

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

From: Saturday, May 06, 2006 7:11 PM
Sent: NIOSH Docket Office
To: Comments on NIOSH Current Intelligence Bulletin for Titanium Dioxide (NIOSH-033)
Subject:

Attachments: Review of NIOSH CIB for TiO2.doc



Review of NIOSH
CIB for TiO2.d...

Attached please find my comments on the NIOSH Current Intelligence Bulletin for Titanium Dioxide (NIOSH-033).

**Review of NIOSH Current Intelligence Bulletin: Evaluation of Health Hazard and
Recommendations for Occupational Exposure to Titanium Dioxide
(Docket # NIOSH-033)**

General Comments

I am very impressed with the quality of the science reflected in the NIOSH Current Intelligence Bulletin for TiO₂. The document is very well written, and presents the elements of the evaluation with clarity and transparency. It is clear that there was a considerable effort by NIOSH to provide as objective a basis as possible for recommendations concerning occupational exposure to TiO₂, using the best available scientific information and state-of-the-art analytical methods. The scientists at NIOSH who participated in this effort are to be congratulated for the obvious care and expertise with which the evaluation was conducted.

My primary concern is what appears to be an inconsistency between the qualitative assessment and the quantitative assessment. The qualitative assessment concludes (Executive Summary, p. iii) that the tumorigenic effects of TiO₂ result from a "secondary genotoxic mechanism associated with persistent inflammation," and that "occupational exposures to low concentrations of TiO₂ produce a negligible risk of lung cancer in workers." As a result, the determination is made by NIOSH that "insufficient evidence exists to designate TiO₂ as a 'potential occupational carcinogen' at this time." Based on these conclusions, I would expect that the quantitative risk assessment for TiO₂ would be conducted on the basis of the relevant non-cancer endpoint, inflammation, under the assumption that protecting against the obligatory precursor, chronic inflammation, would also be protective against cancer. Indeed, NIOSH conducts such a quantitative assessment, using dose-response data for PMN counts in BAL fluid.

However, NIOSH actually bases the proposed RELs on an alternative quantitative approach using data on the dose-response for lung tumors from TiO₂ exposures of rats to estimate a human exposure associated with a lung cancer risk of 1/1000. This analysis is based on the same linear dose-response approaches that would be used for genotoxic carcinogens, despite the fact that the mode of action for TiO₂ is described by NIOSH as "the accumulation of TiO₂ in the lungs, overloading of lung clearance mechanisms, followed by increased pulmonary inflammation and oxidative stress, cellular proliferation, and, at higher doses, tumorigenesis," which clearly is not a description of a genotoxic mode of action that would be expected to be linear to low doses. Moreover, the results of the quantitative analysis are not different from what one would obtain if a direct genotoxic mode of action was assumed, and the results are presented in the same way that the risks of a genotoxic carcinogen would be presented. For example, in the Executive Summary (p. iv) the recommended RELs are described as exposures that "over a working lifetime should reduce risks of lung cancer to below 1 in 1000." Even more surprisingly, the Executive Summary (p. v) states that "NIOSH is concerned about the potential carcinogenicity of ultrafine TiO₂" and "recommends controlling exposures as

low as feasible below the RELs.” These statements are inconsistent with the determination by NIOSH, in the same document, that TiO₂ should no longer be listed as a “potential human carcinogen.”

It is my opinion that the conclusions of NIOSH in its qualitative assessment of TiO₂ carcinogenicity are well supported by the extensive animal toxicity/mechanistic data and human epidemiological data on exposure to TiO₂, and that a number of changes should be made to the quantitative analysis in order to bring it into harmony with the qualitative assessment:

1. the RELs should be determined primarily on the basis of the analysis of the data on inflammation (increased PMNs in BAL fluid)
2. the analysis of lung tumors should be presented only as support for the main analysis (based on inflammation)
3. the lung tumor analysis should be performed using Bayesian model averaging (BMA), excluding the linear approaches that are fundamentally inconsistent with the conclusions of NIOSH regarding the carcinogenic mode of action

The linear approaches that should be *excluded* from the BMA analysis, due to their fundamental inconsistency with the carcinogenic mode of action, include:

- linear extrapolation from the BMD or BMDL at 1/10 risk
- use of the quantal linear model

I believe that a modified tumor analysis conducted as described above would result in estimates of fine and ultrafine concentrations associated with “negligible” (i.e., $\leq 1/10000$, rather than 1/1000) risk that would be consistent with the thresholds for inflammation based on the PMN data. The tumor-based estimates should be presented only in this light (i.e., in a corroborative role), and any unsupported assertions (“concerns”) regarding the potential carcinogenicity of TiO₂ at low human exposures should be eliminated from the document. Instead, the Executive Summary should re-state the fact that epidemiological studies of workers exposed to fine TiO₂ at concentrations exceeding the proposed REL have provided no evidence of increased lung cancer.

Responses to NIOSH Questions

1. Is the hazard identification and discussion of health effects for TiO₂ a full and reasonable reflection of the human and animal studies in the scientific literature?

For the most part, yes. The discussion of the published human and animal studies on the health effects of TiO₂ is relatively thorough and balanced. On most issues, the document provides a full and reasonable description of the major findings, characterizes the nature and implications of key uncertainties, and maintains an admirable level of objectivity and transparency.

Comparison of rat and human response

One important issue that needs attention, however, is the discussion of the relevance of the rat as a model for human lung tumors (in Sections 3.4 and 3.5). The document should

more clearly describe (in Section 3.5.1) the results of the studies by Bermudez et al. (2002, 2004), which show that while the lung dosimetry and acute inflammatory responses to TiO₂ in the mouse and the rat were similar, only the rat exhibited long-term, progressive sequelae involving metaplastic and fibroproliferative lesions. It is this progressive tissue response that appears to predispose the rat to the occurrence of lung tumors from TiO₂.

Of particular importance is the fact that Nikula et al. (1997, 2001) have reported very similar differences in the response of monkeys and humans, as compared to rats, to exposures to diesel exhaust particulates and coal dust. A discussion of the implications of these studies for TiO₂ should be added to the document (in Section 3.5.2), along with the evidence from other experimental or epidemiological results on carbonaceous particles such as coal mine dust to the extent that they contribute to an understanding of the human responses to poorly soluble, low toxicity (PSLT) particles such as TiO₂.

NIOSH asserts (section 3.4.2) that "rats are no more sensitive to these effects [i.e., the carcinogenic effects of particles] than are humans." To support this assertion, NIOSH refers to "evidence from known human carcinogens, such as asbestos and crystalline silica." This assertion is inappropriate because (1) no such evidence is actually cited in its support, (2) evidence on chemical-specific responses to high toxicity particulates such as silica and asbestos is not informative for the non-specific responses to low toxicity particulates such as TiO₂, and (3) the contrary evidence from more relevant studies such as Nikula et al. (1997, 2001) is ignored.

In fact, the weight of the evidence from studies on TiO₂ and relevant materials such as coal dust clearly supports the existence of important differences between the non-specific cellular responses to high particle loads in the rat and human (progressive inflammation and alveolar proliferation vs. interstitialization) that would predispose the rat to lung tumors from TiO₂. This conclusion is quite different from the assertion by NIOSH that the rat is no more sensitive than the human, and clearly has major consequences for the interpretation of the quantitative risk assessment for TiO₂, which is derived using data from rat studies only.

Discussion of Lung Overload

The discussion of lung overload (in Section 3.4.2) is particularly confusing and potentially misleading. It appears to be a misguided attempt to minimize the importance of lung overload in the dose-response for tumorigenicity in the rat lung. For example, the statement: "the lung tumor response of PSLT can be predicted by the particle surface area dose without the need to account for overloading" makes no sense at all. Expressing the dose as surface area of retained particles per gram lung (or, for that matter, mass of retained particles per gram lung) explicitly includes the effects of "lung overload," which is nothing more than a reduction in the rate of particle clearance at high lung burdens. The use of particle surface area dose merely provides a consistent description of the tumor dose-response across studies with different particle sizes (for PSLTs), but the resulting dose-response is still highly nonlinear at least in part because of the nonlinearity

in clearance. The particle surface area dose at which the nonlinearity occurs coincides with the level of lung burden that results in decreased clearance (aka, lung overload).

As can be seen in Figures 3.3 and 3.4, the data are consistent with a threshold for tumor response on the order of $0.2 \text{ m}^2/\text{g}$ lung, which is in the range of surface area doses that has been associated with the onset of lung overload. Of course, the fact that increased tumor incidence is only observed above the lung burdens associated with overload does not necessarily imply that impaired clearance is an obligatory precursor for tumors. However, the sustained inflammatory and proliferative response in rats that is actually likely to be an obligatory precursor to tumors is, in fact, only seen at lung burdens well above overload (Bermudez et al. 2002, 2004).

2. Are the risk assessment and dosimetric modeling methods used in this document appropriate and relevant?

For the most part, yes. The methods applied in the quantitative risk assessment are state-of-the-art and demonstrate a high level of technical competency. NIOSH is to be commended for the high technical quality of their analysis, as well as for the thoroughness, clarity, and transparency with which it was documented. Aspects of the analysis that are noteworthy include:

- the use of highly sophisticated lung deposition and clearance modeling to perform particle dosimetry
- The use of Bayesian model averaging (BMA) to obtain central estimates of risk across alternative dose-response models
- the additional statistical modeling described in the Appendices, in particular the quantitative comparison of animal- and human-based risk estimates.

Documentation of Decision-Making

One area in which the document could be improved is by providing a more thorough documentation of the decisions made in the analysis and their impact on the resulting RELs. At several points in the quantitative analysis, alternative approaches, models, or data are described. In each case the results of choosing the different alternatives are presented at the point where the preferred alternative was chosen, in terms of the values that would be used as input to the next step, but only the chosen alternative is carried forward in the determination of the RELs. Moreover, in some cases the explanation for the choice of alternative is inadequate or entirely missing.

- Rat-to-human extrapolation is conducted on the basis of relative lung mass. The EPA has recommended that animal-to-human extrapolation of particles should be conducted on the basis of relative lung surface. The NIOSH document states that estimates of equivalent worker exposures would be lower by a factor of approximately 1/3 if lung surface area were used, but does not provide an adequate justification for using the less conservative relative lung weight approach. The justification given – that lung surface area was not available for all rat strains used in the analysis – is inadequate. The uncertainty introduced by estimating lung surface area from lung weight in the rat would be small in comparison with the

factor of 3 impact of using the alternative approaches for obtaining the equivalent worker exposure estimates. In my opinion, there does not appear to be any adequate justification for departing from the EPA recommended practice of extrapolating on the basis of relative lung surface area.

- Lung dosimetry modeling is performed using two alternative models: the MPPD/ICRP model and the interstitial/sequestration lung model, but only the results of the MPPD/ICRP model were used in the determination of the RELs. The results in Table 4-3 and 4-6 show that using the interstitial/sequestration lung model would result in equivalent worker exposure estimates that were lower by a factor of approximately 2, but does not explain why only the less conservative MPPD/ICRP model estimates were used. Use of either the more conservative model estimates or the average of the estimates from the two models would be a more typical approach.

Calculation of RELs Based on Critical Lung Dose for Inflammation

Based on the determination made by NIOSH that “insufficient evidence exists to designate TiO_2 as a ‘potential occupational carcinogen’ at this time,” I would expect that the quantitative risk assessment for TiO_2 would be conducted on the basis of the relevant non-cancer endpoint, inflammation, under the assumption that protecting against the obligatory precursor, chronic inflammation, would also be protective against cancer. NIOSH conducts such a quantitative assessment, using dose-response data for PMN counts in BAL fluid, but then bases the proposed RELs on an alternative quantitative approach using data on the dose-response for lung tumors from TiO_2 exposures of rats to estimate a human exposure associated with a lung cancer risk of 1/1000. This analysis is based on the same linear dose-response approaches that would be used for genotoxic carcinogens, despite the fact that the mode of action for TiO_2 is described by NIOSH 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,” which clearly is not a description of a genotoxic mode of action that would be expected to be linear to low doses.

To provide a quantitative risk assessment that is consistent with the conclusions of NIOSH regarding the mode of action for the effects of TiO_2 , NIOSH should base the PELs for TiO_2 on the data for inflammation. The equivalent worker exposure concentrations calculated by OSHA for the two critical studies (Tran et al. 1999, Cullen et al. 2002), shown in Table 4-3, are in the range of 1 to 6 mg/m^3 for fine TiO_2 and 0.1 to 0.7 mg/m^3 for ultrafine. NIOSH should base the RELs on these results, providing a clear documentation of how the values were calculated. For example, using lung surface area scaling, the average of the two dosimetry model estimates, and the average of the results from the two experimental studies would result in a REL for fine TiO_2 of approximately 1 mg/m^3 , and a REL for ultrafines of approximately 0.1 mg/m^3 .

Calculation of RELs Based on Rat Lung Tumor Data

Although the use of tumor data as the basis of the RELs for TiO₂ is inconsistent with the determination made by NIOSH that “insufficient evidence exists to designate TiO₂ as a ‘potential occupational carcinogen’ at this time,” such an analysis could be justified for the purpose of providing corroborative evidence that the RELs based on inflammation would be adequately protective against cancer. However, the main cancer risk analysis conducted by NIOSH is based on the same linear dose-response approaches that would be used for genotoxic carcinogens, and the results of the quantitative analysis are not different from what one would obtain if a direct genotoxic mode of action was assumed, despite the fact that the mode of action for TiO₂ is described by NIOSH as “the accumulation of TiO₂ in the lungs, overloading of lung clearance mechanisms, followed by increased pulmonary inflammation and oxidative stress, cellular proliferation, and, at higher doses, tumorigenesis,” which clearly is not a description of a genotoxic mode of action that would be expected to be linear to low doses.

To avoid this inconsistency, the lung tumor analysis should be performed using the Bayesian model averaging (BMA) approach that is described in the NIOSH document (but not used in the derivation of the RELs), but excluding the linear approaches that are fundamentally inconsistent with the conclusions of NIOSH regarding the carcinogenic mode of action. The approaches that should be excluded from the BMA analysis, due to their fundamental inconsistency with the carcinogenic mode of action, include (1) the use of the quantal linear model and (2) linear extrapolation from the BMD or BMDL at 1/10 risk, regardless of the model used.

3. Are the sampling and analysis methods adequate to characterize worker exposure to fine and ultrafine TiO₂?

Probably. The sampling and analysis methods described by NIOSH appear to provide a reasonable interim approach for conducting an exposure assessment for TiO₂ in the workplace. There are a number of important issues that remain to be clarified, such as how to identify the number and surface area of primary TiO₂ particles in the ultrafine range, particularly in the case of workplace exposures involving particulate other than TiO₂. The recently published data on the primary particle size distribution of commercial TiO₂ pigments (Gibbs et al. 2006) suggests that many applications of TiO₂ will not involve workplace exposure to ultrafine particles. Similar studies with other TiO₂ materials may help to identify exposures of concern.

4. Is the use of particle surface area as a dose metric appropriate for estimating worker risks from inhalation of TiO₂?

At the present time, yes. There are a number of important issues that remain to be clarified. There is reasonable evidence that surface area is the most appropriate dose metric for particles in the fine and ultrafine range, but it is not yet known whether this dose metric is applicable to primary particles with an MMAD on the order of a nanometer. Therefore, there is some uncertainty with regard to its applicability to workplaces involving exposures to true nanoparticles. Even greater uncertainty would

exist in the case of nanoparticles whose surface characteristics had been modified to hinder agglomeration.

5. Are there additional relevant studies or methods that NIOSH should consider in developing its RELs for TiO₂?

If NIOSH believes, as appears to be the case, that the effects of TiO₂ are not chemical-specific, but rather result from non-specific particle responses, then consideration should be given to recasting the evaluation of the RELs for TiO₂ into an evaluation of poorly soluble, low toxicity (PSLT) particles in general. In particular, data from other PSLTs on biomarkers of inflammation, such as PMNs in BAL, could be used to perform a more robust quantitative analysis than is possible with data on TiO₂ alone.