# Response to Peer Reviewer's Comments

## NIOSH Current Intelligence Bulletin (CIB) "Interim Guidance for the Medical Screening of Workers Potentially Exposed to Engineered Nanoparticles" (12-14-07 draft)

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**Questions posed by NIOSH during public review and to Peer Reviewers**

1) Do the data support the conclusions on the document?
2) Are the conclusions appropriate in light of the current understanding of toxicological data?
3) Is medical surveillance appropriate at this time for workers with potential exposure to engineered nanoparticles; if so, what form(s) of medical surveillance are specific for such workers?
4) What are the potential benefits, adverse impacts, and limitations of medical screening of workers potentially exposed to engineered nanoparticles?
5) What are the potential benefits, adverse impacts, and limitations of establishing an exposure registry for workers exposed to engineered nanoparticles?

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The following presents a summary of pertinent comments and the NIOSH response to those comments:

**Comments of Peer Reviewers**

**Peer Reviewer # 1**

Peer Reviewer # 1 provided the following:

1. The recommendations {of the guidance} are summarized as follows:
   - Take prudent measures to control exposures to engineered nanoparticles.
   - Conduct hazard surveillance as the basis for implementing controls.
   - Consider established medical surveillance approaches to help
   - Assess whether controls are effective and identify new or unrecognized problems and health effects.

The recommendations are prudent and sensible- control exposure, conduct assessment of those jobs that carry the greatest risk of exposure and use established surveillance schemes.

The problem of identifying risk and allocating it specifically to engineered NP is difficult for a number of reasons. Most people's major exposure is likely to be from combustion-derived NP even if it's only on the way to work, never mind in the workplace if there are diesel generators or some other combustion source. This makes it difficult to establish the relative role of manufactured NP.

There are unlikely to be any 'new' disease produced by engineered NP except for the remote possibility of brain effects. If the PM10 (combustion-derived nanoparticle-driven) experience is anything to go by then NP will affect susceptible individuals (airways disease and cardio vascular disease). Of these the cardio vascular risk is greatest and the mechanism is not well understood. Workers in the engineered NP industry who have cardio vascular disease (many of the older men) could be especially at risk. There may be types of engineered NP that especially impact on the cardio vascular system , i.e. they especially translocate to the blood, be potent at causing lung inflammation, have effects in the vascular wall or affect heart rat variability; so there needs to be vigilance.

As regards the brain the story is similar – there may be NP that especially tropic to the brain; ongoing hazard research will be important in the context of identifying such types of NP and providing forewarning.

One of the greatest risks, seem to me , to be the risk of asbestos effects from high aspect ratio nanoparticles (HARN) that could act analogously to asbestos. The long lag time from exposure to diagnosis for mesothelioma, the hallmark tumour of asbestos exposure, could be a real problem if it translates to HARN effects. It could be 40 years until we see mesothelioma in workers exposed to HARN and during that time ongoing exposure could be building up a real epidemic. Regulation of fibres is the only dust that relies on counting particles (fibres) rather than weighing them and not all HARN might be visible by the existing asbestos methodology which is based on phase contrast light microscopy. Therefore special attention might be given to this area. In the document emphasis is placed on single wall carbon nanotubes whilst most industrial use is likely be multiwall carbon nanotube in the first instance at least. More research is urgently needed on the asbestos-like hazard of HARN to feed back to industry to provide proper risk assessment.

**Response** – no change to document required.

**Peer Reviewer # 2**

Peer Reviewer # 2 organized his review in direct relation to the questions posed to the reviewers. Below is a summary of his comments and recommendations and the NIOSH response to those comments:

1. Peer Review # 2 recommends that: a) the potential for neurotoxicity from central nervous system translocation of inhaled nanomaterials be mentioned in the CIB (Elder et al, EHP 114:1172 -1178; 2006) and b) that the specific cardiovascular and pulmonary effects associated with ultrafine particle exposure in human epidemiological studies be briefly summarized (e.g. studies in the American Cancer Society cohort relating fine particulate air pollution to cardiopulmonary mortality).

**Response** – Agree - background on toxicity/hazard was expanded with reference to CNS translocation (Oberdorster et al. 2005 and Elder et al. 2006) and with two sentences providing background on air pollution epidemiology studies. Studies with carbon nanotubes recently reported by Takagi et al. 2008 and Poland et al. 2008 were also added to the text describing adverse lung effects observed in experimental animal studies.

2. Peer Reviewer # 2 - The draft CIB appropriately notes that because the purpose of occupational health surveillance (particularly medical screening) is the prevention (chiefly secondary prevention) of adverse health impacts, requisite criteria for such screening should include knowledge of "specific disease endpoints" associated with such exposures as well as sufficient information regarding the absolute, relative or population-attributable health risk. The draft CIB correctly concludes that because existing scientific and medical evidence is insufficient to meet these criteria, programs of specific medical screening cannot currently be recommended. The CIB briefly mentions the potential negative consequences of false positive test results that might be associated with nonspecific medical screening, and it mentions the need for research into biomarkers or clinical tests that have adequate sensitivity, specificity, and predictive value. This reviewer suggests that the narrative be more explicit in stating that the existence of screening modalities of sufficient positive predictive value that can detect adverse health effects early enough in the natural history of the disease to enable secondary prevention is an additional criterion that must be fulfilled prior to the recommendation of specific medical screening for nanomaterial exposed workers.

**Response** – Agree – this sentence was added to the end of the first paragraph in Recommendations on page 12: "Sufficient positive predictive value of a screening modality, to support detection of adverse health effects early enough in the natural history of the disease to enable secondary prevention, is an important factor when considering medical screening."

Peer Reviewer # 2 recommends that the discussion be expanded to mention data elements that might be included in an exposure registry, such as demographics, job duties or tasks, types of nanomaterials encountered, exposure measurements (including potential metrics), and engineering controls. Greater emphasis might be placed on a discussion of how exposure registries would greatly facilitate voluntary epidemiological research, in part because contemporaneous exposure data collected for the registry will avoid the pitfalls (particularly misclassification) of retrospective dose reconstruction…..

**Response** – NIOSH welcomes input concerning the usefulness of exposure registries as they might apply to nanotechnology workers. The detailed comments above are beyond the scope of this guidance focusing on medical screening – no change to document.

3. Other comments from Peer Reviewer # 2:

a) It is suggested that the discussion of "5.1 Take prudent measures to control exposures to engineered nanoparticles" be expanded beyond mere reference to the NIOSH draft document "Approaches to Safe Nanotechnology: An Information Exchange with NIOSH"....

**Response** – we have to strike a balance between length and inclusion of related useful information. No change to the document.

b) In like manner, it would be useful to expand, even modestly, the recommendation in 5.2 concerning "hazard surveillance." For example, brief but explicit guidance on the nature of what constitutes hazard surveillance could be offered, such as the list of bullet points on "hazard surveillance" contained on page 4 of a former NIOSH draft document entitled, "Framework for Considering Occupational Health Surveillance [for] Workers in Operations Involving Nanoparticles."

**Response** – Agree – one sentence of text and the bulleted list from the "draft Framework" document was added to Recommendation 5.2.

c) "Hence, it is suggested that the draft CIB place greater emphasis on the potential utility of an exposure registry".

**Response** – as noted above – expansion of text directly concerning exposure registries is beyond the scope of this document. No change to document.

d) Appendix D includes the sentence, "In addition, virtually no published data exist on occupational exposure concentrations for working in SWCNT operations." Notwithstanding that such data might not yet have been published, it does appear that useful information on nanomaterial exposure associated with workplace activities has been collected and presented at scientific forums (e.g. the platform presentations at the NIOSH/ University of Cincinnati conference on nanotechnology held December 2006 by Matthew Hull of Luna Innovations, the platform presentation at that conference by Doug Evans of NIOSH pertaining to the NIOSH HHE HETA report #2005-0291-3025, and the poster presentation at that conference by Nancy Jennerjohn et al of UCLA). The draft CIB should note the existence of such measurements, and should comment on the potential utility of relating such exposures, via appropriate allometric extrapolations, to dose-response relationships generated in toxicological studies on experimental animals.

**Response** – the point of Appendix D is to highlight current limitations in the evidence base, in the paragraph referenced in this comment, regarding SWCNT. Adding a notation concerning unpublished data does not add to the 'take home message' for this text – no change made. [Readers looking for the latest in unpublished data would very likely realize that the NIOSH Nanotechnology Research Center (NTRC) would be a reasonable source of inquiry].

**Peer Reviewer # 3**

Peer Reviewer # 3 provided the following:

**The hazard identification is a reasonable reflection of the available scientific studies.** The hazards associated with ultrafine particulate exposure primarily from combustion were included in the Current Intelligence Bulletin (CIB) and is informative in regard to the potential risks from exposure to engineered nanoparticles. It is suggested this section be rearranged in the following sequence: animal data on ultrafine particles; human data (morbidity and then mortality) on ultrafine particles; animal data on engineered nanoparticles. These data will help to inform why medical surveillance programs for workers in the engineered nanoparticle industry are indicated as a precautionary principle as applied to secondary prevention. These data also provide guidance as to specific medical screening in regard to the cardiovascular and pulmonary systems. From a toxicology perspective, ultrafine particulates have a higher surface area per unit mass than larger particles, have a very high efficiency of lung disposition, and are capable of gaining entry into the lung interstitium and vascular system and, therefore, are subsequently transported to other organ systems. These properties are size dependent and are applicable to engineered nanoparticles.

The animal data regarding exposure to silicon carbide whiskers provide guidance regarding potential exposure to engineered nanotubes. Silicon carbide whiskers are man-made and have a mono-crystalline structure and from a diameter perspective are in the upper range of engineered nanoparticles. *In vitro* studies demonstrate cytotoxic response equivalent to crocidolite asbestos. Animal studies have demonstrated alveolar, bronchiolar, and pleural thickening and adenomas and hyperphasia of the lung.

It is this reviewer's opinion that potential hazards associated with exposure to nanoparticles and nanotubes based on the correlate findings within the ultrafine particulate literature are not adequately represented from a toxicology perspective. This gap should be strengthened as the data on ultrafine particles justifies a more aggressive approach in regard to medical surveillance and medical screening for those exposed to engineered nanoparticles and nanotubes.

**The discussion of occupational health surveillance including medical screening is consistent with sound occupational health practice.**

The discussion of occupational health surveillance including medical screening follows standard occupational health practice principles but does not provide adequate precautionary guidance in the rapidly expanding engineered nanoparticles industry. This reviewer agrees that there is insufficient data within the nanoparticle toxicology literature to recommend specific medical screening tests for exposed workers. The similarity between ultrafine particles and engineered nanoparticles in regard to size distribution and the animal and human toxicology data regarding ultrafine particle exposure, however, justifies NIOSH taking a more proactive approach regarding recommendations for medical surveillance and medical screening.

The ultrafine particles medical literature supports the need for medical surveillance programs for workers exposed to engineered nanoparticles. Medical surveillance programs should addresses potential pre-existing risk factors for cardiovascular and pulmonary disease, signs and symptoms compatible with cardiovascular and pulmonary disease, and medical screening baseline EKG and spirometric tests. These organ systems are known to be adversely impacted by ultrafine particulate exposure. This type of **baseline** data (post employment/pre-placement) provides an opportunity for evaluating potential early changes in the cardiovascular and pulmonary systems over time both as group aggregate data and on an individual basis where a worker serves as his/her own control. The availability of baseline data provides a powerful tool for evaluating early indicators of change on a longitudinal basis above and beyond that associated with the "normal" aging process.

**The conclusions that form the basis of the recommendations are appropriate.**
The conclusions drawn by NIOSH are appropriate if focused solely on what is currently known regarding potential toxicology specificity associated with engineered nanoparticle exposure. NIOSH does not adequately take into consideration the known toxicity associated with ultrafine particulate exposure and the similarities between ultrafine particulates and nanoparticles in regard to surface area, lung deposition potential, and movement into the vascular system. Because of the potential for pulmonary, transdermal, and gastrointestinal absorption and resultant systemic dosage, there is a clear precautionary indication for medical surveillance as an interim guidance. Workers within the nanoparticle industry should have baseline medical surveillance that focuses on the cardiovascular and pulmonary systems and baseline medical screening EKG and spirometric tests. The frequency and content of subsequent medical surveillance and medical screening should be individualized on an industry by industry basis, potential exposure scenarios, and the evolving scientific literature regarding potential toxicity associated with nanoparticle exposure. NIOSH appropriately and clearly states that hazard surveillance and subsequent control measure to minimize exposure to engineered nanoparticles is indicated within this industry.

**Key points of Peer Reviewer # 3**:

1. The discussion of occupational health surveillance including medical screening is consistent with sound occupational health practice; NIOSH appropriately and clearly

states that hazard surveillance and subsequent control measure to minimize exposure to engineered nanoparticles is indicated within this industry.

2. The hazard identification (literature review of available toxicologic [hazard] data) is a reasonable reflection of the available scientific studies; this reviewer agrees that there is insufficient data within the nanoparticle toxicology literature to recommend specific medical screening tests for exposed workers. This reviewer feels that the NIOSH guidance does not adequately take into consideration the known toxicity associated with ultrafine particulate exposure and the similarities between ultrafine particulates and nanoparticles in regard to surface area, lung deposition potential, and movement into the vascular system (silicon carbide whiskers are specifically mentioned as an example).

3. The NIOSH interim guidance does not adequately translate available toxicologic data into precautionary guidance for medical surveillance. In other words, given available literature concerning nanoparticle and ultrafine exposure (which is adequately summarized in the guidance), this reviewer recommends more precautionary interim guidance concerning medical surveillance.

4. Peer Reviewer # 3 states "The {hazard review} supports the need for medical surveillance programs for workers exposed to engineered nanoparticles. Medical surveillance programs should addresses potential pre-existing risk factors for cardiovascular and pulmonary disease, signs and symptoms compatible with cardiovascular and pulmonary disease, and medical screening baseline EKG and spirometric tests....The frequency and content of subsequent medical surveillance and medical screening should be individualized on an industry by industry basis, potential exposure scenarios, and the evolving scientific literature regarding potential toxicity associated with nanoparticle exposure."

**Response** -These issues have been extensively discussed within NIOSH NTRC and between NIOSH and many external peer reviewers. The NIOSH NTRC is aware of the toxicologic data that has been generated and is being generated. The current draft of the guidance states "The current body of evidence about the possible health risks of occupational exposures to engineered nanoparticles is not sufficient to support the determination of specific medical screening for identifying preclinical changes associated with exposure to engineered nanoparticles. No substantial link has been established between occupational exposure to engineered nanoparticles and adverse health effects. In addition, the toxicological research to date is insufficient to recommend such monitoring, the appropriate triggers for it, or components of it. As the volume of research on the potential health effects increases, continual reassessment will be needed to determine whether medical screening is warranted for workers who are producing or using engineered nanoparticles."

5. Peer Reviewer agrees with the above statement but feels that **generalized** medical screening is indicated: "...workers within the nanoparticle industry should have baseline medical surveillance that focuses on cardiovascular and pulmonary systems..."

**Response** – The NIOSH NTRC has discussed this recommended approach extensively. Among the important issues this approach raises are:
1) the issue of exposure. Exactly who are the workers 'within the nanoparticle industry' – how do we determine who is exposed? and
2) the issue of non-specific medical screening. The NIOSH CIB reviews the criteria for performing medical screening - inherent in the criteria for performing medical screening is that the specific disease endpoint(s) must be known to allow for test selection. Some of the critical aspects of medical screening include:

- Identification of target organ toxicities for each hazard;
- Selection of test for each "screenable health effect"
- Interpretation of test results

Baseline data collected that pertain to non-specific health effects will not be useful (will not be interpretable) until subsequent (follow-up) surveillance can be better defined.

6. Peer Reviewer # 3 recommendation is that, after baseline data are collected, "…the frequency and content of subsequent medical surveillance and medical screening should be individualized on an industry by industry basis, potential exposure scenarios, and the evolving scientific literature regarding potential toxicity associated with nanoparticle exposure."

**Response** -As the current guidance has discussed, important factors such exposure to nanoparticles ("who is exposed") and toxicity (how do the existing toxicity data dealing with *in vitro* testing and animal testing translate into potential occupational hazard and ultimately risk) are not well understood at this time. The ability to make recommendations concerning subsequent medical screening is limited at this time, making the collection of non-specific baseline data not useful for the intended purposes.

**Summary** – no change to document at this time.