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

From:
Sent: Tuesday, April 15, 2008 4:57 AM
To: NIOSH Docket Office (CDC); Niemeier, Richard W. (CDC/NIOSH/EID)
Subject: Peer Review Comments on NIOSH 115 Nano CIB
Attachments: CIB NIOSH -115 nano eview.doc

Attached please find my external peer review comments on the draft NIOSH Current Intelligence Bulletin: Interim Guidance on Medical Screening of Workers Potentially Exposed to Engineered Nanoparticles.

I appreciate the opportunity to offer comments on this important topic.

Sincerely,

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The draft Current Intelligence Bulletin entitled "Interim Guidance for the Medical Screening of Workers Potentially Exposed to Engineered Nanoparticles" describes the existence of *potential* health hazards posed by occupational exposure to nanomaterials, and recognizes that available information regarding specific dose response effects in humans is currently insufficient to recommend specific medical screening of workers. In the interim it recommends that 1) "hazard surveillance" be conducted to characterize and limit exposures in the workplace; 2) information from existing medical surveillance programs be potentially utilized to discern potential health effects resulting from nanomaterial exposure, and 3) additional research be conducted regarding specific health effects and the clinical utility of candidate biomarkers and clinical tests. The document notes that exposure registries would promote epidemiological research on exposure-disease association and health risks, and would facilitate risk communication and risk notification.

I. The first major charge to the reviewers was to address whether the hazard identification in the document was a reasonable reflection of available scientific studies. As a subsidiary consideration, reviewers were asked to assess whether the conclusions made in the document were scientifically supportable and appropriate in light of existing toxicological data.

Response: The draft CIB offers an accurate if sparse discussion of the potential health effects of nanomaterials that is confined primarily to two sentences noting pulmonary and cardiovascular effects (lines 69 to 75). Key primary and secondary source materials concerning potential adverse effects have been cited in those lines and in lines 206 – 207 and 513 – 514. The document notes that the only human epidemiology regarding the potential health impact of nanomaterial exposure exists from studies of exposure to potentially larger "ultrafine" particles, but the specific findings from those studies are not described. This reviewer recommends that a) the potential for neurotoxicity from central nervous system translocation of inhaled nanomaterials be mentioned in the CIB (cf 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).

II. The second major charge to the reviewers was to address whether the discussion of occupational health surveillance including medical screening was consistent with sound occupational medicine practice. As a subsidiary consideration, reviewers were asked to comment on what medical surveillance may be appropriate at this time, and to note potential benefits, adverse impacts, and limitations of medical screening, and exposure registries.

Response: 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 (cf line 115) as well as sufficient information regarding the absolute, relative or population-attributable health risk (cf lines 492 -494). 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 (cf lines 258 – 261), and it mentions the need for research into biomarkers or clinical tests that have adequate sensitivity, specificity, and predictive value (lines 229 – 233). 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.

In Appendix E (lines 569 – 571), the draft CIB appropriately notes that exposure registries "may provide opportunities to determine the exposure-disease association and risk. Also, when practical prospective studies can be designed, registries can be used to establish hypotheses." It also correctly notes (page 33) that the existence of an exposure registry will facilitate future risk communication and risk notification, and actions of primary and secondary prevention. Finally, the narrative reasonably suggests that exposure registries may have value as a public demonstration that "appropriate efforts are being taken to identify and control potential hazards in a timely fashion." This reviewer 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. It is also worth noting that aggregated data analysis from a large, industry wide exposure registry may have increased statistical power to detect trends in adverse health effects, particularly at an early stage in the disease process. Finally, it may be noted that the information contained in an industry wide exposure registry may help to establish industrial hygiene benchmarks that will promote feasible exposure control now and in the future.

III. The third major charge to the reviewers was to assess whether "the conclusions that form the basis of the recommendations are appropriate."

Response: The draft CIB narrative reaches accurate and appropriate conclusions on pages 9 to 11 regarding the insufficiency of current data on specific human health effects, the appropriate metric and magnitude of nanomaterial exposure in the workplace, dose-response relationships, and overall risk characterization. As such, it is appropriate that the draft CIB does not recommend a formal program of medical screening for nanotechnology workers at this time. With respect to the recommendations that are made in section 5.0 (pp 12 – 14), the following reviewer comments are offered:

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". It would increase the value of the CIB to summarize some of the key recommendations of that document, such as those pertaining to use of enclosed systems, dust suppression in housekeeping, and the collection of baseline and periodic exposure measurements.

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."

c) Recommendation 5.3 pertains to the use of existing medical surveillance data generated independent of nanotechnology concerns per se (such as those mandated by OSHA or recommended by NIOSH) to identify whether there is an increased frequency of adverse respiratory and cardiovascular effects associated with nanomaterial exposure. However, such data will be of practical value in addressing this issue only to the extent that the nanomaterial exposure of the workers has been characterized and tracked. Hence, it is suggested that the draft CIB place greater emphasis on the potential utility of an exposure registry. The draft CIB might also note other categories of existing health outcome data that could be analyzed in conjunction with exposure information. This data includes diagnostic codes (e.g. "myocardial infarction") currently collected from disability claim forms, return to work questionnaires, health insurance claim forms, and death benefit programs.

Additional comment: Appendix D includes the sentence (line 508), "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 HHE Heta #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.