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From:
Sent: Thursday, April 27, 2006 4:22 PM
To: NIOSH Docket Office
Cc: Schulte, Paul A. (CDC/NIOSH/EID)
Subject: Reviewer's comment Titanium Dioxide CIB, Docket # NIOSH-033

Attachments: NIOSH Comments.doc; NIOSHConf.pdf; BIOGRAPHICAL NIOSH.doc


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(177 KB)


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Dear Sir:

I am submitting my review comments on titanium dioxide CIB, along with my CV and a signed Conflict of Interest Form.
Thank you for the opportunity to review this document.

(See attached file: NIOSH Comments.doc)(See attached file: NIOSHConf.pdf)(See attached file: BIOGRAPHICAL NIOSH.doc)

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Docket # NIOSH-033

Review Comments on NIOSH Current Intelligence Bulletin: Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide---November 22, 2005

Reviewer:

Date: April 28, 2006

My comments concern about issues involving hazard identification, proposed mode of action (MOA), risk extrapolation from animals to humans, and particle surface area (PSA)as a dosimetric.

I Hazard Identification

Generally speaking, the CIB is a reasonable and balanced document reflecting available scientific data. It is appropriate to conclude that lack of an exposure-response relationship in epidemiologic studies of workers exposed to TiO_2 dust in workplace should not be interpreted as evidence of discordance between the mechanism presumed to operate in rats and the human potential for carcinogenicity. As to be explained, there are more compelling reasons to support this conclusion. Reading through the document, it is apparent that NIOSH has made reasonable efforts to present a balanced picture about the available data and to use appropriate methods and procedures to estimate risk to workers. However, there are some important scientific issues that need to be more carefully addressed and/or discussed. In particular, the proposed MOA needs carefully articulated; otherwise the conceptual basis for this assessment and the data base used for risk calculation could be considered invalid if those issues are not properly addressed.

II Mode of Action (MOA)

The NIOSH CIB states (Line #1541, page 64): "*In considering all the data, NIOSH has determined that a plausible mechanism of action for TiO_2 in rats can be described as the accumulation of TiO_2 in the lungs, overloading of lung clearance mechanisms, followed by increased pulmonary inflammation and oxidative stress, cellular proliferation, and, at higher doses,*

tumorigenesis." Under this MOA, it would be reasonable to assume a threshold effect at low doses where lung overload does not occur. While it may be reasonable to postulate that most (or even all) of tumors observed at high doses were resulting from this MOA, a crucial question is whether it is also necessary for lung tumor to occur. If indeed the proposed MOA were unique for TiO_2-induced lung tumors, it would lend strong support to the argument that rat data are irrelevant to humans because these tumors are only result of high dose effect with lung overloading as prerequisite. Therefore, it is crucial to determine whether the proposed MOA is unique and a threshold effect exists. The key question is whether or not the overloading of lung clearance is required for an increased pulmonary inflammation, oxidative stress, and cellular proliferation. This issue has been discussed by several researchers (e.g., Knaapen et al., 2004, Borm et al., 2004, Hoetl et al., 2004, and Oberdoster, 2000) who questioned the role of lung overloading in tumor induction. Oberdoster (2000) suggested that inhaled low doses of carbonaceous ultra fine particles can cause mild pulmonary inflammation in rodents after exposure for 6 hours; Hoetl et al.(2004) suggested that oxidative stress induced by marcrophage may not be a threshold effect.

Available data does not support threshold effects for pulmonary inflammation, and cellular proliferation. For instance, Bermudez et al. (2004) shows significant dose-response trend of alveolar cell replication up to 13 weeks post exposure(see Table 1 below). The data in Table 1 do not support a threshold effect. A similar but weaker trend for LDH in BAL fluid is also observed in the same study.

In their review of particles with low toxicity, Knaapen et al. (2004) pointed out the possibility of multiple pathways for particle-induced lung cancers and the need for further studies. In other word, the proposed MOA may be considered a reasonable pathway for the observed tumors at high doses but there is no data to support that it is the unique pathway for lung tumor induction.

Table 1. Labeling Index Mean (SD) for Rat Alveolar Cells*

Dose (mg/m^3)	Weeks Post Exposure		
	0	4	13
0	4.53 (1.78)	4.59 (1.05)	5.09 (1.83)

0.5	6.23 (2.42)	6.30 (1.18)	5.48 (2.06)
2	7.81 (1.22)	7.15 (1.44)	7.17 (4.37)
10	12.18 (2.53)	10.06 (0.96)	9.40 (2.66)

*Bermudez et al., 2004.

III Particle Surface Area as Dosimetric

Particle surface is a reasonable dosimetric biomarker relating exposure to toxicity. However, to avoid confusion and unnecessary controversy, it is desirable to make it clear that it is only an empirical biomarker with some but not complete scientific evidence behind it. For this reason, it is desirable to more rigorously reanalyze data (e.g., CIB Figures 3-2, and 3-4) used to justify the use of PSA as dosimetric by taking into account other covariate variables (e.g., some physical characteristics) associated with each particle type, and to answer questions such as variability of potency estimates when data of each particle type is used separately.

IV. Risk Extrapolation to Humans

IV-1 Differences in Background Conditions between Rats and Humans

There is need to consider differences between animals and humans with respect to some relevant background variables when extrapolating risk from rats to humans. These variables include significantly higher lung cancer rates in humans than rats; higher background lung cancer rate implies that there is higher prevalence of pre-cancerous cells in humans waiting to be affected by TiO_2 exposure. Higher background lung cancer rates also make it more difficult to detect a small increased risk in epidemiological studies. Another important issue is whether or not TiO_2 should be considered along with other particulate matter, giving the fact that humans are also exposed to a broad class of chemically and physically diverse particles. Furthermore, since the thermal and mechanical history of particles and adsorption from environment determines characteristics of active surface sites, the induced toxicity may be different from that in animals where original TiO_2 was used, and thus, more uncertainties in human risk assessment due to the surface reactivity with environment and biological medium in human lungs. All these variables have the tendancy to underestimate risks calculated from animal data.

IV-2 Threshold Assumption in Risk Calculations.

The statement on p.55 (Line #1323) "The probability that these threshold would be observed if the true relationship was linear is less than 0.01" could be misconstrued as evidence for a threshold. It should make clear that a real biological threshold effect can not be determined by statistical analysis alone. For instance, it is conceivable that a piece-wise linear model with different slopes (without assuming a threshold) over different dose levels may fit data better than the piece-wise linear threshold model used in the CIB. The statistically derived threshold effect is model dependent because the result is dependent on the observed data and the model used to fit the data. An interesting example that may be used to illustrate why statistical model can not be used to establish a threshold is provided in Morfeld et al (2006). Using Cox regression model with a threshold parameter and data taken from an intratracheal instillation study of 6 types of low and high surface area particles including TiO_2, the authors concluded that a threshold effect exists for tumor prevalence. It is interesting to see that this conclusion is not supported when the data of TiO_2 alone (Table 2 below) is examined. These data clearly do not support a threshold effect, despite a more complex model which pooled different types of data together suggests the existence of a threshold.

Table 2. Tumor Prevalence and Particle Surface Area of TiO_2*

Surface Dose, m^2	Tumor Prevalence (%)
0	0/91 (0%)
0.59	12/46 (26.1)
0.78	21/41 (51.3)
1.19	27/48 (56.3)
1.56	29/47(61.7)
3.06	31/46 (67.4)

* Data taken from Table 1 in Morfeld et al (2006)

V Conclusion/Discussion

As discussed previously, NIOSH has presented a reasonably balanced picture of TiO_2 induced lung tumors. The document can be improved by articulating more about the proposed MOA and its implication to humans risk

extrapolation. When extrapolating (qualitatively or quantitatively) risk to humans, it is important to take into account the fact that humans have much higher background lung cancer incidences than rats; implying that humans have more pre-cancerous cells in lung than rats, and thus are more susceptible to get lung cancers from exposure than rats, under the multistage theory of carcinogenesis. Most of the issues identified in this review seem to result from insufficient collaboration between qualitative and quantitative scientists. Some of these issues can best be addressed jointly by multidiscipline scientists.

An important issue which may be of interest to risk managers is cessation effects after termination or reduction of TiO_2 exposure. Risk managers are often confronted with the question of evaluating the impact after terminating or reducing the exposure from regulatory actions. It is interesting to note that there are several studies with useful data on this compound; perhaps, more data than most others except for smoking. Discussions on this topic can be found in Chen and Gibb (2004).

References (Only those not cited in CIB):

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