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From:
Sent: Sunday, April 30, 2006 8:08 PM
To: NIOSH Docket Office
Cc: Schulte, Paul A. (CDC/NIOSH/EID);
Subject: NIOSH-033
Attachments: NIOSH.PEER REVIEW COMMENTS.doc

Attached please find my comments on the above.

PEER REVIEW COMMENTS (Docket Number NIOSH-033)

NIOSH Current Intelligence Bulletin: Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide

Prepared by:

Introduction:

In preparing this review, I have evaluated the draft of the *Current Intelligence Bulletin* as well as the materials presented at the public meeting on February 27, 2006, which I was unable to attend. In this note, I provide general and specific comments as well as my specific responses to the charge given by NIOSH to the reviewers.

General Comments:

In the *Current Intelligence Bulletin*, NIOSH presents a hazard evaluation and risk assessment for titanium dioxide (TiO_2). The draft is comprehensive in its coverage of TiO_2 and highlights the paucity of data available, and the very limited number of either epidemiological or toxicological studies on TiO_2. The epidemiological studies, while providing little indication of an association of TiO_2 with lung cancer risk, offer imprecise risk estimates that are likely to have been biased towards the null by misclassification. The animal studies are also quite limited and provide only a few data points for modeling dose-response relationships. Because the evidence is of limited scope and informativeness, NIOSH concludes that TiO_2 cannot be labeled as a "potential occupation carcinogen" at this time.

Nonetheless, NIOSH proceeds to carry out a quantitative risk assessment and to recommend exposure limits. The argument for carcinogenicity largely hinges on the potential for lung inflammation caused by retained TiO_2 to cause lung cancer through a secondary, non-specific genotoxic mechanism. Such mechanisms have been proposed in a unifying fashion for linking diverse environmental agents and also host characteristics, e.g., obesity, to increased cancer risk. Given this proposed general mechanism, several questions immediately follow: 1) would not this same mechanism be expected to apply to other "particles not otherwise regulated"?; 2) given this postulated, generic mechanism, there is a broad range of relevant literature that is not reviewed; and 3) are inhalation bioassays for other particles postulated to act through this same mechanism also relevant?

The proposal for exposure limits for fine and ultrafine TiO_2 particles follows from a concern that the tumor risks observed in the rats at the highest exposure concentrations warrants "...the use of prudent health-protective measures for workers until we have a more complete understanding of the possible health risks." This principle merits careful consideration as a basis for moving from high-level bioassay data in an animal model of uncertain relevance to a rationale based in reducing risk for human respiratory cancer, particularly given the absence of epidemiological evidence of increased risk in association with TiO_2. Why isn't NIOSH proposing exposure limits for other particles that may act through the same, nonspecific mechanism assumed in this instance for TiO_2.

I see on major oversight that should be addressed: there is no discussion of the potential effect of TiO_2 in smokers compared with nonsmokers. Smoking is presumed to cause lung cancer through both the presence of specific carcinogens in tobacco smoke and the chronic inflammatory state of the airways and alveoli caused by smoking. How would

the proposed mechanism for TiO_2 intersect with the consequences of smoking for the lung? The differing dosimetry of particles in the lungs of smokers compared with nonsmokers?

Charge to Peer Reviewers

- *Is the hazard identification and discussion of health effects for TiO_2 a full and reasonable reflection of the human and animal studies in the scientific literature?*

NIOSHS has fully reviewed the epidemiological, clinical, and toxicological studies that specifically address the health effects of TiO_2. The epidemiological and animal data are limited and they are adequately described and limitations considered.

However, as noted in my general comments, because NIOSH is postulating that TiO_2 acts through a non-specific mechanism, there is a substantial additional body of evidence that could be reviewed. There is extensive literature on inflammation and injury to target cells for lung cancer by reactive oxygen species, for example. The review of epidemiological studies could be extended with a similar rationale as well.

- *Are the risk assessment and dosimetric modeling methods used in this document appropriate and relevant?*

A principal uncertainty, acknowledged in the draft is the extension of the rat data to humans and workers generally exposed at far lower concentrations. The dose-response relationships from the cancer bioassays are driven by the responses obtained at extremely high exposure concentrations; concentrations that must have produced "lung overload". The overlapping bounds of risk estimates from the rat data with those from epidemiological data are unconvincing, and the discussion in the last paragraph on page 70 is unconvincing.

From a technical viewpoint, the modeling has been done correctly and the approach is adequately described in the body of the text and the related appendices. The dosimetric modeling is limited and largely considers total lung dose without consideration of regional patterns of deposition, relevant given the attempt to have a unified dose-response curve by surface area when aerodynamic size will determine the most heavily dosed regions of the lung. The discussion of clearance and deposition models on page 67 is relatively brief, and might be expanded to strengthen this aspect of the risk assessment.

- *Are the sampling and analysis methods adequate to characterize worker exposure to fine and ultrafine* TiO_2?

Commenting on the details of the sampling and analysis methods is beyond my expertise. I am aware of the complexities of attempting to sample and characterize ultrafine particles in general and NIOSH acknowledges that there is presently no personal sampling device available for ultrafine aerosols.

- *Is the use of particle surface area as a dose metric appropriate for estimating worker risks from inhalation of TiO_2?*

  For airborne particles in general, extensive consideration has been given to those characteristics that may determine toxicity in relation to various health outcomes. This topic has been addressed, for example, in the series of reports from the National Research Council's Committee on Research Priorities for Airborne Particulate Matter. Many candidate characteristics have been proposed, including particle size and by implication surface area. A growing body of evidence addresses ultrafine particles but the focus is on non-malignant and generally short-term effects rather than carcinogenicity.

  In proposing surface area as the dose metric, NIOSH emphasizes model fit in its analysis of the available rodent bioassay data. Considerations with regard to plausibility are limited in the draft; for example, would surface area be important because the smaller particles bring in a greater concentration of attached carcinogens; how does greater surface area produce more inflammation? At present, the evidence is empiric and limited. It overlooks issues of regional dosimetry by particle size in the human lung and the sites of origin of human respiratory cancers. This topic needs mention, along with the trend of recent decades of increasing frequency of adenocarcinoma, presumed to be of peripheral rather than central origin.

  Given the uncertainty around the most appropriate dose metric for particles in general, and more specifically in relation to risk for lung cancer, NIOSH expresses an unwarranted degree of uncertainty. See, for example, proposed explanatory footnotes to the *Pocket Guide* entry for TiO_2. The second sentence refers to rat tumors and the third sentence is unqualified—and would better read: *This effect **may** be related...*

- *Are there additional relevant studies or methods that NIOSH should consider in developing its RELs for TiO_2?*

  As noted in my general comments and those in response to the question concerning hazard identification, the rationale used by NIOSH in developing its risk assessment potentially calls for review of a far broader set of evidence. If needed, I can supply some specific citations as a starting point. Certainly, there is an enormous literature on the health consequences of inhaled particles and a *Current Intelligence Bullet* can only touch the surface; this one may not go deeply enough.

Specific Comments

Line 318: what are the implications of not being soluble for potential reactivity and generation of reactive oxygen species?

Lines 343-344: information available on GSD?

Line 361: limitations of the NOES should be cited here. 1
Lines 471-475: why would alveolar proteinosis be linked to TiO_2 ?

Lines 494-495: comment needed here on the location of the particles which are probably in the mediastinal lymph nodes and perhaps in peri-bronchiolar accumulations as for other particles. Information available?

Line 624: this criticism seems off the mark as methods were not available for collecting ultrafines over the course of the study.

Lines 726-728: this sentence leaves the mistaken impression that an epidemiological study could be designed for this purpose.

Lines 735-744: assays involving other particles might be cited here.

Lines 1027: "correlated better" is too vague.

Lines 1050-1053: the assertion may be correct but it fails to acknowledge differing sites of deposition with the lung.

Lines 1335-1337: would there have been differing patterns of deposition? Are models available for this consideration?