

**Dragon, Karen E. (CDC/NIOSH/EID)**

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**Sent:** Friday, February 18, 2011 10:52 PM  
**To:** NIOSH Docket Office (CDC)  
**Cc:** Niemeier, Richard W. (CDC/NIOSH/EID)  
**Subject:** Stakeholder Comment NIOSH Docket 161-A CIB on Carbon Nanotubes  
**Attachments:** Kosnett nano CIB Docket 161-A comments.doc

**Importance:** High

Kindly see my attached stakeholder review comments to NIOSH Docket 161-A regarding the NIOSH CIB on Carbon Nanotubes and Nanofibers.

Sincerely,

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Stakeholder review comments to draft NIOSH CIB on Carbon Nanotubes and Nanofibers (NIOSH docket number 161-A).

Submitted by

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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 rat inhalation studies is less than  $7 \mu\text{g}/\text{m}^3$ , 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.

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-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.

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 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. 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 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 compare the 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.

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 examinations, laboratory tests, and questionnaires) for the nanomaterial workforce, these elements should be encouraged only in the framework of occupational health research.