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

From: Votaw, James [James.Votaw@wilmerhale.com]
Sent: Friday, February 18, 2011 4:28 PM
To: NIOSH Docket Office (CDC)
Subject: 161-A - Occupational Exposure to Carbon Nanotubes and Nanofibers
Attachments: Comment to Docket NIOSH 161-A.doc

Ladies and Gentlemen,

I enclose for consideration comments on NIOSH's draft Current Intelligence Bulletin: Occupational Exposure to Carbon Nanotubes and Nanofibers.

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February 18, 2011

VIA E-MAIL

National Institute for Occupational Safety and Health
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Robert A. Taft Lab.
4676 Columbia Parkway
Cincinnati, OH 45226

Attention: Docket Number: NIOSH 161-A

Re: Docket Number: NIOSH 161-A
Draft CIB: Occupational Exposure to Carbon Nanotubes and Nanofibers

Ladies and Gentlemen:

Thank you for the opportunity to comment on draft Current Intelligence Bulletin, *Occupational Exposure to Carbon Nanotubes and Nanofibers* (release Dec. 2, 2010) (draft Bulletin). Given the many current and future applications for CNTs, it will be useful to have authoritative norms defining acceptable CNT occupational exposure levels, efficient and effective CNT exposure monitoring techniques, and appropriate exposure mitigating actions and personal protective equipment where CNT exposure cannot be avoided. Such guidelines will be useful to employers, insurers and investors seeking to ensure that appropriate actions to protect worker health are understood and being taken. For this reason, NIOSH's efforts to develop a recommended exposure limit (REL) are appreciated.

That said, 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.[1] 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 concern, and the suitably sensitive surveillance method(s) to assess the endpoint(s)).

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

In contrast, Current Intelligence Bulletins (CIB) 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."[2] 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.[3] 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 unagglomerated; 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.[4]

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 MWCNT studies is appropriate for these materials and should address the uncertainties associated with that conclusion.

Similarly, although the draft Bulletin identifies CNT agglomeration state as a relevant physical property that may be important to relative toxicity,[5] and as a complicating factor in in-

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

3 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).

4 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.

5 E.g., draft Bulletin at 18, 29.

tratracheal instillation studies,[6] the draft never resolves how rationally to draw common inferences from studies made with differently agglomerated CNTs.

A third possible incongruity is the statement in the draft Bulletin that only studies using unground CNT were used in the risk assessment.[7] 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.

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 lead to the 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 assement (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.[8]

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.

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6 E.g., draft Bulletin at 29

7 Draft Bulletin at 99.

8 E.g., draft Bulletin at 99.

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 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.

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.

6. Medical Surveillance. NIOSH's very specific recommendation for a screening medical surveillance program for workers requires additional explanation.[9] 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.[10]

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 one or more distinctive (selective) and objective physical (medical) signs indicative of the disease process or health endpoint of concern; (c) exposures to

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

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

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. Non-specific 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 screening tests, and the lost time and costs of additional diagnostic evaluations.[11]

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 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 occupa-

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[11] 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.

> tional exposure concentrations for working in SWCNT operations. Consequently, there is too little information available at this time to verify disease endpoints. [12]

For these reasons, the draft Bulletin should be revised to address what has changed since NIOSH's last assement 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 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[13] 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 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.

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

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[12] Current Intelligence Bulletin 60 at 61.

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

remote. This suggests that precautionary control measures should be focused principally on operations handling unbound CNT.

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I appreciate the opportunity to submit these comments. Numerical norms will be quite useful when available. But they need to be well considered and their strengths and limitations understood. Pending development of those norms, current practices to minimize exposures to the extent reasonably practicable should be continued.

Very truly yours,

James G. Votaw