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SUBMITTED BY ELECTRONIC MAIL TO: NIOSHDOCKET@CDC.GOV

The Nanotechnology Panel of the American Chemistry Council (ACC) is 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 Panel supports the responsible development of nanotechnology and appreciates the considerable effort NIOSH has invested in the draft CIB. We have identified what we believe to be several important areas for improvement and clarification, and we urge NIOSH to consider our comments in the development of the final CIB.

The Panel supports NIOSH's effort to develop a recommended exposure limit (REL). Such guidelines contribute to the responsible development of carbon nanotube and nanofiber (CNT/F) technology, which will in turn lead to better acceptance by regulators, industrial users, and consumers. The Panel appreciates that NIOSH utilized a specific method (NIOSH 5040, *Diesel Particulate Matter*) for measuring exposure. However, it is important to recognize that 5040 has several limitations in the context of carbon nanomaterials, one of the most critical of which is that it cannot differentiate among different forms of particulate carbon that may be present in the work place.

Method 5040 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.). During the February 3 public meeting to discuss and obtain comments on the draft CIB, NIOSH indicated that typical environmental background levels of EC are in the range of 0.5 $\mu g/m^3$, and thus any workplace exposure levels above the proposed REL could be attributed to CNT/F. However, other sources (*e.g.*, diesel particulate matter) may be present in the workplace and can contribute to EC measurements at or above the proposed

Members of the ACC Nanotechnology Panel include 3M, Arch Chemicals, Arkema Inc., BASF Corporation, Bayer MaterialScience, Cabot Corporation, Cytec Industries, The Dow Chemical Company, DuPont, Evonik Degussa Corporation, Ferro Corporation, and Procter & Gamble.

REL, leading to overestimation of CNT/F presence. While NIOSH recognizes this possibility, its referral to emission assessment guidance that suggests the use of direct-reading, real-time instrumentation to collect both pre- and post-process background samples, in addition to collection of "at source" filter-based air samples for TEM/SEM and mass analysis, would be cost prohibitive and impractical for most employers. Thus, consideration should be given to proposed product-specific monitoring methods, for example those that use a "metallic marker" which is present as a trace quantity impurity in CNTs. Given that 5040 is not specific for type of EC, the CIB would be more useful if it included a discussion of key considerations in background monitoring, expected background levels, and approaches to differentiating sources of background particles from what might be reliably attributed to CNT/F. Any data NIOSH collected through real-time monitoring during the development of the draft CIB should be included in the CIB. Users will find such information extremely helpful.

The Panel appreciates that NIOSH selected an REL that is within current analytical capabilities, such that the approach can actually be implemented. However, as NIOSH notes in the draft CIB, the proposed REL may require adjustment as alternative or improved methods become available. A more appropriate approach might be one that is more closely related metrically to measurements used to understand human health risks from CNT/F (*i.e.*, a fiber-based approach). The CIB acknowledges this issue in the Executive Summary.[1] The Panel realizes that such an approach may not be available at this time, but we believe that the CIB could be strengthened with additional discussion around this issue, particularly its implications for the quantitative risk assessment and the recommended REL.

The Panel also believes that the CIB would be enhanced significantly by a discussion of the fact that not all CNT/F have the same characteristics with respect to purity, length, and other features that are known to influence hazard potential. Indeed, CNT/F can vary significantly in terms of their shape, size, structure, agglomeration state, physical-chemical properties, surface treatment, and functionalization. For this reason, the proposed REL may not be appropriate for all CNT/F. NIOSH should also acknowledge that CNT/F produced by different manufacturers may have different properties and characteristics that lend themselves to more sensitive and specific detection and quantification approaches.[2] There may be instances in which individual manufacturers have the ability to set their own health-protective REL based on hazard assessment specific to their material, and the CIB should incorporate such flexibility.

[1] Page 7: "These data indicate that exposure metrics other than airborne mass concentration (*e.g.*, number concentration of CNT or CNF structures of specified dimensions) may be a better predictor of certain lung diseases (*e.g.*, fibrosis)."
[2] See for example Tabet, L. et al. 2011. *Coating carbon nanotubes with a polystyrene-based polymer protects against pulmonary toxicity.* Particle and Fiber Toxicology 8:3.

The issue of CNT/F variability has significant implications for the way NIOSH approached its risk assessment. NIOSH used a benchmark dose (BMD) estimate to evaluate dose-response, combining data from several studies. Doing so was an appropriate strategy given the disparity in the exposure concentrations. However, for the endpoint or biological metric, NIOSH selected an estimate of lung burden rather than a common biological endpoint such as inflammation. The assumed value of this approach was to allow NIOSH to include data from other studies that utilize routes of administration that directly enter the lung (*e.g.*, intratracheal instillation and oropharyngeal aspiration). Such an approach presents several issues that NIOSH or other regulatory bodies should weigh carefully:

- Lung burden is overestimated. Alveolar deposition fraction of 0.01 was estimated from a study using a single exposure concentration.[3] Furthermore, traditional values for deposition were used based on spherical particles. However, this approach may be incorrect. Modeling and experimental data demonstrate that alveolar deposition of particles less than 100 nm decreases as the size decreases to 1 nm.[4] Unless large agglomerates are expected, a lower lung deposition may be appropriate.

- Lung burden produces dose-response curves that are not easily extrapolated. In fact, Figure A-1 for the two inhalation studies demonstrates that few lung doses are in the linear portion of the response curve. Rather, it would appear that the lung burden curves reflect only the unique responses of the rat (*i.e*, lung overload). Using airborne concentration and a continuous variable such as neutrophil number might better demonstrate a linear response along the entire dose response curve and be more amenable to BMD calculations. Such an approach was used by others with better results.[5]

- Inclusion of data from studies using direct administration methods such as intratracheal instillation or pharyngeal aspiration is questionable. These methods intentionally bypass nasal deposition, which could be significant for particles less than 100 nm. Furthermore, while pulmonary distribution may be even across the lung lobes, this may not reflect airborne exposure. Making matters worse, one study used a single dose level, making calculation of a BMD impossible.[6]

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[3] As cited in draft CIB: Shvedova, A.A. et al. 2008. Inhalation versus aspiration of single walled carbon nanotubes in C57BL/6 mice: inflammation, fibrosis, oxidative stress and mutagenesis. American Journal of Physiology - Lung Cellular and Molecular Physiology 295:L552−L565.

[4] Gradon, L., and Yu, C.P. 1989. Diffusional particle deposition in the human nose and mouth. Aerosol Science and Technology 11:213-220.

[5] Pauluhn, J. 2010. Multi-walled carbon nanotubes (Baytubes): approach for derivation of occupational exposure limit. Regulatory Toxicology and Pharmacology 57: 78–89.

[6] Shvedova study cited previously.

- Extrapolation to a human-equivalent dose does not consider rodent-specific phenomenon that are not relevant for humans (*i.e.*, lung overload). In the extrapolation of effects in the rat to effects in humans, NIOSH assumes that equal responses to equivalent doses are expected. However, clearance mechanisms in the rat are more easily overloaded than in humans.[7] Thus, the effects in rats, especially those at high dose levels, clearly overestimate the effects in humans.

Despite the fact that these weaknesses in the risk assessment were acknowledged in Section A.4.4, Strengths and Limitations, NIOSH seems to have given them insufficient weight. The Panel feels strongly that there is a need to explore these issues in more depth. Given the differences in occupational exposure levels (OEL) cited in Schulte et al., 2010,[8] the Panel strongly recommends that instead of forging ahead on the basis of the current risk assessment, NIOSH would do better to convene a work group of parties whose OEL values were reported in the Schulte et al. paper to attempt to reach consensus on the appropriate approach, given the vast differences in the characteristics of commercially available CNT/F.

While the Panel recognizes that Section 6, Recommendations, largely follows the traditional occupational hygiene hierarchy, we are concerned by NIOSH's recommendation to "substitute a non-hazardous or less hazardous material for CNT and CNF when feasible" (page 9). While we agree that the potential hazards of a material should be considered when evaluating that material for use, the nature and costs of CNT/F are such that substitution is not likely. Also, the statement implies that CNT/F can never be handled or used safely, regardless of risk management controls and protections. We request that NIOSH deleted it from the CIB. The Panel understands that the evaluation of potential risks from CNT/F is a matter of ongoing research, and the Panel sponsors and participates in such research. The Panel fully supports best practices to minimize exposures, implement risk management controls, and provide appropriate guidance to manufacturers and users of CNT/F. We believe that potential risks can be managed effectively with the current state of knowledge, even while hazard and exposure evaluation continues.[9]

Finally, the Panel strongly recommends greater clarity and specificity around the types of personal protective equipment that should be used to limit exposure. Including more detail would significantly improve the practical utility of the CIB. It is our understanding that during the February 3 public meeting, NIOSH staff referenced practices in the pharmaceutical and cosmetic

[7] Morrow, P.A. 1988. Possible mechanisms to explain dust overloading of the lungs. Fundamental and Applied Toxicology 10: 369-384.
[8] Schulte, P.A., et al. 2010. Occupational exposure limits for nanomaterials: state of the art. Journal of Nanoparticle Research 12:1971-1987.
[9] See also Institut de Recherche Robert-Sauvé en Santé et en Sécurité du Travail (IRSST), La Commission de la Santé et de la Sécurité du Travail du Québec (CSST), and Nano Quebec. 2009. Report R-599: Best Practices Guide to Synthetic Nanoparticle Risk Management.

industries. Examples from those industries should be described in more detail if in fact NIOSH believes them to be best practices.

Thank you for the opportunity to provide comments on the draft CIB *Occupational Exposure to Carbon Nanotubes and Nanofibers.* While the Panel believes that occupational exposure guidelines are important for the responsible development of CNT/F technology, we believe that the current draft suffers from critical shortcomings that will diminish its utility and impact. We urge NIOSH to consider our suggestions and recommendations and are open to engaging NIOSH on any of the concerns and recommendations made in this letter.

Sincerely,

Jay West
Senior Director, Chemical Products and Technology Division
ACC Nanotechnology Panel