Miller, Diane M. (CDC/NIOSH/EID)

From:
Sent: Monday, June 12, 2006 6:34 AM
To: NIOSH Docket Office (CDC); Schulte, Paul A. (CDC/NIOSH/EID)
Subject: NIOSH Titanium Dioxide comments

Importance: High

Attachments: schul1206.doc

schul1206.doc (159 KB)

Dear Paul,

Please find attached my comments to the NIOSH Titanium Dioxide draft document.

With best regards,

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Dr. Paul Schulte
NIOSH
Director, EID
Robert A. Taft Lab.
4676 Columbia Parkway
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USA

Dear Dr. Schulte,

Similar to the recent IARC report the NIOSH draft document on TiO_2 presents all available information on these particles. My concern is, that information on similar granular biopersistent particles (GBP) and the cumulating evidence of a similar underlying toxic mechanism have not been considered. Consequently although a non-genotoxic carcinogenicity is assumed and inflammation is seen as a basic mechanism a linear extrapolation is preferred to quantify the risk of human exposure.

In 3.5.2 "Role of Chronic Inflammation in Lung Disease" inflammation is described as one effect of particle toxicity. Such effects have been shown in experimental studies and in humans during particle exposure. It is also described that according to Castranova (1998, 2000) chronic inflammation appears to be important in the etiology of dust-related disease in rats and humans. However, a conclusion, that inflammation is the relevant mechanism not only for chronic obstructive lung diseases but also for carcinogenicity is not taken.
The MAK-commission is presently evaluating GBPs including TiO_2. Especially on the basis of Paul Borm's recent review articles (Borm et al 2004, Knaapen et al 2004), previous workshops on particles and fibers (Greim et al 2001) and the ample literature about particle induced inflammation and carcinogenicity it is concluded, that inflammation is the relevant mechanism for tumor induction and that avoidance of inflammation protects from carcinogenicity. During the recent INIS Conference in Hannover (June 2006), to which David Dankovic contributed the NIOSH TiO_2 risk assessment, Schins of Borm's group presented recent mechanistic studies and myself have presented the regulatory consequences. There was unanimous agreement that GBP are non-genotoxic, the underlying mechanism in carcinogenesis is inflammation and thresholded, so that avoidance of inflammation protects from carcinogenicity.

In the NIOSH draft report 3 options for dose extrapolation are described (4.1.2): the bench-mark dose, the estimated threshold dose and the excess risk calculation.

Although such exercises may provide some information on a hypothetical risk even for non-genotoxic carcinogens, the decision whether a mechanism is thresholded and whether a NOEL can be assumed can only be made by understanding the underlying mechanism. In case of GBP there is the scientific consensus, that this is inflammation, which due to antioxidant mechanisms is not induced at low exposure.

The MAK-commission has adopted this concept and presently seeks for sensitive parameters in experimental animals and humans to identify the NOEL for the onset of inflammation. Several studies seem to be suitable (see References: Dose-response studies with particles in humans and animal studies that indicate parameters to identify the onset of inflammation). They mostly use parameters observed in BAL and indicate that the appearance of inflammatory markers starts below 1 mg/m^3 and seem to be lower for fine particles than for larger ones. Most of these studies determined the effect of Diesel exhaust. In the absence of appropriate studies on GBPs we decided to use this information as well.
So far there is no decision on NOELs, LOELs and possible exposure limits for the workplace. But it is apparent, that even for respirable dusts the tolerable value may be below 1 mg/kg.

I very much understand the need for NIOSH, to describe several approaches to risk assessment for TiO_2 exposure. However, in the light of the available information and the scientific consensus about a threshold mechanism of GBP carcinogenicity, the NIOSH document may also indicate, that there is preference to consider this threshold/NOEL approach rather than a linear extrapolation, which implies that there is a carcinogenic risk at any low exposure.

It was a pleasure to have met you in Dresden for discussion of the risk of Bitumen exposure – a very different situation.

Let me know if you need further information.

Sincerely

References

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Knaapen A, Borm PJA, Albrecht C, Schins RPF: Inhaled particles and lung cancer. Part A: Mechanisms. Int J Cancer 109, 799-809, 2004

Dose-response studies with particles in humans and animal studies that indicate parameters to identify the onset of inflammation

Studies in Humans

Nightingale JA, Maggs R, Cullinan P, Donnelly LE, Rogers DF, Kinnersley R, Chung KF, Barnes PJ, Ashmore M, Newman-Taylor A: Airway inflammation after controlled exposure to diesel exhaust particulates. Am J Respir Crit Med 162, 161-166, 2000

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Animal studies

Bermudes E, Mangum JB, Wong BA, Ashgarian B, Hext PM, Warheit DB, Everitt JI (2004) Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles. Toxicol Sci 77, 347-357

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Driscoll KE, Carter JM, Howard BW, Hassenbein DG, Pepelko W, Baggs RB, Oberdörster G (1996) Pulmonary inflammatory, chemokine, and mutagenic responses in rats after subchronic inhalation of carbon black. Toxicol Appl Pharmacol 136, 372-380

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