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March 11 2011

Re: **Review of NIOSH Current Intelligence Bulletin: Occupational Exposure to Carbon Nanotubes and Nanofibers. Docket # NIOSH 1651-A**

Dear Ms. Miller,

Thank you for inviting me to peer review the NIOSH draft CIB "Occupational Exposure to Carbon Nanotubes and Nanofibers" (Docket # NIOSH 1651-A). Please find my review comments below. In addition, I have attached a copy of the Conflict of Interest form, and my current CV.

Please do not hesitate to contact me if I can be of further assistance.

Sincerely yours,

Review of NIOSH Current Intelligence Bulletin: Occupational Exposure to Carbon Nanotubes and Nanofibers

Docket # NIOSH 1651-A

General comments

The draft NIOSH Current Intelligence Bulletin (CIB) "Occupational Exposure to Carbon Nanotubes and Nanofibers" represents a carefully considered and comprehensive assessment of the state of knowledge on occupational health risks associated with airborne carbon nanotube exposure, and draws well-reasoned conclusions on actions toward reducing health risks associated with exposure. The document responds to both growing awareness of the potential risks associated with carbon nanotube exposure, and increasing use of carbon nanotubes in commercial products. In doing so, it addresses a number of issues that are important to the safe and successful handling and use of carbon nanotubes in workplaces, and does so in a timely manner.

This review addresses five questions on the risk assessment and subsequent recommendations that were asked by NIOSH. Specific answers to each question are given below. However, before getting into the details, I would like to highlight a number of more general or cross-cutting issues here.

First, I would like to commend NIOSH for undertaking this review and assessment. Developing clearer guidelines on the safe handling of carbon nanotubes is critical to their long-term safe, sustainable and successful use. In drafting this document, NIOSH had taken an important lead in beginning to establish such guidelines. However, given the tremendous uncertainty over the physical and chemical nature of carbon nanotubes, the hazards that different types of carbon nanotubes present, the nature of occupational exposures, the validity and interpretation of *in vivo* toxicity studies and the meaning of derived dose-response relationships, this must be viewed as just being the beginning of a process.

In the draft CIB, NIOSH takes the pragmatic step of treating all carbon nanotubes and nanofibers as nominally the same material – whether they are single walled, multiple walled, functionalized, long, short, straight, curved, tangled, agglomerated, having many un-terminated graphene edges or just a few, etc. From a mechanistic perspective, this is hard to justify – while the biological relevance of the specific chemistry and morphology of different carbon nanotubes (including nanofibers) is far from clear, there is strong evidence that chemistry and morphology together have a profound influence over biological interactions and toxicity. Having said this, there is some merit in taking a crude initial stab at establishing exposure limits based on the material family rather than specific components *in the absence of further information*. This is an approach that allows gross common behavior to be captured in a single and implementable exposure level, and provides a route to at least reducing the potential for harm to occur. However, it should be clearly recognized that the approach is a pragmatic compromise, and one that should be revisited and revised on a regular basis. In particular, there is increasing evidence that the mode of action associated with compact or short and straight and long carbon nanotubes is markedly different – the latter being more closely associated with carcinogenic potential – and this should ideally be reflected in subsequent risk assessments and recommendations for reducing risk.[1]

As an associated point, there is considerable lack of clarity in the document concerning the physical nature of carbon nanotubes associated with inhalation exposure. Throughout the document, there is an implication that these are fiber-like entities. However, relatively few carbon nanotube materials conform to most people's understanding of "fiber-like". Specifically, many multi-walled carbon nanotube materials consist of relatively short nanotubes, while some consist of nanotubes that are millimeters to centimeters long; single walled carbon nanotube materials typically have a complex and convoluted morphology, which does not conform to the idea of a straight, isolated fiber; some unprocessed carbon nanotube materials contain appreciable amounts of non-tubular elemental carbon; most carbon nanotube materials exist in an aggregated state, where the size and morphology of the aggregates is dependent on handling and – in exposure studies – the mechanism of aerosolization. Given that morphology is likely to play some role in determining exposure and hazard for these materials, at the very least it would be helpful if the draft CIB could document – ideally using Transmission Electron Microscope images – the range of morphologies potentially encountered.

The Current Intelligence Bulletin also takes the pragmatic approach of recommending a Recommended Exposure Limit (REL) based on respirable mass concentration. Despite the substantial uncertainties over modes of action that raise questions over relevant dose metrics, this would appear to be a sensible and justifiable decision. Current evidence suggests that it is the alveolar region of the lungs that is predominantly susceptible to inhaled carbon nanotube material, supporting the decision to focus in respirable nanotubes. And while there remains uncertainty over whether response is most closely associated with the number, morphology, surface area, mass etc. of deposited fibers or particles, mass concentration is indicated to be a crude but effective indicator of effect in most studies to date. Thus while evidence may well arise suggesting alternative dose metrics in the future, respirable mass concentration is a reasonable starting point.

However, I do have some concerns with the exposure quantification method proposed – especially as the recommended REL is dependent on the analytic limitations of this method. NIOSH Method 5040 is well established for quantifying elemental carbon (EC) concentration in air samples. However, the draft CIB does not present any data suggesting that the method has been extensively evaluated for quantifying airborne concentrations of different forms of carbon nanotubes. If this method is to be the basis of the proposed REL, I would like to see clear evidence of its practical application and validation for single and multi-walled carbon nanotubes, and for various forms of carbon nanofibers.

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[1] Donaldson et al. have suggested that carbon nanotube materials demonstrate particle-like or fiber-like behavior, depending on their physical form (Donaldson, K., R. Aitken, L. Tran, V. Stone, R. Duffin, G. Forrest and A. Alexander (2006). "Carbon nanotubes: A review of their properties in relation to pulmonary toxicology and workplace safety." Toxicological Sciences **92**(1): 5-22.). This hypothesis has been supported by a number of studies, including the work of Poland et al. on the response to long and short multi-walled carbon nanotubes introduced into the abdominal cavity of mice (Poland, C. A., R. Duffin, I. Kinloch, A. Maynard, W. A. H. Wallace, A. Seaton, V. Stone, S. Brown, W. MacNee and K. Donaldson (2008). "Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study." Nature Nanotechnology 3: 423-428.)

There is also some concern over the method's lack of ability to distinguish between different forms of EC. Where carbon nanotube materials are the sole source of EC, this may be less of an issue (although one might wonder whether nanotubes embedded in a respirable particulate matrix such as might be generated while machining a composite material would lead to a measured airborne nanotube concentration that overestimates the risk associated with the particles). But where there are others sources of EC-containing aerosol in a workplace, the applicability of method 5040 might be compromised without the concurrent use of other exposure characterization approaches. This is an issue that the draft CIB ideally needs to address more fully.

Specific comments

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 draft CIB presents a comprehensive review of the published scientific evidence on the potential hazards associated with carbon nanotube and nanofiber inhalation. The key studies are identified and, where deemed appropriate, incorporated into the risk assessment. However, the draft CIB as it stands has two limitations in particular in this: There is a paucity of critical evaluation of the validity and robustness of studies, and there is a marked lack of differentiation between effects associated with particle-like behavior, and effects associated with fiber-like behavior.

On the first limitation, there is still a considerable lack of expertise and "art" in conducting well characterized, interpretable and repeatable inhalation studies with carbon nanotubes. There is uncertainty over how generation and delivery methods alter the physicochemical nature of the material and how this impacts on exposure, deposition and response; there is uncertainty over which material attributes to characterize in studies, and how to appropriately quantify them; and there is uncertainty over the identification and interpretation of endpoints. As a consequence, the validity and comparability of many published studies needs to be approached with some caution – especially if they are to be used as the basis of a quantitative risk assessment. The draft CIB would benefit from a more robust discussion of the limitations and quality of the studies used.

On the second limitation, Donaldson et al.[2] have proposed that different forms of carbon nanotube material demonstrate markedly different modes of action – with compact materials predominantly showing insoluble particle-like behavior in the lungs, and long, thin fiber-like materials demonstrating a biological behavior that conforms to the fiber paradigm. The potential for such markedly different behavior – together with the increased likelihood for carcinogenesis in the latter case – suggests that additional thought should be given to treating all nanotube materials as having the same mode of action.

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[2] Donaldson, K., R. Aitken, L. Tran, V. Stone, R. Duffin, G. Forrest and A. Alexander (2006). "Carbon nanotubes: A review of their properties in relation to pulmonary toxicology and workplace safety." Toxicological Sciences 92(1): 5-22.

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

The risk assessment and dosimetric modeling methodologies used in the draft CIB are in line with conventional practice. However, I do have concerns over the robustness of the assessment, given uncertainty over the quality of the data and how sparse the data are in many cases around the Benchmark Dose (BMD). While the modeling approach adopted is reasonable, I do have concerns that the derivation of quantitative BMDL values in appendix A look qualitatively as if they are likely to be highly dependent on the models used and the uncertainty in the fitted data. In this regard, I would like to see a sensitivity analysis where possible, and indications of confidence or error on the derived values of BMD, BMDL, BMC and BMCL.

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

It is my opinion that the use of respirable mass as a dose metric is appropriate. While alternative metrics may be justified on mechanistic grounds (although the state of the science is not sufficiently advanced to indicate which alternative metrics would be more appropriate), current indications are that mass concentration in the respirable size range is an adequate indicator of potential risk.

That said, the potential for fiber-like behavior does raise the question of whether some forms of carbon nanotubes and nanofibers should be evaluated on a number concentration basis. There is some justification for this where the material is comprised of long, straight fibers, where these fibers are unbound, and where agglomeration is relatively low. However, for materials where the fibers are short, where they are highly agglomerated, where they are encapsulated in another material (in the particulate form), where they are tightly entangled, and where they have complex morphologies number concentration is not indicated as being a useful exposure metric. This holds in particular for single walled carbon nanotubes, which do not exhibit a fiber-like morphology in a conventional understanding of the term.

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

The proposed NIOSH Method 5040 has merit for measuring exposure to carbon nanotube material. However, the draft CIB has negligible information demonstrating the applicability of the technique to these materials. Given the unique nature of carbon nanotubes, I do not think it is sufficient to state that the method works for elemental carbon, with the implicit assumption that it will also work for carbon nanotubes and nanofibers.

As discussed above, there is also a question of background interference from other workplace sources of EC.

Given the apparent lack of validation of the method and the uncertainty associated with interference from other sources of EC, it would be helpful if the draft CIB discussed the limitations of the method in more depth, and suggested alternative or complimentary monitoring methodologies – such as the parallel use of Transmission Electron Microscopy sampling and analysis.

Given the uncertainty over the general applicability of Method 5040 on its own, it may be difficult to support the recommendation of a 7 μg/m^3 REL, as it is entirely based on this exposure characterization method

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

I do not think there are any other studies at present that would change substantially the conclusions and recommendations of the draft CIB. Regarding methods, there has been some suggestion of using metal contaminants as markers for carbon nanotubes, as used by Maynard et al. (2004)[3]. This is an approach that is applicable where the material in question has a clear and consistent fingerprint. But it runs into difficulties where there is wide variation in contaminant levels between processes, or within processes – either as a product is successively processed, or through batch-to-batch variation. There are also some carbon nanotube production processes that result in negligible metal contamination.

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[3] Maynard, A. D., P. A. Baron, M. Foley, A. A. Shvedova, E. R. Kisin and V. Castranova (2004). "Exposure to Carbon Nanotube Material: Aerosol Release During the Handling of Unrefined Single Walled Carbon Nanotube Material." J. Toxicol. Environ. Health **67**(1): 87-107.