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

From: David B Warheit [David.B.Warheit@USA.dupont.com]
Sent: Friday, February 18, 2011 10:26 AM
To: Niemeier, Richard W. (CDC/NIOSH/EID)
Cc: NIOSH Docket Office (CDC); David B Warheit; David.Warheit@gmail.com
Subject: RE: Stakeholder review of NIOSH CIB on Carbon Nanotubes and Nanofibers - Warheit responses
Attachments: david warheit evaluation of the NIOSH CIB on CNTand CNFs.doc

Dear Dr. Niemeier,

Please find attached my review of the NIOSH CIB on Carbon Nanotubes and Nanofibers.

Regards,

David Warheit

From: "Niemeier, Richard W. (CDC/NIOSH/EID)" <rwn1@cdc.gov>
To: David B Warheit/AE/DuPont@DuPont
Date: 12/09/2010 08:24 AM
Subject: RE: Stakeholder review of NIOSH CIB on Carbon Nanotubes and Nanofibers

---

Dr. Warheit: thank you very much for your response and willingness to review and comment. Thanks, Rick

From: David B Warheit [mailto:David.B.Warheit@USA.dupont.com]
Sent: Wednesday, December 08, 2010 1:48 PM
To: Niemeier, Richard W. (CDC/NIOSH/EID)
Cc: David B Warheit; David.Warheit@gmail.com
Subject: Re: Stakeholder review of NIOSH CIB on Carbon Nanotubes and Nanofibers

Dear Dr. Niemeier,

Thank you for the opportunity to review the NIOSH Current Intelligence Bulletin on Carbon Nanotubes and Nanofibers.

I will be happy to provide written comments to you (the public docket) on the document by the specified date of February 18, 2011.

I am unsure whether I will be able to attend the public meeting on February 3rd, but will contact Diane Miller if I am able to attend.

Regards,

David Warheit

From: "Niemeier, Richard W. (CDC/NIOSH/EID)" <rwn1@cdc.gov>
To: David B Warheit/AE/DuPont@DuPont
Date: 12/08/2010 12:11 PM
Subject: Stakeholder review of NIOSH CIB on Carbon Nanotubes and Nanofibers

Dear Dr. Warheit:

The National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention (NIOSH, CDC) is conducting a review of the NIOSH scientific document entitled *NIOSH Current Intelligence Bulletin: Occupational Exposure to Carbon Nanotubes and Nanofibers* (attached). This document has been determined by NIOSH to be a Highly Influential Scientific Assessment according to the Office of Management and Budget (OMB) guidelines under the Federal Data Quality Act 2000 (Public Law 106-554, Section 1(a)(3)[515]). The document summarizes the literature describing the adverse lung effects observed in laboratory animals exposed to carbon nanotubes (CNT) and carbon nanofibers (CNF). The purpose of the CIB is to disseminate recent information about the potential respiratory hazard to workers exposed to CNT and CNF. The intended audience of the CIB is health professionals and regulatory agencies, although the recommended risk management guidance provided in the document can be used by employers and workers where exposures to CNT or CNF occur. This guidance document does not have the force and effect of law. The document is also posted on the NIOSH website at http://www.cdc.gov/niosh/docket/review/docket161A/default.html

The goals of the document are to (1) describe the relevant animal and other scientific evidence on the health effects of CNT and CNF, (2) provide a quantitative risk assessment based on dose-response information from the animal studies, (3) describe the rationale NIOSH used in the development of the draft recommended exposure limit (REL), (4) provide recommendations on how to minimize worker exposure, and (5) provide guidance on how to implement an occupational health surveillance program (hazard and medical).

As a stakeholder, we are requesting your participation in the review process. The charge to the reviewers is to objectively review the document to determine whether:

- the hazard identification is a reasonable reflection of the available scientific studies,

- the risk assessment and dosimetric modeling represent a reasonable methodology for estimating worker risks from exposure to carbon nanotubes and nanofibers,

- the data and analysis used by NIOSH are appropriate for the scientific conclusions that formed the basis of the proposed REL, and

- the recommendations (e.g., risk management, occupational health surveillance) for protecting worker's health are reasonable and appropriate

To facilitate review of this Current Intelligence bulletin, the five questions below should be considered:

1. 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?

2. Is the risk assessment and dosimetric modeling methods used in this document appropriate and relevant?

3. Is the use of respirable mass as a dose metric appropriate for estimating worker risks from inhalation to CNT and CNF?

4. Are the sampling and analytical methods adequate to measure worker exposure to carbon nanotubes and nanofibers?

5. Are there additional relevant studies or methods that NIOSH should consider in developing the REL for CNT and CNF?

Please address only the technical content of this document. The document will have an editorial review after revisions are made based on external peer reviewer and stakeholder comments.

A public meeting will be held on **February 3, 2011** at the

Millennium Hotel Cincinnati,

Grand Ballroom A,

150 West 5th Street,

Cincinnati, OH. 45202,

9:00 AM-4:00 PM (GMT-05:00) Eastern Standard Time.

This will be a forum for scientists and representatives of government agencies, industry, labor and other stakeholders and to discuss the document. The meeting will be open to the public, limited only by the space available. Your attendance at the meeting is optional; if you plan to attend the meeting please contact Diane Miller by January 28, 2011 at the address given below.

We request that your written review comments be submitted by the close of the public docket on **February 18, 2011.** Please return your written comments either by mail (to Diane Miller, NIOSH Docket Office, Robert A. Taft Laboratories, Mail Stop C-34, 4676 Columbia Parkway, Cincinnati, Ohio 45226) or send electronically via e-mail to nioshdocket@cdc.gov. All electronic comments should be formatted as Microsoft Word. Please make reference to docket number **NIOSH 161-A** when you submit your comments. Please be aware that your name, affiliation, and comments will be posted on the NIOSH website along with a peer review report containing the peer review comments and the NIOSH response to each comment.

We greatly appreciate your review of this document and look forward to obtaining your input. If you have questions regarding the document that you wish to discuss, please contact Dr. Rick Niemeier at (513) 533-8388 or rwn1@cdc.gov. Thank you for your assistance in this important review process.

Sincerely, Rick

Richard W. Niemeier, Ph.D.

Senior Scientist/Toxicologist

Associate Director for Science

Education and Information Division

NIOSH

4676 Columbia Pkwy

Cincinnati, OH 45226

Phone: (513) 533-8388

Fax: (513) 533-8588

email: rwn1@cdc.gov

<<carbonNanotubeCIB_PublicReviewOfDraft 11-2010.pdf>>

Richard W. Niemeier, Ph.D.

Senior Scientist/Toxicologist

Associate Director for Science

Education and Information Division

NIOSH

4676 Columbia Pkwy

Cincinnati, OH 45226

February 18, 2011

Comments on the NIOSH draft Current Intelligence Bulletin (CIB) – prepared by David B. Warheit, DuPont Haskell Global Centers, Newark, DE

Dear Dr. Niemeier,

Thank you for the opportunity to review the NIOSH Current Intelligence Bulletin on Carbon Nanotubes and Nanofibers. I am 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 format of my comments is to respond to the five questions that were posed by NIOSH to the Reviewers on issues related to the CIB, namely:

1. 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?

2. Is the risk assessment and dosimetric modeling methods used in this document appropriate and relevant?

3. Is the use of respirable mass as a dose metric appropriate for estimating worker risks from inhalation to CNT and CNF?

4. Are the sampling and analytical methods adequate to measure worker exposure to carbon nanotubes and nanofibers?

5. Are there additional relevant studies or methods that NIOSH should consider in developing the REL for CNT and CNF?

General Comments on the NIOSH CIB: 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:

- 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 MWCNT – given the paucity of relevant hazard data.

Responses to Specific Questions:

1. 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?

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:

- The Tables located on pages 62 – 69 were initially difficult to locate and their locations should have been better identified within the text.

- 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.

- 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 learnings 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 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..

- 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).

- 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 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.

2. Is the risk assessment and dosimetric modeling methods used in this document appropriate and relevant?

- NIOSH estimates of the lung burden based on alveolar deposition are questionable and the calculations are not clearly justified.

- 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).

- 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. Is the use of respirable mass as a dose metric appropriate for estimating worker risks from inhalation to CNT and CNF?

4. Are the sampling and analytical methods adequate to measure worker exposure to carbon nanotubes and nanofibers?

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, 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.

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 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 pressure impactor; 4) transmission electron microscopy; 5) ventilation assessment – the ventilation system was evaluated using "smoke tubes".

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.

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:

What are the best dose metrics to utilize in measuring CNT/CNF exposures? 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?

Can CNT/CNF dimensions such as length and diameter distributions be accurately measured in the occupational setting or in inhalation toxicity studies?

Can CNT/CNF surface area measurements be accurately measured in the occupational setting or in inhalation toxicity studies?

What is the role of CNT/CNF-based metal catalysts and how do they factor into the measurement schemes?

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?

Could surface area metric analyses provide a distinguishing feature between the accurate measurements of SWCNTs, MWCNT, CNF and "background elemental carbon"?

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?

[comment: I am sure that NIOSH is aware that in the 2 published 90-day inhalation studies with MWCNT-types in rats – (Ma Hock *et al.*, Pauluhn), only mass measurements were provided in the publication, while surface area measurements were estimated, and particle number concentrations and particle dimension distributions (lengths and diameters), were not provided. This likely is due to the limitations of the current available technology to measure these physicochemical endpoints accurately from either CNT bulk or air samples. Accordingly, it seems clear that current technical developments will require an upgrade in the measurement methods for evaluating the physicochemical characteristics of SWCNT, MWCNT, or CNF – both as bulk samples and following aerosol generation. The development of these abilities will likely be an important fundamental prerequisite which ultimately could facilitate improvements in the characterization of measurements of aerosolized CNTs – both in the workplace and for toxicology studies.

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 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.

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 are exposed (e.g., surface area, CNT – particle dimension distributions such as length/diameters, particle numbers)?

5. Are there additional relevant studies or methods that NIOSH should consider in developing the REL for CNT and CNF?

I am unaware of any additional, relevant studies at this time.

References used in this response:

Sargent LM, Reynolds SH, Castranova V. Potential pulmonary effects of engineered carbon nanotubes: in vitro genotoxic effects. Nanotoxicology. 4: 396-408, 2010.

Landsiedel R, Kapp MD, Schulz M, Wiench K, Oesch F. Genotoxicity investigations on nanomaterials: methods, preparation and characterization of test material, potential artifacts and limitations--many questions, some answers.. Mutat Res. 681: 241-258, 2009.

Warheit DB, Donner EM. Rationale of genotoxicity testing of nanomaterials: regulatory requirements and appropriateness of available OECD test guidelines. Nanotoxicology. 4:409-413, 2010.

Ma-Hock L, Treumann S, Strauss V, Brill S, Luizi F, Mertler M, Wiench K, Gamer AO, van Ravenzwaay B, Landsiedel R. Inhalation toxicity of multiwall carbon nanotubes in rats exposed for 3 months. Toxicol. Sci. 112: 468-481, 2009.

Pauluhn J. 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: 226-242, 2010.

Han JH, Lee EJ, Lee JH, So KP, Lee YH, Bae GN, Lee SB, Ji JH, Cho MH, Yu IJ. Monitoring multiwalled carbon nanotube exposure in carbon nanotube research facility. Inhal Toxicol. 20: 741-749, 2008.

Lee JH, Lee SB, Bae GN, Jeon KS, Yoon JU, Ji JH, Sung JH, Lee BG, Lee JH, Yang JS, Kim HY, Kang CS, Yu IJ. Exposure assessment of carbon nanotube manufacturing workplaces. Inhal Toxicol. 22: 369-381, 2010.

Methner MM, Birch ME, Evans DE, Ku BK, Crouch K, Hoover MD. Identification and characterization of potential sources of worker exposure to carbon nanofibers during polymer composite laboratory operations. J Occup Environ Hyg. 4 : D125-30., 2007.