic study of multiple types of CNT and CNF using the same study design." And, as pointed out earlier comments, the air monitoring method is of limited value in measuring exposure to CNT and CNF. On page 42 of Section 5 NIOSH states "Measurement results from NIOSH Method 5040 should provide a reasonable estimate of worker's respirable exposure to CNT and CNF .... when the predominant workplace exposure to EC material is CNT or CNF. For these reasons AIA believes that NIOSH should set a REL only when it has sufficient data (and adequate sampling/analytical methodology) to set a limit that is protective of worker health. **Recommendations** In general terms, the recommendations presented (beginning on page 8) are sensible and already in place in many AIA member companies. However, AIA would like to respond to some specific recommendations below: 1) **NIOSH Recommendation**: When possible,	those from the subchronic studies (Appendix A). Although these studies showed variability in animal responses to the various types of CNT or CNF across the studies (which also differed in study design, animal species, and response endpoints), all studies resulted estimates of low mass concentration over a working lifetime (Tables A-3 through A-5). Given that workers are currently producing and using CNT, NIOSH has determined that it is prudent to use the best available data to develop an REL and other guidance to protect workers. 1) Consistent with the hierarchy of	CNT and CNF were added in which Method 5040 was used. 1) No revisions

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Goldberg, Aerospace Industries Association (AIA) (cont.)	substitute a non-hazardous or less hazardous material for CNT and CNF when feasible. When substitution is not possible, use engineering controls as the primary method for minimizing worker exposure to CNT and CNF. **AIA Response**: For many aerospace applications the CNT and CNF used by AIA members are the only materials available for the specific use required and it is not feasible to substitute a non-hazardous or less hazardous material. AIA agrees that engineering controls should be the primary method for minimizing worker exposure.	control measures for potentially hazardous materials is the substitution with a non-hazardous or less hazardous substance. We acknowledge that the manufacturing and use of CNT and CNF is for a specific commercial use and thus can't easily be substituted with a different material. However, there are some indications that by changing the surface chemistry, size, and/or the functionalization of the CNT/CNF it may decrease its toxicity while not affecting its potential commercial application. Additional research is needed to confirm these preliminary findings.	required.
	2) **NIOSH Recommendation**: Provide facilities for showering and changing clothes with separate facilities for storage of non-work clothing, to prevent the inadvertent cross-contamination of nonwork areas (including take-home contamination). **AIA Response**: Providing facilities for showering and changing clothes may not be possible at some sites. AIA agrees that	2) NIOSH recommends that separate facilities for showering and changing clothes is important for preventing contamination of non-work sites and reducing the likelihood of "take-home contamination" While it might not be possible to have separate showering facilities at all work sites, NIOSH believes these recommendations are good public health practice.	2) No revisions required.

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Goldberg, Aerospace Industries Association (AIA) (cont.)	precautions need to be taken to prevent cross-contamination and believes this can be accomplished through engineering controls.		
	3) **NIOSH Recommendation**: Use light-colored gloves, lab coats, and work bench surfaces to facilitate observation of contamination by dark CNT and CNF. **AIA Response**: Observation of contamination by dark CNT and CNF will be virtually impossible unless there is a large amount of the contaminate present (for example, if suspended in a drop of liquid).	3) The visual appearance of contamination (CNT and/or other material) on clothing and work surfaces can serve as a preliminary qualitative means for assessing whether in- place engineering controls and/or work practices are working properly.	3) No revisions required.
	1. **Other Comments** AIA offers the following comments on the sections identified below:		
	1.1 Worker participation (p. 10) AIA believes that medical screening is an important issue. However, line item b) assumes that a work area is constantly being monitored and that the process would	1.1 The reviewer makes an important point. The guidance in the CIB is intended to allow for quantitative determinations for inclusion in the screening program (1.1.1.a and 6.7.1 1st bullet), but also for qualitative	1.1 Revisions made to Section 6.7.1 *Worker participation* and Executive Summary. 2nd

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Goldberg Aerospace Industries Association (AIA) (cont.)	observe an excursion in concentrations in excess of the REL. The methodology specified in method 5040 is not real time and AIA questions its validity for measuring and monitoring CNTs and CNFs.	(1.1.1.b and 6.7.1 2nd bullet). The test for this latter determination was not intended to require quantitative assessment.	bullet to read as: "Workers in areas or in jobs who are qualitatively determined (by the person charged with program oversight) to have the potential for exposure to intermittent elevated airborne concentrations, of CNT or CNF (for example, workers involved in the transfer, weighing, blending, or mixing of bulk CNT or CNF, or the cutting, grinding, or drilling of composite materials containing CNT or CNF, or workers in areas where such activities are carried out by

Commenter	Summary of Comments Received	Response	Changes to CIB
Goldberg Aerospace Industries Association (AIA) (cont.)			others and are at risk of being exposed.
	6.2 Engineering controls (p. 48) AIA supports this section. Engineering controls will be critical, especially if appropriate monitoring and sampling methods are still being developed.	6.2 Agree. NIOSH believes that the use of engineering controls (LEV, containment) can reduce exposures below the REL.	6.2 No revisions required. Tables 6.6 and 6.7 added on engineering controls.
	6.4-6.6 AIA supports the use of personal protective clothing and respirators if engineering controls are proven not to be sufficient to protect employee health.	6.4-6.6 Agree.	6.4-6.6 Tables 6.6 and 6.7 added on possible engineering controls that could be used to reduce CNT and CNF workplace exposures.
	Conclusion AIA and its members look forward to working with NIOSH to contribute to the orderly, safe and environmentally responsible development of nanotechnology in the United States.		

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Kojola, AFL-CIO	The AFL-CIO appreciates the opportunity to provide comments on the draft Current Intelligence Bulletin, "Occupational Exposure to Carbon Nanotubes and Nanofibers". We are quite pleased that NIOSH has initiated this document. This is a very important and welcomed effort by NIOSH to identify two engineered nanomaterials that pose a risk to exposed workers and to recommend exposure controls and other measures designed to protect workers. We fully support this initiative and recommend that NIOSH finalize this CIB as quickly as possible so that it can be implemented in workplaces where exposures to carbon nanotubes (CNT) and nanofibers (CNF) exist. Overall, we believe this draft CIB is a sound and scientifically well reasoned document that reflects our current understanding of the scientific literature regarding carbon nanotubes and nanofibers. We have several comments and suggestions below that we believe, if incorporated into the final version, will enhance its strength and effectiveness in protecting workers.		
	1) As the executive summary correctly states in its lead sentence, there are no human	1) Executive Summary has been revised.	1) The first sentence of the Executive

Commenter	Summary of Comments Received	Response	Changes to CIB
Kojola, AFL-CIO (cont.)	studies that provide evidence of adverse health effects. However, there exists ample evidence from animal studies that these substances can produce serious adverse consequences following exposure. That animal evidence alone is sufficient for NIOSH to issue this CIB. While it is important to mention the absence of human evidence, NIOSH should not lead with such a statement because it undercuts both the rationale for issuing this CIB and the importance of taking precautionary action in the workplace to protect workers based on the evidence we have on hand at this point in time. **Risk Assessment and Recommended Exposure Limit (REL)** 1) The CIB employs well established health risk assessment methodology using animal data to assess risk to exposed humans that form the basis for the NIOSH recommended exposure limit (REL) of 7 $\mu g/m^3$ elemental carbon. We believe this approach is appropriate at the present time given the limitation in our current understanding of the health consequences in animals and the REL, which is set at the current upper limit of quantitation (LOQ) of	1) The REL has been lowered to 1 $\mu g/m^3$ which reflects improvements in the sampling and analysis of CNT and CNF. The REL is at a lower LOQ of Method 5040.	Summary was revised to indicate evidence of adverse respiratory effects in animals exposed to CNT and CNF. 1) The REL has been revised from the public review draft document. The REL has been established at the optimal LOQ of Method 5040 because of improvements in sampling and

Commenter	Summary of Comments Received	Response	Changes to CIB
Kojola, AFL-CIO (cont.)	the existing mass-based analytical method for assessing exposure.		analysis. See Section 6.
	2) Substantial risk to human health remains at the REL, however. While we recognize this remaining substantial risk, we support the REL as a provisional limit. We would urge NIOSH to add some discussion to the CIB on why this REL ought to be considered "provisional". That discussion would cover the significant risk at the REL, the use and limitations of using mass per volume exposure metrics for engineered nanomaterials, other exposure metrics and analytical methods that may be more appropriate for carbon nanotubes and nanofibers (particles or fibers per volume, surface area, influence of metals etc.), and the absence of chronic animal inhalation exposure studies.	2) NIOSH has stated in the CIB that the REL for CNT and CNF should be used while ongoing research is conducted to determine whether a different exposure metric should be used for protecting worker's health. Also discussed (Chapter 7) are the research needs to develop more sensitive and specific sampling and analytical methods for CNT including use of other metrics besides mass; animal dose-response data based on other dose metrics including CNT number concentration of specific types and sizes of structures; and standard electron microscopy methods for CNT structure counting; as well as the need for chronic studies.	2) The research need in Section 7.1 to develop more sensitive measurement methods has been revised to include CNT count metrics by electron microscopy and identification of the structures of greatest toxicological concern.
	3) We would further urge NIOSH to strongly recommend that a vigorous research effort be undertaken in the critical areas that intersect with developing a protective REL. That research would include determining	3) Agree.	3) Section 6.1.1 *Exposure monitoring program* was added to the CIB

Commenter	Summary of Comments Received	Response	Changes to CIB
Kojola, AFL-CIO (cont.)	the most appropriate exposure metric, improving the analytical method(s) for assessing exposure, determining the most sensitive exposure metric for expressing adverse health consequences, and additional animal toxicology studies that should be conducted. We would hope, with advances in new research that NIOSH would commit to quickly revisit this CIB and issue a revised REL that more adequately protects workers as new evidence warrants.		to describe how to optimize sample collection and analysis using Method 5040. Information is provided in Chapter 5 *CNT Risk Assessment and Recommended Exposure Limit* describing the level of risk at the REL.
	4) Finally, because there is significant risk to workers at the proposed REL, NIOSH must emphasize in the CIB that employers must implement control measures that keep exposures well below that of the REL. The REL must not be viewed as some bright line to be achieved -instead, employers should seek to keep exposures as low as possible.	4) Agree. NIOSH recommends in the CIB that exposures should be reduced as low as feasible below the REL to prevent fibrosis and lower the risk for other adverse respiratory effects.	4) Section 7 *Research Needs* lists the types of research that are needed to provide better risk management recommendations including a REL.
	Worker Training		
	5) Adequate and effective worker training is an essential component of any	5) Agree	5) Section 6.3 *Worker*

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Kojola, AFL-CIO (cont.)	comprehensive effort to protect workers from hazards in the workplace. We believe the training elements of the draft CIB needs to be reorganized and expanded. In the draft CIB, a very limited amount of worker training language appears as one element in the medical screening and surveillance section (6.6) of the recommendations chapter (Chapter 6). In our view, the worker training element of the CIB needs to exist as a stand-alone recommendation within Chapter 6 – placing it in the medical screening section implies that training would only be provided to those workers who are included in the screening program. In our view, this is inappropriate -all workers who are potentially exposed to CNT and CNF must receive training and not just those included in the medical screening efforts of the employer. The purpose of training is to engage those who are potentially exposed so that those workers are aware of the risks resulting from exposure and the measures that are being used to control exposure and reduce risk. Only a separate section on training in the recommendations chapter will achieve this objective and we urge NIOSH to adopt this suggested change in its final CIB.		*education and training* has been added to the document to emphasize the importance of educating and training workers on the hazards of the materials and steps to be taken to protect themselves. Reference is made to the OSHA Hazard Communication standard and the Hazardous Waste Operation and Emergency Response standard as guidance on establishing requirements for an education and training program. The guidance prepared by

Commenter	Summary of Comments Received	Response	Changes to CIB
Kojola, AFL-CIO (cont.)	At a minimum, the CIB should recommend that the stand-alone worker training section identify a comprehensive set of elements that need to be included in a worker training program. Those elements should include, at a minimum, the following topics: (a) hazards. risks and routes of exposure of CNT and CNF; (b) operations/materials/processes/tasks where CNT and CNT are present and where potential exposure exists; (c) exposure assessment strategy and NIOSH REL; (d) role and effective use of exposure control measures, including engineering. workpractice, and PPE measures; (e) emergency/process upset/clean-up procedures; (f) objectives and procedures of the medical screening and surveillance program; and (g) Importance of handwashing, showering and changing clothes. **Medical Screening and Surveillance** We applaud NIOSH for including a medical screening and surveillance in this CIB. The AFL-CIO, along with other labor and environmental organizations, has long		Kulinowski and Lippy [2010] on workers exposed to nanomaterials was also cited.

Commenter	Summary of Comments Received	Response	Changes to CIB
Kojola, AFL-CIO (cont.)	argued in support of establishing medical screening for workers potentially exposed to engineered nanomaterials. We believe it is appropriate and important for NIOSH to include this provision in the final document, especially given the hazard and risk information that we currently have on CNT and CNF.		
	1) The draft CIB proposes to include workers in the medical screening program only those who are exposed to CNT or CNF at concentrations In excess of the REL "or" workers in areas or jobs who have the potential for intermittent elevated air concentrations to CNT or CNF. We believe these criteria for inclusion into a medical screening program are too restrictive and we recommend expanding the population of workers who would receive screening. As NIOSH has documented in this CIB, significant risk of adverse health consequences remains at exposure levels below the REL. Thus, the REL is not a "safe" exposure limit. Consequently, we believe that medical screening should be made available to all workers who are potentially exposed to CNT or CNF -not	1) The reviewer makes an excellent point, and feels "…that medical screening should be made available to all workers who are potentially expose to CNT and CNF…". The state of exposure assessment currently for these substances is such that determining whether a person is "exposed" to CNT/CNF may need to be a qualitative assessment. The guidance in the CIB is intended to allow for other quantitative and qualitative determinations for inclusion in the screening program. The quantitative assessment is based on the REL; the draft CIB also allows for a qualitative assessment. The change to the document related to this latter issue is noted above in response	1) See revisions as noted above in response to AIA comment.

Commenter	Summary of Comments Received	Response	Changes to CIB
Kojola, AFL-CIO (cont.)	merely to those workers who experience exposures in excess of the REL or those who experience an undefined "intermittent elevated" or episodic exposure. Expanding coverage of the worker population Included in the medical screening program as we recommend will, in our view, capture workers who may also be at risk of adverse health effects over those whose exposures are intermittent or exceed the REL. Our recommendation is more protective and precautionary than that in the draft CIB and we urge NIOSH to adopt our suggestion in the final document.	to AIA comments.	
	2) We also believe that the surveillance aspect of this CIB needs to be strengthened by stressing the importance of employers following groups of workers over time who are exposed to CNT and CNF and those who have been included in the medical screening programs. NIOSH should also consider establishing a national exposure registry and health surveillance program. These long-term surveillance efforts will be crucially important for carrying out future studies to assess health effects among exposed populations of workers.	2) Regarding this comment concerning "surveillance" – ongoing evaluation of data – the NIOSH guidance states "Standardized medical screening data should be periodically aggregated and evaluated to identify patterns of worker health that may be linked to worker activities and practices that require additional primary prevention efforts. This analysis should be performed by a qualified health professional or other knowledgeable person to identify patterns of worker health that may be linked to worker	2) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Kojola, AFL-CIO (cont.)		activities or exposures. Confidentiality of worker's medical records should be enforced in accordance with all applicable regulations and guidelines." Therefore, we feel the current document addresses the reviewer's concern. NIOSH supports further consideration of exposure registries, the development of which may lead to analysis of medical screening data across workplaces.	
	Labeling Products		
	1) It has been our experience that many workers have no knowledge as to whether or not the products or materials they work with contain engineered nanomaterials. This is a major impediment to addressing hazards posed by these materials and implementing measures designed to protect workers from exposures. To confront this problem, we would like to see NIOSH recommend in the CIB that all products containing CNT and CNF should be properly labeled. Labeling is a fundamental	1) NIOSH believes it's important that appropriate warnings about the hazard be made on labels and in MSDS's.	1) The CIB recommends that the requirements of the OSHA Hazard Communication standard be followed at a minimum, and that the information contained in the CIB be used in

Commenter	Summary of Comments Received	Response	Changes to CIB
Kojola, AFL-CIO (cont.)	component of any comprehensive approach to ensuring that workers and employers understand that there is exposure potential depending on how the product is used throughout its life cycle -and that implementing measures to control those exposures is essential if workers are to be protected. **Other** 1) The AFL-CIO is very pleased that NIOSH has taken the initiative to issue the CIB on CNT and CNF. We strongly support the Issuance of a final document as quickly as possible due to the rapid development of nanotechnology and the need for providing effective guidance on how to control exposures and protect workers. While this document is confined only to CNT and CNF, including an REL based on a sufficient animal toxicology data, we think NIOSH ought to consider issuing a document addressing all engineered nanomaterials and the measures necessary to effectively protect workers. By doing so, NIOSH will assist in establishing a precautionary framework to help assure that workers will not experience adverse health effects from all nano-products.	1) NIOSH previously published the report *Approaches to Safe Nanotechnology [2009]* that provides guidance on the control of exposure to nanomaterials in the absence of specific health data. NIOSH continues to conduct *in vivo* and *in vitro* studies with various nanomaterials to gain a better understanding of their toxicity. NIOSH is also assessing the data to determine whether there are specific physical and/or chemical characteristics that influence their potential toxicity; commonality of specific physicochemical parameters might lead to improved risk management practices.	developing MSDS's. 1) No revisions required.

Commenter	Summary of Comments Received	Response	Changes to CIB
Stafford, Building and Construction Trades/AFL-CIO Stafford	**The CIB should explicitly cover workers beyond primary and secondary manufacturers and researches** 1) The CIB appears to be written for employers who use CNTFs who are fully aware they are using them, such as the primary producers of materials and some secondary manufacturers or researchers. The document presumes the employer knows which products contain CNTFs. Primary and secondary manufacturers and researchers will likely have very good workplace controls in place given the well recognized fact that there is a great deal of uncertainty as to the health risks of exposure. However, we believe the larger risk is to workers further downstream. Employers and workers further down the supply chain may not know they are exposed to CNTFs, and therefore be unaware that controls to exposure should be implemented. If we are to protect workers exposed to CNTFs the risk associated with the lifecycle of products containing these	1) Agree. Most of the reported exposure data for CNT and CNF come from workers employed in laboratories and pilot manufacturing facilities. NIOSH acknowledges in the CIB that the potential for exposure exists throughout the life cycle of the material. The recommendations in the CIB pertain to all workplaces. Requirements for educating and training workers have been expanded in the CIB.	1) No revisions required. See above response to Kojola.

Commenter	Summary of Comments Received	Response	Changes to CIB
Stafford, Building and Construction Trades/AFL-CIO (cont.)	nanomaterials must be considered. The use of CTNFs in building materials is escalating at an astounding pace. These materials not only pose unknown risk to the construction workers currently installing CTNF-containing products, they will pose future risks to workers and the general population in the built world as materials degrade or become disturbed over the lifecycle of the building or installations. Renovation or demolition of containing CNTFs will pose unknown risks to future construction workers as well as building occupants. Informing other employers and workers about CNTFS can be achieved through labeling and worker education. **Specific Worker Protections** **2.1 Training** 1) Currently, the CIB discusses worker training in the medical surveillance section. Worker training should be required wherever these materials are being used or present in a construction material. By discussing worker training in the context of medical surveillance, the CIB implies that worker training should only be considered where an employer has determined the need to implement a medical surveillance program. If employers do not recognize the	1) Agree. A separate Chapter/section on worker education and training was added to the CIB.	1) See above response to Kojola.

Commenter	Summary of Comments Received	Response	Changes to CIB
Stafford, Building and Construction Trades/AFL-CIO (cont.)	need to train all potentially exposed workers, we fear most will have no awareness of the potential risks of exposure and safe handling protocols.		
	2) NIOSH should recommend a hazard awareness and control training program for all workers who may be exposed to nanomaterials. We recommend NIOSH confer with the National Institute of Environmental Health Sciences on worker training, as that agency's Worker Education and Training Program is developing an excellent worker training curriculum on this topic.	2) Requirements have been added to the CIB on following, at a minimum, the recommendations contained in OSHA Hazard Communication standard. A recommendation was also made to follow the guidance developed by Kulinowski and Libby [2011] for the training and education of workers handling nanomaterials.	2) See responses to Kojola on education and training of workers.
	MSDS's		
	1) Material Safety Data Sheets (MSDSs) are one of the basic tenants of the OSHA Hazard Communication Standard. Employers rely on MSDSs to develop effective programs. In this CIB, NIOSH should set MSDS specifications. These specifications should recommend that all products capable of releasing CNTFs during products' lifecycle identify the presence of this material on the MSDS.	1) Recommendation was made on completing an MSDS.	1) Recommendation added to CIB on the incorporation of material into an MSDS. See above responses to Kojola.

Commenter	Summary of Comments Received	Response	Changes to CIB
Stafford, Building and Construction Trades/AFL-CIO (cont.)	Currently, here is little guidance for manufacturers as to when to include information on nanomaterials on their MSDSs and recent research suggests this information is often not available to workers. Please see the attached paper from Bruce Lippy Ph.D., CIH, CSP with more detailed recommendations on MSDS for nano-materials. **Labeling** 1) In addition to requiring information on MSDSs, all products containing CNTFs should be properly labeled. All products containing CNTFs should be labeled, and that label would follow the CNTF-containing raw materials and products as they are used down the manufacturing chain. Labels should remain in place for the entire life cycle of the product. As far as we are aware, the only systematic labeling of nanomaterials occurs at Brookhaven National Laboratories, and we suggest NIOSH recommend a label such as is used there, and reproduced below. **---Contains Nanomaterials---** _____ _	1) Requirements of the OSHA Hazard Communication Standard recommended.	1) Provisions of the OSHA Hazard Communication standard to be followed for labeling and completing an MSDS.

Commenter	Summary of Comments Received	Response	Changes to CIB
Stafford, Building and Construction Trades/AFL-CIO (cont.)	**Unknown nature of risk** **Expand discussion of measurement techniques, based on concern that the OEL is based on mass**		
	1) Although we agree there are few alternatives to a mass-based REL, we believe there are significant pitfalls to this approach. By design, nanomaterials are very light. Additionally, some studies have raised concern that the shape and behavior of the product is the main problem; more details on measurement of CNTFs are provided in the attached article from Paul Schulte. The mass of just a few fibers may be too low to accurately measure, but these few fibers may be highly hazardous. Accurate SEM/TEM sampling and analytic methods must be developed. Although those methods have not been developed yet, we think the CIB should include a discussion of benefits of these methods in a way that will encourage both the public and private sector to research and develop accurate measurement techniques. We are somewhat concerned if NIOSH, and subsequently OSHA, uses a mass-based REL now the industry will be locked into	1) Based on available information from animal research studies, a mass dose metric best describes the toxicological response (e.g., pulmonary fibrosis). NIOSH acknowledges in the CIB that there may be a better dose metric (e.g., tube dimension/concentration) and that NIOSH would reevaluate its REL when additional toxicity data become available. A recommendation is given in the CIB that air samples should be collected for electron microscopy analysis in which CNT and CNF are counted and sized.	1) No revisions required.

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Stafford, Building and Construction Trades/AFL-CIO (cont.)	that approach for years to come.		
	2) Another limitation to the mass-based sampling approach is that CNTFs are manufactured using metal catalysts. All engineered CNTFs contain residual amounts of these metals. The purer the grade of nanotubes, the lower the metal concentration. There is uncertainty as to the role associated metal catalysts play in the health and safety concerns related to CNTF exposures. For this reason, a simple mass-based approach may underestimate the toxicity of the material in question.	2) The available toxicological data on the purified and unpurified CNT (with various types and amounts of metal catalysts) have been discussed in several sections of the CIB (Executive Summary, Introduction, Sections 3, 4, 5, and Appendix A) Some of these studies do indicate that certain metal contaminants may be associated with greater toxicity (e.g., Lam et al. 2004; Shvedova et al. 2005, 2008)]. The risk assessment includes various types of CNT (purified or unpurified with different metal content), and the working lifetime exposure concentration estimates were relatively low mass concentrations for all types of CNT (Tables A-3 through A-6).	2) No revisions required.
	3) In addition, given the grave concern of working with these particles and the clear limitations of a mass-based REL, NIOSH should stress the importance of not relying on the REL to determine if workers are "safe" but rather guide employers to use the upmost precautions in handling and using	3) NIOSH provides a list of various risk management practices all aimed at maintaining exposures to CNT and CNF below the REL.	3) No revisions required.

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Stafford, Building and Construction Trades/AFL-CIO (cont.)	these materials to keep exposures to the lowest possible levels. **Areas for more research and collaboration**		
	1) NIOSH is encouraged to confer with DOD, EPA, OSHA and DOE for any toxicity information they may have on CNTFs. We believe there may be adequate worker populations in the defense or energy complex who have potentially been exposed to CNTFs for at least 30 years. **NIOSH should establish a registry for Nano Workers**	1) NIOSH is closely working with other Federal agencies in collecting and evaluating exposure information and sharing data on the control of exposures. NIOSH has ongoing research efforts to determine the feasibility of establishing exposure registries and the feasibility of conducting epidemiology studies.	1) No revisions required.
	2) NIOSH should develop a plan to have a registry for workers exposed to nanomaterials. We expect that primary manufacturers will have good controls to minimize worker exposure. Secondary manufacturing is expected to have looser controls on the hazards, but still some recognition of the material being used to manufacture products. It is essential to track the use of these materials throughout the industry, and track the workers exposed to these materials, so that the opportunity exists to investigate human	2) NIOSH is studying the feasibility of establishing an exposure registry. A NIOSH study has be initiated to identify the US workforce exposed to CNT to determine the feasibility of conducting an epidemiological study and establishing an exposure registry.	2) No revisions required.

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Stafford, Building and Construction Trades/AFL-CIO (cont.)	health effects a decade from now. This registry should include both baseline health monitoring and follow-up data as well as surveillance data tracking trends over time. **We would suggest some editing to change the tone of the document**		
	1) We do not dispute that there are currently no studies in the literature reporting adverse effects among workers exposed to CNTFs. However, by beginning the executive summary with this statement, NIOSH seems to suggest to the reader that the concern of the occupational safety and health community may be over exaggerated. It almost questions the basis for issuing the CIB, and draws into question the overall need for attention of the public.	1) The first sentence of the Executive Summary has been change to emphasize the importance of the animal data that showed adverse respiratory effects of exposure to CNT and CNF.	1) First sentence of the Executive Summary revised.
	2) It is important to begin the executive summary articulating why the document is needed-that there have been numerous studies raising significant concern and uncertainty related to worker exposure to NT, and that these studies warrant quick and decisive action to reduce worker	2) The beginning of the Executive Summary has been revised.	2) The Executive Summary was revised to emphasize the adverse respiratory effects observed in

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Stafford, Building and Construction Trades/AFL-CIO (cont.)	exposure to these materials until more can be learned about their long term health implications.		animals exposed to CNT and CNF and the importance of implementing a risk management program to reduce worker exposure.
	The focus of the Current Intelligence Bulletin on CNT is too narrow		
	1) The Current Intelligence Bulletin (CIB) is too narrow in that the scope of exposure to nanoparticles is much broader and of great concern. NIOSH should consider expanding the scope of the CIB to all engineered nanomaterials due to the uncertain health risks of exposure. We understand that it is not possible to set RELs for all engineering or naturally occurring nanomaterials, but we recommend that NIOSH discuss health implications of exposures to nanomaterials in general in the document.	1) NIOSH previously published the report *Approaches to Safe Nanotechnology [2009]* that provides guidance on the control of exposure to nanomaterials in the absence of specific health data. NIOSH continues to conduct *in vivo* and *in vitro* studies with various nanomaterials to gain a better understanding of their toxicity. NIOSH is also assessing the data to determine whether there are specific physical and/or chemical characteristics that influence their potential toxicity; commonality of specific physicochemical parameters might lead to improved risk management practices.	1) No revisions required.

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Morawetz, International Chemical Workers Union (ICWU)	The ICWU represents workers at a number of carbon black facilities, a nano material in significant production in a variety of industries. This represents a significant occupational population that this document is of interest to.		
	1) Although this document is specifically limited to nanofibers and nanotubes, we are troubled that given these particles similar size although different shapes, this is not addressed further. We support NIOSH in issuing a CIB with the focus on CNT and CNF but a section should be added that at a minimum recommends that employers would be prudent to follow the same recommendations and controls. In addition, there is a clear need for additional research to document the similar or different toxicity of carbon black, CNT and CNF.	1) The CIB recommends that all types of carbon nanotubes and nanofibers follow the same risk management practices including the control of worker exposures below the REL. Although dimension and size probably is a significant characteristic related to toxicity, the data are lacking for making specific recommendations.	1) No revisions required.
	2) The section on worker participation and training should be separate sections, not within section 1.1 Medical Screening and Surveillance. In particular, worker participation is vital throughout the implementation of any control plan and should be included in exposure assessment, engineering	2) A new section was added to the CIB to address recommendations for worker education and training.	2) Section 6.3 *Worker education and training* added to the CIB.

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Morawetz, International Chemical Workers Union (ICWU) (cont.)	controls, work practices, clean-up and disposal, personal protective clothing and respirators. Although these areas are primarily the obligations and duty of site management, the input of workers exposed to CNT and CNF can be invaluable in understanding actual workplace exposures and practices and assist in accomplishing the goals of this CIB.		
	3) The training section needs to be expanded to describe the frequency of training, reference CNT and CNF as covered by the Hazard Communication standard, 1910.1200 and should explicitly require training in all subjects mentioned in the CIB. It should clearly state the advantage of worker involvement in the design of curriculum, implementation and evaluation of training. There needs to be a specific section on the labeling on nano materials, an omission in the current document.	3) Requirements have been added to the CIB on following, at a minimum, the recommendations contained in OSHA Hazard Communication standard. A recommendation was also made to follow the guidance developed by Kulinowski and Libby [2011] for the training and education of workers handling nanomaterials.	3) Section 6.3 *Worker education and training* added to the document.