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

From: GALLET Sébastien [sga@cefic.be]
Sent: Friday, February 18, 2011 10:47 AM
To: NIOSH Docket Office (CDC)
Cc: PATERNOSTRE Peng
Subject: 161-A - Occupational Exposure to Carbon Nanotubes and Nanofibers
Attachments: Comments from PACTE on the draft NIOSH Bulleting on CNT.pdf

Importance: High

Sir,

Please find attached the comments of the Cefic (European Chemical Industry Council) Sector Group PACTE (Producers Association of Carbon Nanotubes in Europe) on the draft NIOSH Bulleting on CNTs.

Please do not hesitate to contact me if further information is needed.

Best Regards,

Sébastien Gallet

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Comments on: NIOSH Bulletin 2010 draft

The CEFIC- Producer Association of Carbon Nanotubes in Europe (PACTE) supports the responsible development of nanotechnology and appreciates the great effort NIOSH has invested in the draft Current Intelligence Bulletin (CIB) *Occupational Exposure to Carbon Nanotubes and Nanofibers* (NIOSH Docket Number: NIOSH 161-A). 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.

PACTE supports NIOSH's effort to develop a recommended exposure limit (REL). Such guidelines contribute to the responsible development of carbon nanotubes (CNTs) technology, which will in turn lead to better acceptance by regulators, industrial users, and consumers.

General Issue of Generalisation

PACTE believes that the CIB would be enhanced significantly by a discussion of the fact that not all CNTs have the same characteristics with respect to purity, length, and other features that are known to influence hazard potential. PACTE 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.

CNTs are treated in the document in a very undifferentiated manner and no attempt is made to correlate the effects described with certain physico-chemical characteristics. Differences in CNTs morphology and physico-chemical features might indeed modulate their toxicity and some CNTs types may be much more innocuous than others. In addition, even though the range of effects is quite large, some of them may in part depend on experimental protocols and/or interferences with test systems used leading to various artefacts. The consequence of grouping all CNTs together is that the worst adverse effects found for one specific type of CNTs are assigned to the whole class.

For this reason, the proposed REL may not be appropriate for all CNTs. NIOSH should acknowledge that CNTs produced by different manufacturers may have different properties and characteristics that lend themselves to more sensitive and specific detection and quantification approaches.
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.

For some specific CNT types a number of long-term studies are available that are suitable to derive an OEL (Pauluhn (2010), Ma-Hock (2009)). The NIOSH recommendation should point to the possibility of derivatisation of a product-specific OEL when sufficient information for a specific CNT-type is available.

Specific Issues on Endpoints

Specific endpoints (such as fibrosis and granulomas) should be discussed in more details in the context of study designs and test materials. Otherwise it may lead to the misrepresentation

that all CNTs produce irreversible fibrotic and granulomatous lesions irrespective of the route of exposure, the exposure concentration or the exposure duration.

No definition is given as to how 'fibrosis' is characterized. The term is used in an inconsistent manner across the document as well as in the literature quoted. Due to the unspecificity of the marker a correct wording in many cases may be inflammatory collagen and not fibrosis. Indeed inflammatory fibrosis and granulomatous findings should be discussed in the context of high loading and may be consistent with overload related phenomena.
Specifically in some publications indications are given that inflammatory collagen cannot systematically be equated to fibrosis and that some histopathological markers are not specific to fibrosis. For example in Ellinger-Ziegelbauer et al (2009) "*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*" or in Ryman-Rasmussen et al. (2009) "*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*".
Page 28: The reference to Lam et al. (2004) is inappropriate as the authors mentioned that: "At the doses used in the present study, no fibrosis was observed in the lung.".

Specific Issue of Dermal Penetration

For CNT no report of penetration can be found in the literature (Crosera, 2009). The literature references quoted in the CIB on dermal penetration deal with fullerene and quantum dots (Rouse 2007 and Ryman-Rasmussen 2006). It would be preferable to assess the potential for penetration from the available data on dermal toxicity and dermal sensitisation (e.g. MWCNT Baytubes dermal acute toxicity LD50>2000mg/kg; no sensitisation).
In our view there is no evidence for any significant dermal penetration of CNT.

Exposure Measurement Method

PACTE 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 not specific for CNTs and will be sensitive to all elemental carbons (such as soot, diesel exhaust gas or cigarette smoke). This may lead to an overestimation of the real concentration of CNTs in the air.
Other possible methods should be listed, for example the use of a metallic marker presents as impurity in the CNTs in traces quantity as described for CNTs in Maynard et al. (2004).

Ref:

- Ellinger-Ziegelbauer et al (2009). 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.
- Ryman-Rasmussen JP, Cesta MF, Brody AR, Shipley-Phillips JK, Everitt JI, Tewksbury EW, Moss OR, Wong BA, Dodd DE, Andersen ME, Bonner JC [2009b]. Inhaled carbon nanotubes reach the subpleural tissue in mice. Nature Nanotechnology DOI: 10.1038/NNANO.2009.305.
- Lam CW, James JT, McCluskey R, Hunter RL [2004]; Pulmonary toxicity of single-wall carbon nanotubes in mice 7 and 90 days after intratracheal instillation. Toxicol. Sci. 77(1): 126-34.
- Elgrabli D, Abella-Gallart S, Robidel F, Rogerieux F, Boczkowski J, Lacroix G [2008]. Induction of apoptosis and absence of inflammation in rat lung after intratracheal

instillation of multiwalled carbon nanotubes. Toxicology. Nov 20; 253(1-3):131-6.
- Rouse JG, Yang J, Ryman-Rasmussen JP, Barron AR, Monteiro-Riviere NA [2007]. Effects of mechanical flexion on the penetration of fullerene amino acid-derivatized peptide nanoparticles through skin. Nano Letters 7(1):155-160.
- Ryman-Rasmussen JP, Riviere JE, Monteiro-Riviere NA [2006]. Penetration of intact skin by quantum dots with diverse physicochemical properties. Toxicological Sciences 91(1):159-165.
- Crosera et al.; Int. Arch. Occup. Environ. Health 82, 1043-1055, 2009 "Nanoparticle dermal absorption and toxicity: a review of the literature"
- Pauluhn (2010). Multi-walled carbon nanotubes (Baytubes®): Approach for derivation of occupational exposure limit. Regul. Toxicol. Pharmacol. 57, 1, 78-89.
- Pauluhn (2011). Poorly soluble particulates: Searching for a unifying denominator of nanoparticles and fine particles for DNEL estimation. Toxicology 279(1-3), 176-88
- Maynard et al. (2004). Exposure to carbon nanotube material: aerosol release during the handling of unrefined singlewalled Carbon nanotube material. Journal of Toxicology and Environmental Health, Part A, 67:87–107.
- Ma-Hock L, Treumann S, Strauss V, Brill S, Luizi F, Mertler M, Wiench K, Gamer AO, Ravenzwaay B, Landsiedel R [2009]. Inhalation toxicity of multi-wall carbon nanotubes in rats exposed for 3 months. Toxicological Sciences 112(2): 468-481.