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

From: juergen.pauluhn@bayer.com
Sent: Tuesday, February 08, 2011 5:18 AM
To: NIOSH Docket Office (CDC)
Subject: Docket no. NIOSH 161-A
Attachments: Review of the NIOSH CIB.docx

Dear Sirs,

attached you receive the requested review.

With kind regards/Mit freundlichen Grüßen

Juergen Pauluhn

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Review of the NIOSH scientific document entitled NIOSH Current Intelligence Bulletin: Occupational Exposure to Carbon Nanotubes and Nanofibers

The CIB is a comprehensive and state-of-the-art review of the current literature. The interpretation of data is sound taking into account that the focus of the CIB is to derive a "PAN-CNT REL". By default, such approach must be ultimately conservative in order to address all possible pathomechanisms. The uncertainty involved in the derivation of OELs from substance-specific data is likely to be markedly reduced, especially in the presence of PBPK-based study design, verification of lung dosimetry by empirical data, and a mechanism-based target organ dose-effect analysis. In such cases; any product-specific OEL should supersede the generic more conservative REL.

There are yet no internationally harmonized or regulatory binding testing guidelines for poorly soluble micronsized or nanosized particles; however the more recent OECD#GD39 gives advice what type of minimal testing standard is necessary to produce meaningful data for quantitative risk characterization. Overwhelming published evidence appears to support a stratified approach which categorizes toxicology findings from repeated exposure inhalation studies in terms of 'below, in the range of, and markedly exceeding particle lung overload'. Any OEL or REL derivation should focus on the primary response to particles at the lower end of the dose-response curve rather than to the secondary response(s) at higher cumulative doses at overload conditions. For reversible findings, an ordinal approach should be given preference to an 'all or nothing' approach. Suffice it to say, reversibility is tightly linked to the extent of lung overload (see below) and associated kinetic variables of particle clearance.

Many studies presented in the CIB do not have the depth of validation or even that level of GLP compliance that have OECD-compliant testing methods. Most of the research-based publications utilize single bolus pharyngeal or intratracheal regimens. Single administration studies have limited validity to simulate the outcomes of repeated long-term inhalation exposure studies or even the recurrent chronic exposure occurring at the workplace. In the absence of data showing the particle morphology of the deposited and retained material in the lung over a time period that would be long enough to cover at least one or multiples of the physiological clearance half-time of approximately 60 days, research-based studies cannot necessarily provide that type of information required for quantitative risk characterization. One of the major shortcomings of the alternative dosing protocols is that kinetic data on lung burdens are rarely available and adequate positive and negative benchmark dusts (micronsized vs. nano sized reference dusts) are often missing to demonstrate the diagnostic/prognostic power of the devised protocol. In the absence of such data, it appears to be difficult to attribute findings to specific nano- or micron-size particle characteristics. Retained lung dose may be contingent on numerous methodological variables. Many effect-focused data lack actual measurements of lung burdens. In none of the cited toxicity studies the proposed NIOSH 5040 method was used for measurements of either airborne concentrations or lung burden measurements. Before promulgating NIOSH 5040 as the mandated analytical method, one would have wished to see empirical data from controlled inhalation studies to better judge its benefits and limitations of this method relative to other methods.

The CIB does not attempt to appropriately categorize the various types of CNTs. Some types (short, thin and tangled) have been shown to be thermodynamically present in an assembled, coiled structure while the more rigid CNTs may be present as agglomerates of thick/long tubes which may liberate isolated

tubes with fiber-like structures under certain circumstances. Their surface properties can make them hydrophilic or lipophilic and surface/matrix bound residual impurities of catalysts may potentially exert modified local toxicities and clearance/translocation kinetics. The critical mode of toxic action of each subtype may differ from one category of CNTs to another.

The basic concept of risk assessment is to articulate the likely mode of action decisive for the outcome of short-term (acute) and long-term (subchronic + postexposure period) inhalation studies and why CNTs are considered to elicit a different toxic potency than other types of biopersistent poorly soluble particles. So far, the scientific community has not yet unanimously agreed which metric of dose is causal for the most critical effect observed. Nonetheless, prevailing evidence supports the mechanistic concept of volumetric particle lung overload (Morrow's overload hypothesis). This concept describes the dynamic decrease in clearance with increasing fractional particle load of the lung. Thus, the changes in lung clearance is not necessarily a substance-specific property, it may solely be related to the accumulated or administered 'particle volume dose'-dependent decreased clearance. Therefore, the conclusions drawn in regard to the regression and persistence should be related to the degree as to which a non-physiological pulmonary overload has been attained or exceeded. Accordingly, a more thorough understanding of the underlying cause of product-specific effects appears to be more relevant when several subcategories of materials (CNF, SWCNT and MWCNT, including their subcategories) with differing characteristics are grouped for the purpose of establishing a common or generic OEL such as the REL proposed in the CIB. Therefore, whenever sufficient and adequate product-specific data are available, any product-specific data-based recommendation of an OEL should be given preference to the generic REL.

When using the concept of the Human Equivalent Concentration it is important to recognize the sequence of events taking place in the lung. Dosimetry considerations need to distinguish target organ sub-compartments where the deposition and accumulation of particles occur and what specific type of toxicity ensues. Using the alveolar surface area as the denominator to adjust the retained dose may be a valid approach for soluble particles with short half-times; however, for essentially insoluble particles this approach does not necessarily reflect the dominating pathway of particle clearance taking place in the lung. A wealth of published information provides ample evidence that the lung burden-dependent recruitment of inflammatory cells, not the particle as such, orchestrates the severity of disease and is causal for the terminal outcome.

Pulmonary fibrosis to the histopathologist is typified by deposition of collagen in excessive amounts (in diffuse or nodular form) or abnormal deposition in an incorrect location (pleural, peribronchial, intra-alveolar) which results in disruption of the normal lung architecture. The biochemist regards pulmonary fibrosis as increase in total lung collagen as assessed from measurements of hydroxyproline. Both definitions are very simplistic, especially at disease stages where acute inflammation prevails. The latter produces a marked increase in soluble intra-alveolar collagen and fibrin perambulating the septal interstitium. Following lung injury, fibroblasts proliferate, differentiate into myofibroblasts expressing α-smooth muscle actin and migrate towards the fibrinous exudate inside the alveolar airspace or perivascular space. In the absence of any (myo)fibroblasts proliferation and secretion of cross-linked collagen types or fibrosing alveolitis, the term 'fibrosis' as perceived irreversible lesion, should be used

cautiously, especially when exudative acute inflammation is still ongoing. The various stages of fibrotic changes are generally described in an ordinal manner. Lower grades may be reversible, higher not. When using ordinal data for any type of quantitative risk assessment, one would have expected to see generalized definitions of the severity categories applied equally by all pathologists involved with lung pathology. In none of the studies cited, the more quantitative scoring according to Ashcroft was used. As long such harmonized guidance is not defined in even in the current OECD Series of Testing and Assessment No. 125 "Guidance Document on Histopathology for Inhalation Toxicity Studies, supporting TG412 and TG413", histopathology findings the CIB notes that early-stage fibrotic and inflammatory lung responses were selected and were characterized as lung inflammation, granuloma and interstitial fibrosis.

In cases where the opinion reflected in the CIB is at variance from that of the scientific investigator one would have wished to see a clear rationale for doing so.