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

From: Barbara Cummings [barbara.cummings@bayerbms.com]
Sent: Friday, February 18, 2011 4:49 PM
To: NIOSH Docket Office (CDC)
Subject: 161-A - Occupational Exposure to Carbon Nanotubes and Nanofibers
Attachments: BMS Comments NIOSH CIB CNT-CNF.doc

Importance: High

To whom it may concern:

Please find attached comments prepared by Bayer MaterialScience regarding the NIOSH Current Intelligence Bulletin "Occupational Exposure to Carbon Nanotubes and Nanofibers." Further, per the request of NIOSH, the attached electronic copy is formatted as a Microsoft Word Document.

Kind Regards,

Barbara J. Cummings, CIH
Manager Product Safety
Bayer MaterialScience
Product Safety & Regulatory Affairs Department
Phone: (412) 777-3454
Fax: (412) 777-7484
Email: barbara.cummings@bayer.com

Bayer MaterialScience

Bayer MaterialScience LLC
Product Safety & Regulatory Affairs
100 Bayer Road
Pittsburgh, PA 15205-9741

NIOSH Docket Number: NIOSH 161-A

Bayer MaterialScience, LLC (BMS) is pleased to provide comments on the National Institute of Occupational Safety and Health (NIOSH) Current Intelligence Bulletin (CIB) "Occupational Exposure to Carbon Nanotubes and Nanofibers."

BMS, as a Responsible Care® Company, supports and promotes the safe use and manufacture of nanotechnology products. Consistent with its commitment to Responsible Care®, BMS engaged in a proactive process to thoroughly document the characteristics of its multi-walled carbon nanotube (MWCNT) Baytubes®, and provide extensive toxicity and other safety testing results. This list of toxicity studies included an acute and subchronic inhalation study of Baytubes®. This method of testing is considered to represent the most appropriate means of evaluating the potential respiratory health hazards of MWCNTs for extrapolation to human health risk assessment. Thus, we believe that it is premature to judge all carbon nanotubes (CNTs) (or carbon nanofibers (CNFs)) as being the same in characteristics and toxicity, as each CNT/CNF may have a distinct toxicity profile.

General Comments

The NIOSH CIB appropriately identifies the need to handle nano-based materials in a safe manner. In fact, we at BMS, as part of our Product Stewardship Program (BayCare®) have published guidelines for the safe handling of Baytubes® entitled, Baytubes® Carbon Nanotubes; Safe Handling Guidelines (BMS, 2009). These guidelines are consistent in many ways with the recommendations offered by NIOSH, particularly those identified in the CIB on pages 8-15. For example: (1) use of available information to continually assess current hazard potential related to CNTs/CNF; (2) identifying and characterizing processes and job tasks where workers come into contact with CNTs/CNF; (3) educating workers on the sources and job tasks that may expose them to CNTs/CNFs; (4) use of engineering controls (e.g., exhaust ventilation systems, enclosures, etc.); and (5) the proper selection of personal protective equipment, to name a few. However, while BMS supports many of the principles and recommendations outlined in this CIB, we respectfully offer comment on the document as identified in the following sections.

Toxicology Comments

We support the use of subchronic inhalation toxicity studies as the critical studies for determination of a REL. Studies utilizing other modes of test substance administration such as intratracheal instillation or aspiration have sufficient methodologic limitations leading to uncertainties when compared to inhalation exposures that they may serve to inform on potential toxicologic concerns but should not be used to extrapolate findings to derive estimates of acceptable human exposures. Even the use of acute inhalation toxicity studies may be of limited value to assess more chronic health sequelae.

The CIB did not correctly apply the definition of adversity in the benchmark dose-response analysis.

One of the critical elements in the derivation of a REL in the CIB is selection of the key studies and the identification and assessment of critical endpoints. As indicated earlier, the subchronic inhalation toxicity studies are considered to represent the key studies for examination of critical endpoints. However, a key flaw in the CIB is not having appropriately defined adversity for the various outcomes reported in the subchronic studies. The CIB notes that early-stage fibrotic and inflammatory lung responses were selected and were characterized as lung inflammation, granuloma and interstitial fibrosis. In contrast to the conclusions operative in the CIB, caution against such conclusions for fibrosis is expressed by several investigators studying CNTs. For example, Ellinger-Ziegelbauer and J. Pauluhn (2009) state "*These findings support the hypothesis that the sirius red stained collagen using the Sircol assay likely reflects the exudated, inflammation related collagen rather than the (myo-) fibroblast synthesized septal collagen*" and Ryman-Rasmussen et al. (2009) state "*A caveat is that the fibrosis score relied on trichrome staining, which, although commonly used, could stain other cell matrix components and contribute to the observed pleural wall thickness.*" Thus, these investigators are attempting to distinguish their findings from that where significant tissue remodeling occurs with the presence of mature, cross-linked fibroblast-derived collagen. The histopathologic findings described by Pauluhn (2010) are not consistent with pulmonary interstitial fibrosis and do not meet the criteria for "adverse effect" as defined by the USEPA (USEPA-IRIS). The CIB specifically notes on page 103 that "A benchmark dose has been defined as "… a statistical lower confidence limit for the dose corresponding to a specific increase in level of [adverse] health effect over the background level" [Crump 1984]". Thus, in using the benchmark dose model, the CIB has not followed the prescribed input for the model. A related limitation to the assessment in the CIB is the use of only incidence data and disregarding the severity of response both as a function of exposure concentration and time. Solely using incidence data led to the input of dichotomous data to the benchmark model and the resultant outcome of a 10% risk being less than the NOAEL determined in the study by Pauluhn (2010). This disregard of severity of response overlooks a key component essential to the determination of an adverse dose-response. Thus, the results of the benchmark analysis

of dose-response for the study by Pauluhn (2010), as described in the CIB, are considered inappropriate for derivation of a REL.

The CIB should explicitly allow for other product-specific occupational exposure limits (OELs).

Where sufficient data leads to product specific recommendations of an OEL that diverge from the REL in the CIB, there should be an explicit acknowledgement that allows for acceptance of other product-specific RELs or comparable occupational exposure limits (OEL). The CIB describes experimental evidence that point to differences in toxicologic potency and/or differences in the type of response for different substructural materials. Even if the role of specific characteristics of CNTs such as shape, aspect ratio, physical and chemical properties, reactivity, etc that may interact to induce differential response are not clearly understood, it is possible to develop recommended OELs for specific products through product-specific testing. A more thorough understanding of the underlying cause of product-specific effects is more relevant when several subcategories of materials (CNF, SWCNT and MWCNT) with differing characteristics are grouped for the purpose of establishing a common OEL such as the REL proposed in the CIB. Although these materials may display some biologic responses in common such as an inflammatory response in the lung, there are sufficient differences even within a single category of materials (e.g., MWCNT) to warrant consideration of exceptions to a common REL. Thus, where sufficient and relevant toxicological data has been developed to warrant a product-specific recommended OEL and where such a recommendation has been made as in the case of Baytubes® (Pauluhn, 2010; Pauluhn, 2011), the CIB should provide a more specific and detailed justification as to why a product-specific recommended OEL is not acceptable based on scientific grounds, or alternatively explicitly provide for the allowance of product-specific OELs.

Baytubes® have not been associated with precursor events suggestive of mesothelioma.

In further support of a product specific recommended OEL for Baytubes®, this product does not meet some of the criteria in the CIB that suggests potential health concerns. A major potential health concern was the prospect of exposures leading to mesothelioma and the CIB attempts to relate three lines of experimental evidence to suggest the plausibility of this possible health threat: migration to the pleura; asbestos-like pathology; and evidence for genotoxicity. The study reporting migration of MWCNT to the pleura did not use Baytubes® and differences in shape (long and thin versus short and coiled) may play a role in movement through various tissues. In addition, the subchronic inhalation toxicity study of Baytubes® (Pauluhn, 2010) did not indicate any effects on the lung pleura; even premonitory indications suggesting a potential progression to mesothelioma (i.e., the key histopathologic landmarks) were not detected in the pleura. Furthermore, to the point of inducing asbestos-like pathology, in addition to the absence of any histopathologic evidence of effects on the pleura, it is noted that the predominant response to Baytubes® in the lungs was an acute inflammatory response with attendant collagen exudation and interstitial thickening. This pattern of response is not consistent with that typically associated with the sequence of events leading to mesothelioma.

Lastly, the study cited as demonstrating evidence of genotoxicity used SWCNT (Sargent, et. al., 2009). It is significant to note that the results of a chromosome aberration test using Chinese Hamster V79 cells (Wirnitzer, et. al., 2009), Ames Salmonella reverse mutation assay (Wirnitzer, et. al., 2009), and HGPRT forward mutation using Chinese Hamster V79 cells (BMS, 2010) did not show a mutagenic or clastogenic potential for Baytubes®. In a recent publication by Thurnherr, et. al., (2011), where in vitro- comet assay and -micronucleus assay were performed, Baytubes® didn't display any genotoxic potential. The study by Thurnherr, et. al. (2011) also examined other endpoints to compare the response of human pulmonary epithelial cell line A549 and showed marked differences in response between Baytubes® and crocidolite asbestos. The overall weight of evidence from all three lines of inquiry do not indicate a concern for an outcome of mesothelioma from potential exposure of workers to Baytubes®.

Overall Conclusion

The benchmark dose-response analysis of the data from Pauluhn (2010) does not accurately reflect the potential health hazard of Baytubes® as used to derive the REL, and that a separate product-specific OEL is justified.

Section 6 (Recommendations) Comments

NIOSH has identified six recommendation categories in Section 6 of the CIB, Pages 45-58. These include: exposure assessment, engineering controls, work practices, personal protective equipment, respirators and medical screening and surveillance. Comments are provided as follows:

Exposure Assessment

NIOSH is recommending that a mass-based airborne concentration measurement be used to monitor the workplace for airborne CNT/CNFs. The mass-based measurement technique is one technique/metric commonly proposed. Others include number (i.e., particle counting) and volume (i.e., surface area) estimates. Each technique presents its own challenge. While we support the use of a mass-based measurement technique the method recommended by NIOSH to measure airborne levels of CNTs/CNFs (NIOSH Method 5040) is not specific for these substances. This method is designed to identify total carbon (TC) with an elemental carbon (EC) exposure marker. Thus, it would be sensitive to all elemental carbon (e.g., soot, diesel exhaust, carbon black, cigarette smoke, etc.). In this regard, an overestimation of the airborne concentration of CNT/CNF is anticipated. There also is some question as to the commercial availability of the thermal-optical analyzer which is integral to the analysis of the airborne sample. Further, high sample volumes are needed to achieve lower limits of detection which is counter to typical CNT/CNF use and handling scenarios that more often are short-term in nature (i.e., 5- to 15-minutes). The suggestion by NIOSH to use other analytical techniques (e.g., TEM, SEM, etc.) when interferents are anticipated is understood, but not practical. In reality, this may be needed in all cases which would be cost prohibitive for most

employers. Thus, other consideration should be given to proposed monitoring methods, for example, those that use a "metallic marker" which is present as a trace quantity impurity in CNTs. NIOSH has experience with such methods, where both iron and nickel tracers were used (Maynard, et. al., 2004). This method allowed for the discrimination between the metal containing CNTs and other airborne materials. Note: since metal concentrations can vary with each production batch it is highly recommended to submit a bulk sample with the filter analysis.

Engineering Controls

NIOSH is recommending that engineering controls be installed to control worker exposure to CNT/CNF. Engineering controls are widely recognized as the best means of controlling potential worker exposure. We agree with and support the use of engineering controls such as source enclosures, local exhaust ventilation, and handling of the material in a less air-dispersible form (e.g., as a paste, solution, etc.). Further, as NIOSH has recommended, the exhaust ventilation unit should be properly designed according to recognized principals such as those provided by the American Conference of Governmental Industrial Hygienists (ACGIH, 2010).

Work Practices

NIOSH is recommending that formal procedures (e.g., SOPs) be developed to include good work practices, proper selection of PPE, worker training/education, hygienic practices, and clean-up/disposal practices. We agree with and support the recommendation of SOPs to address these considerations. Further, the practices described under 6.3.1 to reduce the potential for exposure during clean-up and disposal (e.g., HEPA-filtered vacuum cleaners, wet wiping techniques, etc.) are recognized "best practices" for these types of materials.

Personal Protective Equipment

NIOSH is recommending the use of protective clothing and gloves when "all technical measures to eliminate or control release of exposure to CNT and CNF have not been successful or, in emergency situations." This is considered an industry "best practice" which we believe to be essential to the safe handling of nanomaterials. Further, NIOSH recognizes that the data is limited as to which material type (e.g., latex vs. nitrile vs. cotton) and product garment (e.g., suit vs. apron vs. lab coat) is appropriate in all cases. For example, while an impermeable Level A suit offers a high level of protection, it is the least comfortable to wear and has a low user/worker acceptance. Thus, a balance between protection and user comfort/acceptance needs to be considered. These factors should be included when conducting a PPE hazard assessment, as required under the OSHA PPE standard, 29CFR 1910.132(d)(1). As part of the assessment CNT/CNF manufacturers and commercial PPE manufacturers should also be consulted to aid in the proper selection of PPE garments.

Respirators

NIOSH is recommending the use of respiratory protection "when engineering controls and work practices cannot reduce worker CNT and CNF exposures to below the REL…" or, "…for certain work tasks that place workers at risk of potentially high peak concentrations of CNT and CNF…" We also support the use of applicable respiratory protection (1) when a recognized/representative OEL is/can be exceeded, (2) when CNT/CNF exposure levels are unknown, and (3) during potential high airborne (e.g., peak) concentrations. Of course, when respiratory protection is specified, it must meet the requirements specified in OSHA standard 29CFR 1910.134.

Medical Screening and Surveillance

NIOSH is recommending the implementation of a medical screening and surveillance program for CNT/CNF workers based on their potential for adverse respiratory health effects. This conclusion is based upon limited (and nonspecific) toxicology studies/data which has been extrapolated across a "family" of comparable nanomaterials to support a recommendation for medical surveillance.

Primary prevention strategies are based, in significant part, on exposure mitigation via engineering and administrative controls, and the proper use of PPE. Certainly these five elements (i.e., exposure assessment, engineering controls, work practices, personal protective equipment, and respiratory protection) are recognized best practices for nanomaterials safe handling. While it is well understood that medical surveillance protocols are prevention-focused their effectiveness, in secondary prevention, is based upon well-defined and recognized health end point(s) (e.g., specific disease(s), target organs, etc.) which can then be medically monitored for early disease detection.

For CNT/CNF's such health end point(s) are not generally recognized nor agreed upon at the present time. Further, by focusing on respiratory effects, it is entirely possible that additional or unexpected health outcomes may be completely overlooked or not recognized, thus sharply limiting the goals of secondary prevention. Thus, the justification for establishing a specific respiratory medical surveillance program, at this time, appears to be preliminary and somewhat discriminatory in its focus.

The prevention and detection of CNT/CNF occupational injury and illness is an area of research and understanding which is still in many ways in its infancy. The current recommendations do not appear to be based on sufficient evidence that support its proposed design nor enable more powerful scientific inquiry/study. It may be more fruitful to collect more definitive exposure information which can then be correlated with various health data sources to monitor health and exposure trends, view CNT/CNF

worker cohort experience in relationship to explicit risk assessment information, such as a formal registry mechanism would afford. Sources of information include clinical evidence and case reports, diseases registries, epidemiological studies of occupationally exposed workers, national health data resources, etc. Thereafter, and with appropriate ongoing analysis and scientific inquiry, it may be possible to make more definitive recommendations concerning effective medical monitoring component(s) of a CNT/CNF medical surveillance program which would directly support disease monitoring and prevention.

Overall Conclusion

Consideration should be given to other monitoring methods, particularly those that have specificity to the CNT/CNF source. Applicable and appropriate engineering controls, work practices, PPE, and respiratory protection are a necessary to effectively control potential exposure to CNTs/CNFs. At this time, establishing a specific respiratory medical surveillance program appears to be preliminary and potentially discriminatory in its focus.

References

ACGIH, American Conference of Governmental Industrial Hygienists: Industrial Ventilation, A Manual of Recommended Practice. 27th Edition. Cincinnati, Ohio (2010).

BMS, Bayer MaterialScience AG: V79-HPRT test in vitro for the detection of induced forward mutations. Report No. AT06031 (2010). (unpublished report)

BMS, Bayer MaterialScience, LLC: Baytubes® Carbon Nanotubes: Safe Handling Guidelines (April 2009).

Crump, K.S. A new method for determining allowable daily intakes. Fundamental and Applied Toxicology 4(5):854-871 (October 1984).

Ellinger-Ziegelbauer, H.; Pauluhn, J. Pulmonary toxicity of MWCNT (Baytubes®) relative to a-Quartz following a single 6h inhalation exposure to rats and a 3 months post-exposure period. Toxicology 266: 16–29 (2009).

Maynard, A.D.; Baron, P.A.; Foley, M.; Shvedova, A.A.; Kisin, E.R.; Castranova, V.: Exposure to carbon nanotube material: aerosol release during the handling of unrefined single-walled carbon nanotube material. Journal of Toxicology and Environmental Health 67(1): 87-107 (January 2004).

Pauluhn, J. Multi-walled carbon nanotubes (Baytubes®): Approach for derivation of occupational exposure limit. Regul. Toxicol. Pharmacol. 57(1):78-89 (2010).

Pauluhn, J. Poorly soluble particulates: Searching for a unifying denominator of nanoparticles and fine particles for DNEL estimation. Toxicology 279(1-3):176-88 (2011).

Ryman-Rasmussen, J.P.; Cesta, M.F.; Brody, A.R.; Shipley-Phillips, J.K.; Everitt, J.I.; Tewksbury, E.W.; Moss, O.R.; Wong, B.A.; Dodd, D.E.; Andersen, M.E.; Bonner, J.C.; [2009b]: Inhaled carbon nanotubes reach the subpleural tissue in mice. Nature Nanotechnology DOI: 10.1038/NNANO.2009.305.

Sargent, L.M., Shvedova, A.A., Hubb, A.F., Salisbury, J.L., Benkovic, S.A., Kashon, M.L., Lowry, D.T., Murray, A.R., Kisin, E.R., Friend, S., McKinstry, K.T., Battelli, L., Reynolds, S.H. Induction of aneuploidy by single-walled carbon nanotubes. Environ Mol Mutagen 50 (8): 708-717 (2009).

Thurnherr, T., Brandenberger, C., Fischer, K., Diener, L., Manser, P., Maeder-Althaus, X., Kaiser, J.P., Krug, H.F., Rothen-Rutishauser, B., Wick, P. A comparison of acute and long-term effects of industrial multiwalled carbon nanotubes on human lung and immune cells *in vitro*. Toxicology letters 200 (3): 176-186 (February 2011).

United States Environmental Protection Agency (USEPA): IRIS, Integrated Risk Information System: http://www.epa.gov/IRIS/help_gloss.htm.

Wirnitzer, U.; Herbold, B.; Voetz, M.; Ragot, J.: Studies on the in vitro genotoxicity of baytubes®, agglomerates of engineered multi-walled carbon-nanotubes (MWCNT). Toxicology letters 186(3):160-5 (2009).