

**Miller, Diane M.**

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**From:** Barbara Christianson [BChristianson@lawbc.com]  
**Sent:** Friday, March 31, 2006 3:38 PM  
**To:** NIOSH Docket Office  
**Cc:** Lynn L. Bergeson; Jonathon T. Busch  
**Subject:** NIOSH-033 – Comments of the American Chemistry Council Titanium Dioxide Panel - 1 of 2 E-Mails  
**Attachments:** 101LT001.pdf; 101CM001D.pdf

We received a notice indicating that our original e-mail with the comments and attachments came back with an unsuccessful delivery. We will send two e-mails -- the first e-mail appends the transmittal letter with the comments, and the second e-mail will append the attachments. A hard copy of these documents have been sent to by regular mail. Please let us know if you have any questions.

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**From:** Barbara Christianson  
**Sent:** Friday, March 31, 2006 2:19 PM  
**To:** 'niocindocket@cdc.gov'  
**Cc:** Jonathon T. Busch ; Lynn L. Bergeson  
**Subject:** NIOSH-033 -- Comments of the American Chemistry Council Titanium Dioxide Panel

Appended are a cover letter, comments, and attachments submitted on behalf of the American Chemistry Council Titanium Dioxide Panel. A hard copy of these documents are also being sent by regular mail. Please let us know if you have any questions.

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March 31, 2006

Via E-Mail and Regular Mail

NIOSH Docket Office  
Attn: Diane Miller, Mailstop C-34  
Robert A. Taft Laboratories  
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Re: NIOSH Current Intelligence Bulletin: Evaluation of Health Hazard and  
Recommendations for Occupational Exposure to Titanium Dioxide; 70  
Fed. Reg. 77399 (Dec. 30, 2005); NIOSH-033

Dear Ms. Miller:

Appended are comments submitted on behalf of the American Chemistry Council Titanium Dioxide Panel. These comments respond to the National Institute of Occupational Safety and Health's *Federal Register* notice announcing the availability of the above-referenced draft document. Please do not hesitate to call or e-mail with any questions.

Your assistance is appreciated.

Sincerely,

Lynn L. Bergeson  
Counsel to the American Chemistry Council  
Titanium Dioxide Panel

Attachment

BEFORE THE  
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

COMMENTS OF THE TITANIUM DIOXIDE PANEL  
OF THE AMERICAN CHEMISTRY COUNCIL  
AND  
THE TITANIUM DIOXIDE MANUFACTURERS ASSOCIATION  
AND THE PHYSICAL SUNSCREEN MANUFACTURERS ASSOCIATION  
OF THE EUROPEAN CHEMICAL INDUSTRY COUNCIL

ON

NIOSH CURRENT INTELLIGENCE BULLETIN:  
EVALUATION OF HEALTH HAZARD AND RECOMMENDATIONS FOR  
OCCUPATIONAL EXPOSURE TO TITANIUM DIOXIDE

Meeting and Opening of the  
Public Comment Period  
70 Fed. Reg. 77399 (Dec. 30, 2005)

NIOSH-033

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March 31, 2006

## EXECUTIVE SUMMARY

The Titanium Dioxide Panel of the American Chemistry Council and the Titanium Dioxide Manufacturers Association and Physical Sunscreen Manufacturers Association of the European Chemical Industry Council (hereinafter referred to collectively as Panel) jointly submit these comments on the National Institute for Occupational Safety and Health's (NIOSH) December 30, 2005, *Federal Register* notice announcing the February 27, 2006, public meeting in Cincinnati and seeking public comment on the draft *NIOSH Current Intelligence Bulletin: Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide* (draft CIB). 70 Fed. Reg. 77399. The Titanium Dioxide Panel consists of the major producers of titanium dioxide (TiO<sub>2</sub>) in the United States, while the Titanium Dioxide Manufacturers Association consists of the major TiO<sub>2</sub> producers in Europe. The Physical Sunscreen Manufacturers Association consists of the major producers of physical sunscreens in Europe.

The Panel appreciates the opportunity to comment on the draft CIB, and requests that NIOSH and the draft CIB Peer Reviewers give full consideration to the Panel's comments and recommendations, which supplement the comments and recommendations made by Panel members and representatives at the February 27, 2006, public meeting in Cincinnati. As manufacturers, the validity of the scientific basis for the draft CIB, and its suitability for purposes of proposing recommended exposure limits (RELs), are highly important to the Panel.

The Panel agrees with and supports NIOSH's determination that there is insufficient evidence to designate TiO<sub>2</sub> as a "potential occupational carcinogen." The Panel has, however, concerns regarding NIOSH's assessment of TiO<sub>2</sub>, and these concerns go to the core of the draft CIB's conclusions, and include:

- ACC-1 Ch.1 ■ **NIOSH Should Not Rely on Outdated Data That Overestimate the Number of Workers Potentially Exposed to TiO<sub>2</sub>:** The Panel urges NIOSH to remove references to the National Occupational Exposure Survey (NOES), or, alternatively, revise its discussion to address the deficiencies of NOES, namely, that the data are over 25 years old and greatly overestimate the number of domestic workers potentially exposed to TiO<sub>2</sub> because they do not account for the lack of worker exposure once TiO<sub>2</sub> is incorporated into an organic or inorganic matrix.
  
- ACC-2 Ch. 2 ■ **NIOSH's Consideration of the Epidemiology Studies Should Recognize the Strengths of These Studies:** The draft CIB unfairly focuses on individual limitations of these studies without consideration of their strengths or their value when considered together. The draft CIB is, for that reason, biased and not scientifically objective in that it focuses inordinate attention on "methodologic and epidemiologic limitations" and no attention on the strengths of the Chen and Fayerweather (1988), Fryzek, *et al.* (2003), and Boffetta, *et al.* (2004) cohort studies. The Panel urges NIOSH to recognize in the draft CIB that there is: (1) no evidence of an exposure effect in over 20,000 workers in the United States and



Europe who have been exposed to TiO<sub>2</sub> since the 1930s; and (2) no evidence of an effect in the highest cumulative exposure groups from the Fryzek, *et al.* (2003) and Boffetta, *et al.* (2004) studies.

ACC-3 Ch. 3

- **Some of the Draft CIB Conclusions Are Erroneous, and Must Be Corrected, Because They Are Based on Misrepresentations or Misinterpretations of Some of the Animal Studies and Because They Fail To Consider Several Studies That Are Critically Important:** Section 3 of the draft CIB should be revised to correct misrepresentations and misinterpretations of many of the animal studies it summarizes. Equally important, the draft CIB should be revised to incorporate a discussion of a number of studies that are extremely critical but not addressed in the current draft. In particular, NIOSH has failed to consider two important studies by Nikula, *et al.* The failure to consider these critical data has resulted in erroneous conclusions in the draft CIB that must be corrected if the CIB is to be scientifically defensible.

ACC-4 Overall

- **NIOSH Should Review All the Scientific Data Relevant to the Human Health Effects of Coal Mine Dust, Including Epidemiology Studies:** The Panel urges NIOSH to consider and incorporate in the CIB relevant epidemiology studies and related reviews on evidence regarding coal mine dust and lung cancer to increase the statistical power of this line of evidence.

ACC-5 Ch. 4

- **NIOSH Should Rely Upon Different Modeling Approaches in Its Quantitative Risk Assessment That Are Not Driven by Tumor Responses at Very High Doses and Should Not Ignore Evidence from More Relevant Levels of Exposure:** The Panel urges NIOSH to use threshold models to reflect mechanism of action conclusions instead of benchmark dose (BMD) modeling and linearized multistage approaches.

ACC-6 Overall

- **NIOSH's Proposed RELs Are Not Scientifically Defensible:** Due to the factors described above, particularly NIOSH's arbitrary selection of risk assessment models, the proposed RELs in the draft CIB are too low and not scientifically defensible. Use of threshold modeling is more appropriate, and would result in higher RELs that are scientifically defensible.

ACC-7 Ch. 6

- **NIOSH Has Failed to Provide Industry with a Confirmed Method(s) for the Analysis of TiO<sub>2</sub> in the Workplace Sufficient to Support the Proposed RELs:** Under the provisions of the Occupational Safety and Health Act of 1970 (Public Law 91-596), NIOSH is charged with the responsibility of "monitoring or measuring employee exposure." A method for measuring workplace exposures based on aerosol surface area is preferred by NIOSH. In the draft CIB, NIOSH admits, however, that "personal sampling devices that can be routinely used in the workplace for



measuring particle surface area are not currently available." In addition, the NIOSH proposed method is confusing and possibly unworkable for certain smaller manufacturers. The Panel urges NIOSH to remove recommendations for a workplace exposure analysis until such time as appropriate measurement techniques are available.

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## INTRODUCTION

The Titanium Dioxide Panel of the American Chemistry Council and the Titanium Dioxide Manufacturers Association and Physical Sunscreen Manufacturers Association of the European Chemical Industry Council (hereinafter referred to collectively as Panel) jointly submit these comments on the National Institute for Occupational Safety and Health's (NIOSH) December 30, 2005, *Federal Register* notice announcing the February 27, 2006, public meeting in Cincinnati and seeking public comment on the draft *NIOSH Current Intelligence Bulletin: Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide* (draft CIB). 70 Fed. Reg. 77399.<sup>1</sup> The Titanium Dioxide Panel consists of the major producers of titanium dioxide (TiO<sub>2</sub>) in the United States, while the Titanium Dioxide Manufacturers Association consists of the major TiO<sub>2</sub> producers in Europe.<sup>2</sup> The Physical Sunscreen Manufacturers Association consists of the major producers of physical sunscreens in Europe.<sup>3</sup>

Presentations  
included:

The presentations provided by Drs. John Gibbs, John Tomenson, and David Warheit at the February 27, 2006, meeting are appended at Attachment 1.

<sup>2</sup> Titanium Dioxide Panel member companies include: DuPont; Huntsman Corporation; Kronos Inc; Lyondell Chemical Company; and Tronox Incorporated (formerly Kerr McGee Chemical). Titanium Dioxide Manufacturers Association member companies include Cinkarna Celje, Inc.; Huntsman Tioxide; Kemira Pigments Oy; Kronos Worldwide Inc; Lyondell Chemical Europe Inc/Millennium Chemicals; Precheza AS; Sachtleben Chemie GmbH; and Tronox Pigments International GmbH.

<sup>3</sup> Physical Sunscreen Manufacturers Association member companies include: Degussa AG; Kemira Pigments Oy; Merck KGaA; Mitsubishi International GmbH; Sachtleben Chemie GmbH; and Uniqema.

NIOSH has stated that the goals of the draft CIB are three-fold: (1) to describe the relevant animal, human, and *in vitro* studies on the health effects of TiO<sub>2</sub>; (2) to provide a quantitative risk assessment based on dose-response information from the rat and human lung dosimetry modeling; and (3) to describe the rationale NIOSH used in the development of the draft recommended exposure limits (REL).<sup>4</sup> In preparing these comments, the Panel has been guided by the five questions that NIOSH posed for the Peer Reviewers:

1. Is the hazard identification and discussion of health effects for TiO<sub>2</sub> a full and reasonable reflection of the human and animal studies in the scientific literature?
2. Are the risk assessment and dosimetric modeling methods used in this document appropriate and relevant?
3. Are the sampling and analysis methods adequate to characterize worker exposure to fine and ultrafine TiO<sub>2</sub>?
4. Is the use of particle surface area as a dose metric appropriate for estimating worker risks from inhalation of TiO<sub>2</sub>?
5. Are there additional relevant studies or methods that NIOSH should consider in developing its RELs for TiO<sub>2</sub>?<sup>5</sup>

The Panel also has been guided by the Information Quality Act (IQA) guidelines applicable to NIOSH, the U.S. Department of Health and Human Services' (HHS) *HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public* and the Centers for Disease Control and Prevention's

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<sup>4</sup> See NIOSH, "Draft Document for Scientific Peer Review: Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide," available at <http://www.cdc.gov/niosh/review/peer/tio2/#a>.

<sup>5</sup> *Id.*



(CDC) *Guidelines for Ensuring the Quality of Information Disseminated to the Public*.<sup>6</sup> The HHS and CDC Guidelines were developed in accordance with the provisions of the IQA<sup>7</sup> and the Office of Management and Budget's (OMB) government-wide *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies*.<sup>8</sup>

The HHS and CDC IQA Guidelines "ensure and maximize the quality, objectivity, utility, and integrity of information" that NIOSH disseminates to the public.<sup>9</sup> "Objectivity" refers to whether disseminated information "is accurate, reliable, and unbiased," both as to its substance and its presentation.<sup>10</sup> As "influential scientific information," NIOSH must ensure that the draft CIB "use[s] the best available science and supporting studies conducted in accordance with sound and objective scientific practices" and "specif[ies], to the extent practicable . . . [d]ata gaps and other significant uncertainties identified in the process of the [quantitative] risk assessment and the studies that would assist in reducing the uncertainties

<sup>6</sup> U.S. Department of Health and Human Services, *HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public* (HHS Guidelines), available at <http://aspe.hhs.gov/infoquality/Guidelines/index.shtml>; *Guidelines for Ensuring the Quality of Information Disseminated to the Public -- Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry* (CDC Guidelines), available at <http://aspe.hhs.gov/infoquality/Guidelines/cdcinfo2.shtml>.

<sup>7</sup> 44 U.S.C. § 3516, note.

<sup>8</sup> 68 Fed. Reg. 8452 (Feb. 22, 2002), available at <http://www.whitehouse.gov/omb/fedreg/reproducible2.pdf>.

<sup>9</sup> CDC Guidelines at II; HHS Guidelines at I.A; *see also* IQA § (b)(2)(A).

<sup>10</sup> CDC Guidelines at V.A; HHS Guidelines at I.D.2.c.

[as well as] [a]dditional studies not used in the risk assessment that support or fail to support the findings of the assessment and the rationale of why they were not used.”<sup>11</sup>

ACC-8 Overall

To ensure the “quality, objectivity, utility, and integrity” of the draft CIB, NIOSH also should apply the standards set forth in OMB’s *Proposed Risk Assessment Bulletin*.<sup>12</sup> Although still only a proposal, this OMB document is intended “to enhance the technical quality and objectivity of risk assessments prepared by federal agencies by establishing uniform, minimum standards,” and identifies NIOSH CIBs among its specific examples of “influential risk assessments.”<sup>13</sup> The Panel believes that NIOSH should implement the standards set forth in the Proposed RA Bulletin to ensure the quality and objectivity of the CIB.

Because Panel members are manufacturers and users of TiO<sub>2</sub>, the validity of the scientific basis for the draft CIB, and its suitability for purposes of proposing RELs, is highly important to the Panel. The Panel is vitally interested in ensuring that the CIB, when issued in final form, accurately reflects the existing animal and human data on the health effects of TiO<sub>2</sub> and also provides a scientifically sound risk assessment. The Panel notes that NIOSH states in the draft CIB that it has reviewed “the relevant animal and human data for assessing the carcinogenicity of TiO<sub>2</sub> [in reaching its] conclusions.”<sup>14</sup> Moreover, an agency decision is

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<sup>11</sup> CDC Guidelines at VII.

<sup>12</sup> OMB, *Proposed Risk Assessment Bulletin* (Jan. 9, 2006) (Proposed RA Bulletin), available at [http://www.whitehouse.gov/omb/inforeg/proposed\\_risk\\_assessment\\_bulletin\\_010906.pdf](http://www.whitehouse.gov/omb/inforeg/proposed_risk_assessment_bulletin_010906.pdf).

<sup>13</sup> *Id.* at 3, 9.

<sup>14</sup> Draft CIB at iii.

arbitrary and capricious if the agency has ignored information in its possession or reached a decision that runs counter to the evidence before the agency.<sup>15</sup>

ACC-9  
Overall

As discussed below, there are studies that are highly relevant to this analysis that are not discussed in the draft CIB, while other studies that are discussed are not afforded proper attention. These factors call into question the objectivity and, hence, the quality of the draft CIB. The Panel urges NIOSH and the draft CIB Peer Reviewers to give full consideration to the Panel's comments and recommendations.<sup>16</sup> To do otherwise would gravely compromise the scientific integrity of the document and NIOSH (and other agency) decisions that will be based upon it, as well as the public participation process, all to NIOSH's, the Panel's, and the public's detriment.

ACC-10  
Overall

I. THE PANEL SUPPORTS NIOSH'S DECISION TO REMOVE ITS DESIGNATION OF TiO<sub>2</sub> AS A "POTENTIAL OCCUPATIONAL CARCINOGEN"

The Panel notes its support of NIOSH's determination "that insufficient evidence exists to designate TiO<sub>2</sub> as a 'potential occupational carcinogen.'"<sup>17</sup> As the draft CIB notes, TiO<sub>2</sub> has been classified by NIOSH as a potential occupational carcinogen since 1988.

<sup>15</sup> See *Retail Store Employees Union, Local 880, R.C.I.A. v. FCC*, 436 F.2d 248, 254 (D.C. Cir. 1970) (citations omitted); see also *Sierra Club v. Interstate Commerce Comm'n*, 1978 U.S. App. LEXIS 12538 (D.C. Cir. 1978).

<sup>16</sup> In addition to the comments stated herein, the Panel endorses fully the comments submitted under separate cover by the American Chemistry Council Nanotechnology Panel.

<sup>17</sup> Draft CIB at 87.

ACC-10 cont.  
(Overall)

The Panel concurs with NIOSH's findings that the tumorigenic effects of TiO<sub>2</sub> exposure in rats are not chemical-specific or a direct action of TiO<sub>2</sub> itself, but rather "a function of particle size and surface area acting through a secondary genotoxic mechanism associated with persistent inflammation," and that "occupational exposures to low concentrations of TiO<sub>2</sub> pose a negligible risk of cancer in workers."<sup>18</sup> These conclusions, which are based on NIOSH's review of the pertinent animal and human data, are indeed supported by the weight of the evidence, and for that reason the Panel supports NIOSH's removal of the current classification of TiO<sub>2</sub> as a potential occupational carcinogen.

ACC-11 Ch. 1

II. NIOSH SHOULD NOT RELY ON OUTDATED DATA THAT OVERESTIMATE THE NUMBER OF WORKERS POTENTIALLY EXPOSED TO TiO<sub>2</sub>

In Section 1.3 of the draft CIB, after acknowledging that "[a]n estimate of the number of workers currently exposed to TiO<sub>2</sub> dust is not available," NIOSH refers to the National Occupational Exposure Survey's (NOES) estimate of the number of domestic workers potentially exposed to TiO<sub>2</sub>.<sup>19</sup> As the draft CIB points out, though, NIOSH conducted NOES from 1981-1983 -- more than 25 years ago. NOES, then, is a much outdated survey of the number of workers in the United States potentially exposed to TiO<sub>2</sub>.

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<sup>18</sup> *Id.* at 87, 92.

<sup>19</sup> *Id.* at 2-3.



Moreover, NOES overestimates the number of workers potentially exposed to TiO<sub>2</sub>. As NIOSH knows, the 25-year-old estimates in NOES reflected observation of the actual use of a specific agent or "the use of a tradename product known to contain the specific agent."<sup>20</sup> With respect to the latter, it is important to note that NOES does not account for the fact that the first step in all downstream uses of TiO<sub>2</sub> (e.g., paints, coatings, plastics, rubber, inks, foodstuffs) is the incorporation of the compound into an organic or inorganic matrix. Once incorporated, the TiO<sub>2</sub> is enclosed within the matrix such that, from that point forward, there is virtually no TiO<sub>2</sub> dust exposure to subsequent downstream workers, to consumers, or to the environment (i.e., the only exposure occurs when TiO<sub>2</sub> particles are unbound and respirable).

The total universe of TiO<sub>2</sub>-exposed persons is limited to two types of workers: (1) those in the so-called "white" end of TiO<sub>2</sub> production plants (industry currently estimates this figure to be approximately 1,100 workers nationwide); and (2) those involved in the initial compounding of downstream products. Although a reliable estimate of the number of workers involved in the initial compounding of downstream TiO<sub>2</sub> products is not available, it is important to note that exposure levels for these workers are expected to be at or below the levels encountered in TiO<sub>2</sub> production plants.

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<sup>20</sup> NIOSH, "National Occupational Exposure Survey (1981 - 1983): Estimated Numbers of Employees Potentially Exposed to Specific Agents by Occupation within 2-Digit Standard Industrial Classification (SIC)," available at <http://www.cdc.gov/noes/noes4/m0913sco.html>. Included among those found in the NOES to be potentially exposed to TiO<sub>2</sub> were 108,653 textile mill products employees, 93,124 electric and electronic equipment workers, 192,970 machinery (except electrical) employees, and 80,854 electric, gas, and sanitary services workers. *Id.*



ACC-11  
cont.  
(Ch. 1)

In sum, NOES is outdated and grossly overestimates the number of workers in the United States with potential respiratory exposure to  $\text{TiO}_2$ . For these reasons, the draft CIB should not reference or rely upon NOES. If the discussion on NOES is retained in the final CIB, NIOSH should revise its discussion to address the deficiencies of NOES, namely, that the data are over 25 years old and greatly overestimate the number of domestic workers potentially exposed to  $\text{TiO}_2$  because NOES does not account for the lack of worker exposure once  $\text{TiO}_2$  is incorporated into an organic or inorganic matrix.

ACC-12  
Overall

Given NIOSH's concern regarding respiratory exposure to fine and ultrafine  $\text{TiO}_2$  and considering that  $\text{TiO}_2$  that is tightly bound in final products (such as paints and plastics for fine  $\text{TiO}_2$  and physical sunscreens for ultrafine  $\text{TiO}_2$ ), we request that any final REL determined by NIOSH be modified as "free and unbound." Specifically, we request the following modifications:

- that lines 55-57 be revised to read: "Therefore, NIOSH recommends exposure limits for fine and ultrafine free and unbound  $\text{TiO}_2$  to minimize any risks that might be associated with the development of pulmonary inflammation and cancer";
- that lines 1646-47 be revised to read: "...; thus, NIOSH determined that it is reasonable and prudent to recommend  $1.5 \text{ mg/m}^3$  as the REL for free and unbound fine  $\text{TiO}_2$ "; and
- that lines 1651-52 be revised to read: "...; thus, NIOSH determined that it is reasonable and prudent to recommend  $0.1 \text{ mg/m}^3$  as the REL for free and unbound ultrafine  $\text{TiO}_2$ ."

### III. NIOSH'S CONSIDERATION OF THE EPIDEMIOLOGY STUDIES SHOULD RECOGNIZE THE STRENGTHS OF THESE STUDIES

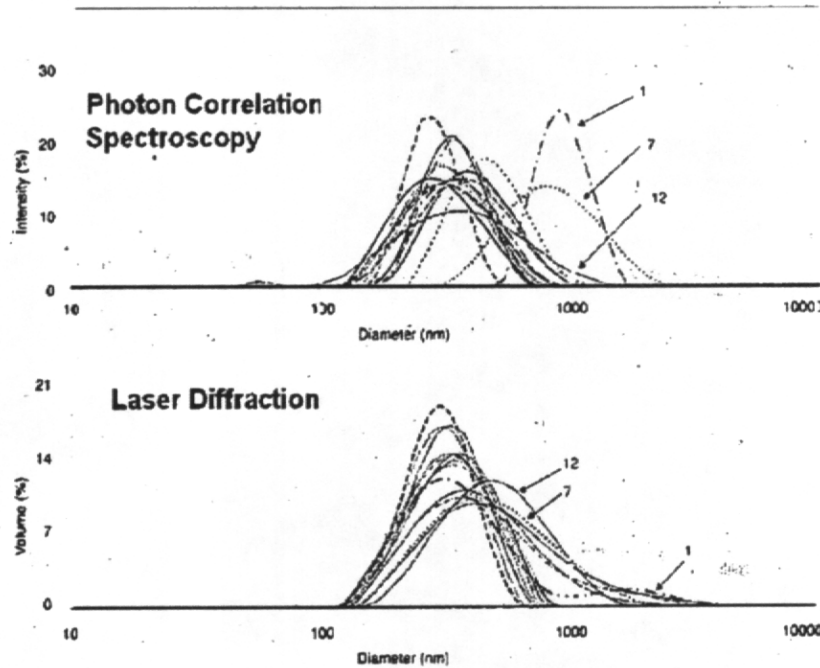
The draft CIB's description of the epidemiology studies that have been conducted must be revised, as in its current form it is not scientifically objective. Scientific objectivity means, *inter alia*, that the epidemiology studies must be presented by NIOSH "in an accurate . . . and unbiased manner."<sup>21</sup> NIOSH has not met this objectivity standard by emphasizing the "methodologic and epidemiologic limitations" of the Chen and Fayerweather (1988), Fryzek, *et al.* (2003), and Boffetta, *et al.* (2004) studies, while ignoring the individual and combined strengths of those studies. The Panel urges NIOSH to review and better incorporate pertinent data from these studies. Of particular significance, the Panel urges NIOSH to acknowledge in the final CIB that there is no evidence of an exposure effect in over 20,000 workers in the United States and Europe who have been exposed to TiO<sub>2</sub> since the 1930s.

NIOSH states on line 2091 that "[g]iven the particle size dimensions of fine TiO<sub>2</sub> (~0.1 μm to 4 μm, avg. of 0.5 μm) [Malvern Instruments 2004], it is reasonable to conclude that a significant fraction of total dust measurements reported for TiO<sub>2</sub> are comprised of respirable particles." The cited reference analyzed particle size distributions of primary particles from 15 representative high volume TiO<sub>2</sub> pigments produced in the U.S. To conduct those analyses, the pigment samples were dispersed using ultrasound to overcome the strong Vanderwals forces that tend to make fine particles agglomerate. It is important to point out that the primary particle size range identified was all above 100 nm as shown in Figure 1 below. The TiO<sub>2</sub> dust that workers

<sup>21</sup> HHS Guidelines at I.D.2.c; Proposed RA Bulletin at 24.

are exposed to in pigment plants is agglomerated but a significant fraction of the exposure is to respirable agglomerated particles. Based upon the MMAD (1.4  $\mu\text{m}$ ) of the ultrafine (primary particle diameter = 0.21  $\mu\text{m}$ ) dust generated in rodent studies (Bermudez *et al.* 2004), occupational exposures to ultrafine  $\text{TiO}_2$  likely are also mostly respirable.

FIGURE 1



Comparison of Primary Particle Size Distributions as Analyzed PCS and by Laser Diffraction

ACC-15  
Ch. 6

NIOSH also suggests that “fine rutile  $\text{TiO}_2$  may be micronized to produce an ultrafine particle fraction for product applications such as cosmetics.”<sup>22</sup> As an industry, we have significant experience with the micronization process, and we do not believe that fine  $\text{TiO}_2$  could

<sup>22</sup> Draft CIB at 101.

be micronized to an ultrafine material. We cannot cite a scientific reference to document this point, but request that NIOSH delete this assertion unless it documents that it is possible.

The Panel further requests that NIOSH clarify the type of TiO<sub>2</sub> exposure experienced by workers in the occupational epidemiological studies as follows:

- ACC-16 Ch. 2      ■      By revising lines 506-507 of the draft CIB to read: "A few epidemiologic studies have evaluated the carcinogenicity of fine TiO<sub>2</sub> in humans; they are described here and in Table 2-1."
  - ACC-17 Ch. 2      ■      By revising lines 716-717 to read: "Overall, these studies provide no clear evidence of elevated risks of lung cancer mortality or morbidity among those workers exposed to fine TiO<sub>2</sub> dust."
  - ACC-18 Ch. 2      ■      By revising lines 726-728 to read: "In addition to the methodologic and epidemiologic limitations of the studies of workers exposed to fine TiO<sub>2</sub>, there are no studies available of workers exposed to ultrafine TiO<sub>2</sub>."
- A.      The Chen and Fayerweather (1988) Study Provides Valid Mortality Data That NIOSH Cannot Dismiss

ACC-19 Ch. 2      Section 2.2.1 of the draft CIB cites seven "serious limitations" of the Chen and Fayerweather study.<sup>23</sup> The study, however, contains several different components -- cohort mortality, cohort cancer incidence, nested case control studies of lung cancer and chronic respiratory disease, and a cross-sectional study of lung fibrosis -- and NIOSH neglects to point out that the limitations cited do not apply to each and every one of the study components. In fact, none of the limitations cited by NIOSH invalidate the mortality component of the study, which provides valuable hazard data on workers in the domestic TiO<sub>2</sub> industry before 1960 to

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<sup>23</sup>      *Id.* at 14.

ACC-19  
cont.  
(Ch. 2)

supplement the data supplied by the Fryzek, *et al.* (2003) study. In particular, the Chen and Fayerweather study "did not report statistically significant increased mortality from lung cancer, chronic respiratory disease, or fibrosis associated with titanium exposure."<sup>24</sup> There is no evidence that the study missed lung cancer deaths; indeed, Chen and Fayerweather indicated that they were able to ascertain vital status for 94 percent of the cohort and had death certificates for 94 percent of the deaths. Given these facts, the mortality data in the Chen and Fayerweather study simply cannot be dismissed by NIOSH and must be considered with the body of other epidemiological studies, all of which show no evidence of an exposure-related effect on lung cancer mortality.

With respect to the seven "serious limitations" set forth by NIOSH, the Panel offers the following observations:

ACC-20 Ch. 2

1. NIOSH states that "it is unclear whether quantitative exposure data for respirable TiO<sub>2</sub> existed after 1975 and if so, whether those measurements were used in the analyses."<sup>25</sup> Chen and Fayerweather stated that no quantitative exposure data existed before 1975 and that exposure classification committees evaluated the exposure of each TiO<sub>2</sub>-exposed job. The clear implication is that quantitative exposure data existed after 1975.

ACC-21 Ch. 2

2. NIOSH states that the "type of measurement (e.g., total, respirable, or submicrometer), type of sample (e.g., area or personal), number of samples, sampling location and times, and nature of samples (e.g., epidemiologic study or compliance survey), and breathing zone particle sizes were not reported."<sup>26</sup> Very few studies provide the level of detail

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<sup>24</sup> *Id.*

<sup>25</sup> *Id.*

<sup>26</sup> *Id.*



ACC-21 cont.  
(Ch. 2)

that NIOSH states as a limitation in the reporting of the study, and this study should not be held to a standard different than other studies. In addition, it is reasonable to assume that Chen and Fayerweather were describing total dust.

ACC-22 Ch. 2

3. NIOSH notes that "duration of exposure was not described."<sup>27</sup> The study does provide the quartiles for exposure duration. The quartiles show that only 25 percent of the cohort was exposed for more than four years, which the Panel concurs is a limitation of the study.

ACC-23 Ch. 2

4. NIOSH states that "the presence of other chemicals and asbestos could have acted as confounders."<sup>28</sup> This is correct, but it would be most likely to result in increased mortality from lung cancer (inasmuch as one would expect that the workers would have been more likely to be exposed to other chemicals and asbestos than the general public). Mortality due to lung cancer was reduced in the study (9 observed deaths versus 17.3 expected based on U.S. white male mortality rates), however. NIOSH should note that this limitation does not explain reduced lung cancer mortality.

ACC-24 Ch. 2

5. NIOSH notes that "incidence and mortality data were not described in detail and could have been affected by the healthy worker effect."<sup>29</sup> While the incidence and mortality data are not described in detail, the healthy worker effect is highly unlikely to have concealed an exposure-related effect on lung cancer mortality.

ACC-25 Ch. 2

6. NIOSH notes that "chest X-ray films were not available for retired and terminated workers."<sup>30</sup> The unavailability of chest X-ray films does not affect or in any way invalidate the cross-sectional component of Chen and Fayerweather's study. More important, it is completely irrelevant to the mortality component of the study.

ACC-26 Ch. 2

7. NIOSH states that "company registries were the only apparent source for some information (e.g., company records may have been based on those workers eligible for pensions, and thus not typical of the general workforce)."<sup>31</sup> While this may have been true of the cancer incidence

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*Id.*

*Id.*

*Id.*

*Id.*

*Id.*

component of the study, with respect to the mortality component, Chen and Fayerweather indicated that they were able to ascertain vital status for 94 percent of the cohort and had death certificates for 94 percent of the deaths. Hence, it is highly unlikely that they failed to ascertain many, if any, lung cancer deaths.

B. NIOSH's Description of the Fryzek, *et al.* (2003) Study Should Be Revised Because It Is Biased and Inaccurate

Section 2.2.2 of the draft CIB makes several inaccurate statements about the Fryzek, *et al.* (2003) study. First, NIOSH mistakenly asserts that "company records from the early period were destroyed or lost."<sup>32</sup> Nowhere in their paper did Fryzek, *et al.* state this. Instead, they referred to the possibility "that some company records from the early periods in the plants may have been destroyed or lost," and explained that they "found no evidence to support such an assumption."<sup>33</sup> NIOSH should correct line 621 of the draft CIB accordingly.

More significant, NIOSH relies in the draft CIB on a comment made by Beaumont, *et al.* (2004) that the use of a time-independent exposure variable may have resulted in artificially low relative risks (RRs). That particular comment was relevant only to one table, Table 8, in the Fryzek, *et al.* study.<sup>34</sup> NIOSH fails to make clear, as it should, that Fryzek, *et al.* responded to the Beaumont, *et al.* letter to the editor by performing the very analyses suggested

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<sup>32</sup> *Id.* at 16.

<sup>33</sup> Fryzek JP, Chadda B, Marano D, White K, Schweitzer S, McLaughlin JK, Blot WJ (2003). A cohort mortality study among titanium dioxide manufacturing workers in the United States. *J. Occup. Environ. Med.* 45:406.

<sup>34</sup> Beaumont JJ, Sandy MS, Sherman CD (2004). Titanium dioxide and lung cancer [letter to the editor]. *J. Occup. Environ. Med.* 46(8):759.

-- what the draft CIB refers to only as “[f]urther data analyses”<sup>35</sup> -- and demonstrated that time-dependent and time-independent exposure variables yielded almost identical RRs.<sup>36</sup> In addition, the Panel believes it is misleading for NIOSH to repeat the Beaumont, *et al.* criticism in Table 2.1, where the comments refer to “questionable modeling methods [Beaumont *et al.* 2004]” without also explaining that the modeling methods did not give incorrect results.<sup>37</sup>

Finally, NIOSH evidences bias in its presentation of the Fryzek, *et al.* “[f]urther data analyses” by mentioning the non-significant hazard ratio of 1.3 for the “medium” cumulative TiO<sub>2</sub> exposure group in the time-dependent analysis with a 15-year lag, but not mentioning the far more relevant hazard ratio of 0.7 for the “high” cumulative exposure group in that analysis.<sup>38</sup> To be accurate, as well as fair and balanced, NIOSH must discuss the latter hazard ratio as well.

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<sup>35</sup> Draft CIB at 17.

<sup>36</sup> Fryzek JP, Cohen S, Chadda B, Marano D, White K, McLaughlin JK, Blot WJ. Titanium dioxide and lung cancer [letter to the editor]. *J. Occup. Environ. Med.* 46(8):760; Fryzek JP, Cohen S, Chadda B, Marano D, White K, McLaughlin JK, Blot WJ. Errata: RE Fryzek *et al.*, August 2004. *J. Occup. Environ. Med.* 46(11):1189.

<sup>37</sup> Draft CIB at 25.

<sup>38</sup> Fryzek JP, Cohen S, Chadda B, Marano D, White K, McLaughlin JK, Blot WJ. Titanium dioxide and lung cancer [letter to the editor]. *J. Occup. Environ. Med.* 46(8):760; Fryzek JP, Cohen S, Chadda B, Marano D, White K, McLaughlin JK, Blot WJ. Errata: RE Fryzek *et al.*, August (2004). *J. Occup. Environ. Med.* 46(11):1189.

C. NIOSH Should Revise the Discussion of the Boffetta, et al. (2004) Study, Which Is Erroneously Described in the Draft CIB

In its discussion of the Boffetta, et al. mortality study, NIOSH misstates one of the authors' suggestions regarding the lack of exposure-response relationships. Point number 2 on lines 704-705 of the draft CIB<sup>39</sup> should be revised in relevant part to read "(2) *the lack of inclusion of workers who were employed before the beginning of the followup period when exposure concentrations tended to be high.*" In addition, to be accurate, NIOSH should explain that the study authors felt that this lack of exposure-response relationships was not problematic, insofar as they stated: "We cannot exclude that this phenomenon had occurred and resulted in loss of power. However, the results of the analysis on the inception cohort, composed of workers whose employment is entirely covered by the follow-up, are remarkably similar to the results of the whole cohort, arguing against survival bias."<sup>40</sup>

Moreover, contrary to lines 705-706 of the draft CIB, Boffetta, et al. did not suggest "that the statistically significant SMR for male lung cancer could represent (1) heterogeneity by country."<sup>41</sup> Rather, they stated:

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<sup>39</sup> Draft CIB at 20.

<sup>40</sup> Boffetta P, Soutar A, Cherrie JW, Granath F, Andersen A, Anttila A, Blettner M, Gaborieau V, 2265 Klug SJ, Langard S, Luce D, Merletti F, Miller B, Mirabelli D, Pukkala E, Adami H-O, Weiderpass E (2004). Mortality among workers employed in the titanium dioxide production industry in Europe. *Cancer Causes Control* 15:704.

<sup>41</sup> Draft CIB at 20.



The lung cancer SMR results presented some heterogeneity by country. Because of the important effort made to standardize exposure estimates across factories and countries, this heterogeneity should be explained by chance and differences in the effect of potential confounders rather than by factors linked to TiO<sub>2</sub> dust exposure.<sup>42</sup>

To be accurate and objective, NIOSH must make this point clear in the final CIB.

In Appendix F of the draft CIB, NIOSH states that "the exposure data in [the Fryzek, *et al.* (2003) and Boffetta, *et al.* (2004)] studies was primarily based on the total dust fraction [and] limited data were available for exposure to respirable particles."<sup>43</sup> While Fryzek, *et al.* only used personal samples of total dust, a range of exposure data, including respirable dust measurements, was available from European plants.

D. NIOSH's Summary of the Epidemiologic Studies in Section 2.3 of the Draft CIB Is Deficient and Should Be Revised to Correct Those Deficiencies

In the draft CIB's summary of epidemiologic studies, where NIOSH discusses deaths from non-malignant respiratory diseases, NIOSH neglects to mention that the Boffetta, *et al.* (2004) study also reported a deficit of mortality from this cause (201.9 observed and 228.4 expected male deaths; 0 observed and 2.4 expected female deaths). In addition, although none of the epidemiology studies report on mortality due to pneumoconiosis, there is considerable discussion of four pleural cancer deaths in Boffetta, *et al.* (2004) (even though there was a deficit

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<sup>42</sup> Boffetta, *et al.* (2004) at 704.

<sup>43</sup> Draft CIB at F-1.



ACC-33 cont'.  
(Ch. 2)

of observed deaths with 5.2 expected deaths). A similar discussion of any pneumoconiosis deaths in Boffetta, *et al.* (2004) would have been expected had there been any, given the authors' focus on a possible association between TiO<sub>2</sub> exposure and pleural plaques and thickening, and this point should be included in the final CIB.

E. Contrary to What NIOSH Indicates in the Draft CIB, the Boffetta, *et al.* (2004) Study Has Reasonable Power to Detect a Dose Response, and the CIB Should Be Revised Accordingly

ACC-34, Appendices E, F,  
Ch. 4

On lines 3141-3150 of the draft CIB, NIOSH argues that a significant dose-response relationship for TiO<sub>2</sub> exposure and lung cancer "would not be expected to be observed" in the Boffetta, *et al.* (2004) study because the upper confidence limit on excess risk at the median cumulative exposure was estimated to be quite low.<sup>44</sup> The draft CIB derives estimates of 56.5 and 78.1 milligrams per cubic meter (mg/m<sup>3</sup>) per year for the midpoint of cumulative exposure in the highest quartile group, however.<sup>45</sup> These values are 29 and 39 times higher than the median cumulative exposure value and are significantly more relevant to the determination of whether the study had adequate power to detect a dose response.

ACC- 34 cont'.

While the Boffetta, *et al.* (2004) study did not provide information on its power, the full report of the European study -- Boffetta, *et al.* (2003) -- did discuss study power, stating:

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<sup>44</sup> *Id.* at F-6.

<sup>45</sup> *Id.* at E-6.

In the internal analysis, the power of the study to detect (at a level of 0.05) a relative risk of 2 in the highest versus the lowest quartile of cumulative exposure was above 99%, that for a relative risk of 1.7 was 90% and that for a relative risk of 1.5 was 74%. It is therefore unlikely that we have missed a moderate-to strong association (relative risk above 1.5) because of lack of power.<sup>46</sup>

ACC-34 cont.  
(Ch. 4,  
Appendices E,  
F)

The draft CIB's derived estimates of 56.5 and 78.1 mg/m<sup>3</sup> per year for the midpoint of cumulative exposure in the highest quartile group equate to average lifetime exposures of 1.26 and 1.74 mg/m<sup>3</sup> (45 years of exposure). Table E-2 of the draft CIB indicates that the upper confidence limits on excess risk at those concentrations (using the appropriate model) correspond to a relative risk of 1.5. Contrary to the draft CIB, the Boffetta, *et al.* (2004) study does have reasonable power to detect such risks and a dose response, and the final CIB should be revised accordingly.

F. NIOSH Should Not Discuss Human Study Case Reports Where There Is Insufficient Information on the Role That TiO<sub>2</sub> Played

ACC-35 Ch. 2

NIOSH includes in Section 2.1 a case study that has insufficient evidence provided about the role, if any, TiO<sub>2</sub> played in the death of a worker reported in that case study. Although NIOSH states that "[f]urther information about the role of TiO<sub>2</sub> was not provided," the existing paragraph strongly suggests that TiO<sub>2</sub> was to blame for the worker's sudden death.<sup>47</sup> No

<sup>46</sup> Boffetta P, Soutar A, Weiderpass E, Cherrie J, Granath F, Andersen A, Anttila A, Blettner M, Gaboricau V, Klug S, Langard S, Luce D, Merletti F, Miller B, Mirabelli D, Pukkala E, Adami H-O (2003). Historical cohort study of workers employees in the titanium dioxide production industry in Europe. Stockholm, Sweden: Karolinska Institute, Department of Medical Epidemiology. Unpublished.

<sup>47</sup> Draft CIB at 10.

ACC-35 cont.  
(Ch. 2)

autopsy report is cited by NIOSH, and there is no indication whether particulate of the cleaning mixture that the worker was using to pressure-clean the tank was ruled out as the cause of death. Absent further verifiable information about the role of  $\text{TiO}_2$ , if any, NIOSH should delete lines 477-479.

IV. SECTION 3 OF THE DRAFT CIB SHOULD BE REVISED TO CORRECT MISREPRESENTATIONS OR MISINTERPRETATIONS OF SOME OF THE ANIMAL STUDIES, TO CONSIDER SEVERAL STUDIES THAT ARE OF CRITICAL IMPORTANCE BUT NOT ADDRESSED IN THE DRAFT, AND TO CORRECT ERRONEOUS CONCLUSIONS THAT ARE BASED ON THESE CRITICAL ERRORS AND OMISSIONS

ACC-36 Ch. 3

Many of the animal studies summarized in Section 3 of the draft CIB either have been misrepresented or misinterpreted by NIOSH. For example, NIOSH's summaries of the two mechanistic studies by Bermudez, *et al.* are inaccurate. Those studies revealed significant species differences in lung responses to overload concentrations of both pigment-grade and specific ultrafine-grade  $\text{TiO}_2$  particles. Based on the summary descriptions in the draft CIB, one would have no idea that the rat has a unique lung response when compared to the mouse and hamster, and that this likely is the responsible mechanism for lung tumor development in rats but not mice or hamsters.

ACC-37 Ch. 3

Equally important, the draft CIB ignores a number of studies that are extremely critical. In particular, as explained more fully below, NIOSH has failed to consider two important studies by Nikula, *et al.* that demonstrate the fundamental differences in lung responses to low solubility dusts when comparing pulmonary responses in rats to those in humans and nonhuman primates.

These critical errors and omissions cause NIOSH to conclude erroneously that because humans have a slow dust clearance response leading to particle overload, the human response is similar to the rat response, possibly leading to lung tumors. There are two fundamental flaws in NIOSH's argument. First, the available occupational epidemiology data are negative for lung cancer. Second, the lung response in humans is different from the lung response in rats, both with respect to clearance kinetics and with respect to inflammatory and pathological responses. Ultimately, the basis for NIOSH's risk assessment modeling approach is flawed.

For organizational purposes, the following comments on the various subsections of Section 3 are presented in the same order in which the draft CIB is organized.

A. Section 3.1.1 (Genotoxicity and Mutagenicity)

With respect to the studies cited in Section 3.1.1 of the draft CIB, NIOSH states that "[o]verall, these studies suggest that TiO<sub>2</sub> may have some genotoxic potential, under some conditions."<sup>48</sup> This conclusion is not representative of the large majority of study papers which suggest that TiO<sub>2</sub> was negative for genotoxic potential in most of the studies.<sup>49</sup>

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<sup>48</sup> *Id.* at 27.

<sup>49</sup> See Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers, Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers Concerning Titanium Dioxide (Oct. 24, 2000), available at

B. Section 3.2.1 (Intratracheal Instillation)

ACC-40 Ch. 3

Most of the studies cited in Section 3.2.1 fail to identify the crystal structure of the TiO<sub>2</sub> particles utilized in the studies (e.g., rutile, anatase, or P25, which is 80 percent anatase and 20 percent rutile). In fact, throughout the draft CIB, NIOSH does not adequately characterize the crystal structures as well as the particle sizes used by the investigators in the various studies. Ultrafine TiO<sub>2</sub> particles are comprised of different crystal structures -- anatase or rutile -- and different particle sizes, and it is inappropriate, for example, to suggest that P25 is representative of all ultrafine TiO<sub>2</sub> particles.

C. Section 3.2.2 (Short-Term Inhalation)

The Panel offers the following line-by-line comments on Section 3.2.2 of the draft CIB:

ACC-41 Ch. 3

- The Panel urges NIOSH to mention on lines 815-821 that the fine TiO<sub>2</sub> was rutile-type and that the point of the Warheit, *et al.* (1997) study was to demonstrate that inhalation of high concentrations of low toxicity dusts such as pigment-grade TiO<sub>2</sub> and carbonyl iron particles results in impaired pulmonary clearance mechanisms and persistent inflammation in rats. This is a nonspecific response to particle overloading in the lungs of rats.

ACC-42 Ch. 3

- With respect to the Baggs, *et al.* (1997) study discussed on lines 822-826, NIOSH should provide better physical characterization of the ultrafine

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[http://www.europa.eu.int/comm/health/ph\\_risk/committees/sccp/documents/out135\\_en.pdf](http://www.europa.eu.int/comm/health/ph_risk/committees/sccp/documents/out135_en.pdf).



TiO<sub>2</sub> (*i.e.*, particle size, crystal structure) and also the pigment-grade TiO<sub>2</sub> particles, if such data are available.

ACC-43 Ch. 3

- On line 832, "52 days" should be replaced with "32 days." Unless the authors of the Donaldson, *et al.* (1990) study did not provide it, a better description of the physical characterization of "fine TiO<sub>2</sub>" is needed. Additionally, NIOSH should complete the study discussion by providing the conclusions of the study authors.

ACC-44 Ch. 3

- With respect to the Warheit, *et al.* (2005) study, the draft CIB provides an inadequate physical characterization of the different fine formulations of TiO<sub>2</sub> and an incomplete summary of the key findings of the study.

D. Section 3.2.3 (Subchronic Inhalation)

ACC-45 Ch. 3

NIOSH states on lines 866-867 that "[i]nhaling 50 or 250 mg/m<sup>3</sup> fine TiO<sub>2</sub> for 13 weeks caused histopathological changes consistent with alveolar epithelial cell hypertrophy and hyperplasia in all species [Everitt *et al.* 2000]."<sup>50</sup> This study summary is erroneous and NIOSH should correct the draft CIB to note the following conclusions of the Everitt, *et al.* study, as described by Bermudez, *et al.* (2002):

Burdens of pigment-grade TiO<sub>2</sub> in the lungs and in the lung-associated lymph nodes increased in a concentration-dependent manner. Retained lung burdens following exposure were greatest in mice. Rats and hamsters had similar lung burdens immediately postexposure when assessed as milligrams of pigment-grade per gram of dried lung. Particle retention data suggested that pulmonary overload was achieved in both rats and mice at the exposure levels of 50 and 250 mg/m<sup>3</sup>. Under the conditions of the present study, hamsters were better able to clear pigment grade TiO<sub>2</sub> particles than were similarly exposed mice and rats. Pulmonary histopathology revealed both species and

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<sup>50</sup> *Id.* at 33.

ACC-45 cont.  
(Ch. 3)

concentration-dependent differences in pigment grade particle retention patterns. Inflammation was noted in all three species at 50 and 250 mg/m<sup>3</sup> as evidenced by increases in macrophage and neutrophil numbers and in soluble indices of inflammation in bronchoalveolar lavage fluid (BALF; rats>mice, hamsters). In mice and rats, the BALF inflammatory response remained elevated relative to controls throughout the entire postexposure recovery period in the most highly exposed animals. In comparison, inflammation in hamsters eventually disappeared, even at the highest exposure dose, due to the more rapid clearance of particles from the lung. Pulmonary lesions were most severe in rats, where progressive epithelial- and fibroproliferative changes were observed in the 250 mg/m<sup>3</sup> group. These epithelial proliferative changes were also manifested in rats as an increase in alveolar epithelial cell labeling in cell proliferation studies. Associated with these foci of epithelial proliferation were interstitial particle accumulation and alveolar septal fibrosis. In summary, there were significant species differences in pulmonary response to inhaled pigment grade TiO<sub>2</sub> particles. Under conditions in which the lung pigment grade TiO<sub>2</sub> burdens were similar and likely to induce pulmonary overload, rats developed a more severe and persistent pulmonary inflammatory response than either mice or hamsters. Rats also were unique in the development of progressive fibroproliferative lesions and alveolar epithelial metaplasia in response to 90 days of exposure to a high concentration of pigment grade TiO<sub>2</sub> particles.<sup>51</sup>

ACC-46 Ch. 3

In addition, NIOSH misrepresents on lines 866 to 882 of the draft CIB the findings of the Bermudez, *et al.* (2002) study, which concluded that there are significant rodent species differences in lung responses to particle overload, and that the rat develops a unique adverse response. In particular, the study found that pulmonary lesions were most severe in rats, where progressive epithelial and fibroproliferative changes were observed in the 250 mg/m<sup>3</sup> group. These epithelial proliferative changes were also manifested in rats as an increase in

<sup>51</sup> Bermudez E, Mangum JB, Asgharian B, Wong BA, Reverdy EE, Janszen DB, Hext PM, Warheit DB, Everitt JI (2002). Long-term pulmonary responses of three laboratory rodent species to subchronic inhalation of pigmentary titanium dioxide particles. *Toxicol. Sci.* 70 (1):86-97.

ACC-46 cont.  
(Ch. 3)

alveolar epithelial cell labeling in cell proliferation studies. Associated with these foci of epithelial proliferation were interstitial particle accumulation and alveolar septal fibrosis. In summary, there were significant species differences in pulmonary response to inhaled pigment-grade TiO<sub>2</sub> particles. Under conditions in which the lung pigment-grade TiO<sub>2</sub> burdens were similar and likely to induce pulmonary overload, rats developed a more severe and persistent pulmonary inflammatory response than either mice or hamsters. Rats also were unique in the development of progressive fibroproliferative lesions and alveolar epithelial metaplasia in response to 90 days of exposure to a high concentration of pigment-grade TiO<sub>2</sub> particles.

ACC-47 Ch. 3

NIOSH also errs by failing to discuss in Section 3.2.3 the Bermudez, *et al.* (2004) study, in which female rats, mice, and hamsters were exposed to aerosol concentrations of 0.5, 2.0 and 10.0 mg/m<sup>3</sup> of ultrafine (80 percent anatase, 20 percent rutile) TiO<sub>2</sub> particles for 13 weeks. Following the exposure period, animals were held for recovery periods of 4, 13, 26, or 52 weeks (49 weeks for hamsters). The study concluded as follows:

Retained lung burdens increased in a dose-dependent manner in all three species and were at a maximum at the end of exposures. Mice and rats had similar retained lung burdens at the end of the exposures when expressed as mg of TiO<sub>2</sub>/mg dry lung, whereas hamsters had retained lung burdens that were significantly lower. . . . The retardation of particle clearance from the lungs in mice and rats of the 10 mg/m<sup>3</sup> group indicated that pulmonary particle overload had been achieved in these animals. Pulmonary inflammation in rats and mice exposed to 10 mg/m<sup>3</sup> was evidenced by increased numbers of macrophages, neutrophils and soluble biomarkers. . . . Progressive epithelial and fibroproliferative changes were observed in rats of the 10 mg/m<sup>3</sup> group. These lesions consisted of foci of alveolar epithelial proliferation of metaplastic epithelial cells (so-called alveolar bronchiolization) circumscribing aggregated foci of heavily particle-laden macrophages. The observed epithelial proliferative changes were

also manifested in fats as an increase in alveolar epithelial cell labeling in cell proliferation studies. Associated with these foci of epithelial proliferation were interstitial particle accumulation and alveolar septal fibrosis. These lesions became more pronounced with increased time postexposure. Epithelial, metaplastic and fibroproliferative changes were not noted in either mice or hamsters. In summary, there were significant species differences in the pulmonary responses to inhaled uf-TiO<sub>2</sub> particles. Under conditions where the lung uf-TiO<sub>2</sub> burdens were equivalent, rats developed a more severe inflammatory response than mice, and subsequently, developed progressive epithelial and fibroproliferative changes. Clearance of particles from the lung was markedly impaired in mice and rats exposed to 10 mg/m<sup>3</sup> uf-TiO<sub>2</sub>, whereas clearance in hamsters did not appear to be affected at any of the administered doses. These data are consistent with the results of a companion study using inhaled pigmentary (fine mode) TiO<sub>2</sub> (Bermudez, *et al.* [2002]) and demonstrate that the pulmonary responses of rats exposed to ultrafine particulate concentrations likely to induce pulmonary overload are different from similarly exposed mice and hamsters. These differences can be explained both by pulmonary response and by particle dosimetry differences among these rodent species.<sup>52</sup>

In sum, NIOSH misinterprets the conclusions of the very important mechanistic Bermudez, *et al.* (2002) study with pigment-grade TiO<sub>2</sub> particles, which demonstrated that despite the fact that rats and mice have similar lung burdens, inflammation, and particle overload, only rats develop histopathological lung tissue changes consistent with fibroproliferative disease, alveolar epithelial proliferation, and septal fibrosis. This is extremely critical because only rats -- not mice or hamsters -- develop lung tumors in response to chronic inhalation-induced particle overload in the lung. NIOSH also omits the highly important conclusions of the Bermudez, *et al.* (2004) study with interspecies comparisons of lung response.

<sup>52</sup> Bermudez E, Mangum JB, Wong BA, Asgharian 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.



ACC-48 cont' to inhaled ultrafine TiO<sub>2</sub> particles (see Section IV.F below). This omission is critical because  
(Ch. 3) virtually the same conclusions are derived following the development of particle overload in rats.

E. Sections 3.3.1 (Rat Tumor Lung Response) and 3.3.2 (Chronic Oral)

The Panel offers the following line-by-line comments on Sections 3.3.1 and 3.3.2

of the draft CIB:

ACC-49 Ch. 3

ACC-50 Ch. 3

- Line 887: The "ultrafine TiO<sub>2</sub>" in the Heinrich, *et al.* (1995) study should be better characterized in terms of size and crystal structure.

ACC-51 Ch. 3

- Line 890: The word "carcinomas" should be replaced with "tumors" inasmuch as most of the described carcinomas likely were keratin cysts.

- Lines 902-905: These lines are inaccurate, particularly as they relate to the Boorman, *et al.* (1996) reference, and should be revised so that they are consistent with the new Warheit and Frame (2006) manuscript, which states as follows:

Using current diagnostic criteria, this [study] summarize[d] the microscopic review of 16 proliferative squamous lesions, previously diagnosed as cystic keratinizing squamous cell carcinoma, in the lungs of rats from a 2-year inhalation study with pigment-grade titanium dioxide particles. . . . Unanimous agreement was reached as to the diagnosis of each of the lesions. Two of the lesions were diagnosed as squamous metaplasia and one as a poorly keratinizing squamous cell carcinoma. The remaining 13 lesions were diagnosed as non-neoplastic pulmonary keratin cysts. [The authors concluded that] [t]hese keratin cysts are a species-specific lesion that is unique to the rat lung under conditions of particle overload exposure.<sup>53</sup>

<sup>53</sup> Warheit DB, Frame SR. Characterization and reclassification of titanium dioxide-related pulmonary lesions. *J. Occup. Environ. Med.* (in press; manuscript appended as Attachment 2).



- ACC-52 Ch. 3 ■ Lines 915-924: The exposure regimen in the Heinrich, *et al.* (1995) study should be clarified (17 hours/day x 5 days/week), and the ultrafine test substance should be better described as 80 percent anatase, 20 percent rutile.
- ACC-53 Ch. 3 ■ Lines 928-930: NIOSH should state that under the conditions of the study, exposure to ultrafine TiO<sub>2</sub> particles in mice was negative.
- ACC-54 Ch. 3 ■ Line 931: A section summary of pulmonary effects should be provided.
- ACC-55 Ch. 3 ■ Line 946: NIOSH inexplicably omits other negative oral toxicity studies on TiO<sub>2</sub>. For example, Bernard, *et al.* conducted a study in which groups of 50 male and female Fischer 344 rats, 8 weeks of age, were fed diets containing 0, 1.0, 2.0 or 5.0 percent TiO<sub>2</sub>-coated mica for up to 130 weeks. The authors found no evidence of carcinogenic effects.<sup>54</sup>

F. Section 3.4.1 (Rodent Lung Responses to Fine and Ultrafine TiO<sub>2</sub>)

ACC-56 Ch. 3 NIOSH states on line 950 of the draft CIB that “[b]oth fine and ultrafine TiO<sub>2</sub> are capable of eliciting pulmonary inflammation in the rat.”<sup>55</sup> This statement is overly broad and inaccurate because any particle in sufficient doses can elicit pulmonary inflammation. NIOSH, moreover, does not draw a distinction between short-term and long-term pulmonary inflammation, nor does it specify the particle sizes and crystal structure of the fine and ultrafine TiO<sub>2</sub> particles. For example, P25 is not likely to be representative of all ultrafine TiO<sub>2</sub> particles.<sup>56</sup>

<sup>54</sup> Bernard BK, Osheroff MR, Hofman A, Mennear JH (1990). Toxicology and carcinogenesis studies of dietary titanium dioxide-coated mice in male and female Fischer 344 rats. *J. Toxicol. Environ. Health* 29: 417-429.

<sup>55</sup> Draft CIB at 36.

<sup>56</sup> See Warheit DB, Webb TR, Sayes CM, Colvin VL, Reed KL (2006). Pulmonary instillation studies with nanoscale TiO<sub>2</sub> rods and dots in rats: toxicity is not dependent upon particle size and surface area. *Toxicol Sci.* Appended as Attachment 3.

ACC-57 Ch. 3

NIOSH misrepresents and misinterprets the Bermudez, *et al.* (2004) study, which found significant species differences in lung responses to ultrafine TiO<sub>2</sub>. Pulmonary lesions were most severe in rats, where progressive epithelial and fibroproliferative changes were observed in the 10 mg/m<sup>3</sup> group. These epithelial proliferative changes also were manifested in rats as an increase in alveolar epithelial cell labeling in cell proliferation studies. Associated with these foci of epithelial proliferation were interstitial particle accumulation and alveolar septal fibrosis. In summary, there were significant species differences in pulmonary response to inhaled ultrafine TiO<sub>2</sub> particles. Under conditions in which the lung pigment-grade TiO<sub>2</sub> burdens were similar and likely to induce pulmonary overload, rats developed a more severe and persistent pulmonary inflammatory response than either mice or hamsters. Moreover, lesions in high-dose rat lungs seen at the end of the exposure period continue to develop in an aggressive manner throughout the one-year post-exposure period. Indeed, they start to take on the appearance of the foci of effects from which tumors are considered to arise in long-term studies. This is not the case with mice or hamsters.

ACC-58 Ch. 3

The Maronpot, *et al.* (2004) study requires a much more detailed explanation than the one offered by NIOSH on lines 993-995. First, the data do not support the conclusion that “the pulmonary adenomas and adenocarcinomas seen in TiO<sub>2</sub>-exposed rats are similar to pulmonary neoplasms in humans.” Second, NIOSH erroneously utilizes this statement as a rather questionable basis for conducting a quantitative risk assessment between rats and humans. The draft CIB ignores the guidance given in the International Life Sciences Institute’s (ILSI) Rat Lung Overload document, wherein fundamental distinctions are made between the lung tumors

observed in humans and those observed in rats (different cell types, different anatomic locations, etc.).<sup>57</sup>

ACC-59 Ch. 3

The draft CIB also should consider in Section 3.4.1 the forthcoming Warheit and Frame study, wherein 16 lung lesions originally described as cystic keratinizing squamous cell carcinomas were reevaluated according to current diagnostic criteria.<sup>58</sup> As discussed in Section IV.E above, two of the lesions were diagnosed as squamous metaplasia and one as a poorly keratinizing squamous cell carcinoma. The remaining 13 lesions were diagnosed as non-neoplastic pulmonary keratin cysts, which the authors concluded are a species-specific lesion unique to the rat lung under conditions of particle overload exposure.

ACC-60 Ch. 3

The draft CIB does not, but should, include in Section 3.4.1 a discussion of the final report issued by The Presidential/Congressional Commission on Risk Assessment and Risk Management.<sup>59</sup> Established under Section 303 of the Clean Air Act Amendments of 1990, the Commission was directed by Congress "to make a full investigation of the policy implications and appropriate uses of risk assessment and risk management in regulatory programs under various Federal laws to prevent cancer and other chronic human health effects which may result

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<sup>57</sup> ILSI Risk Science Institute, "The Relevance of the Rat Lung Response to Particle Overload for Human Risk Assessment: A Workshop Consensus Report" (1998).

<sup>58</sup> See *supra*, footnote 52.

<sup>59</sup> The Presidential/Congressional Commission on Risk Assessment and Risk Management, "Risk Assessment and Risk Management in Regulatory Decision-making: Final Report, Volume 2" (1997) (Volume 2), available at <http://www.riskworld.com/Nreports/1997/risk-rpt/volume2/pdf/v2epa.PDF>.

ACC-60 cont.  
(Ch. 3)

from exposure to hazardous substances.”<sup>60</sup> Volume 2 of the Commission’s final report observed that “[t]here are . . . cases . . . where rodent tumor responses have been shown to be irrelevant to humans or may occur at doses far exceeding any recognized human exposures including workplace exposure.”<sup>61</sup> Indeed, the Commission identified TiO<sub>2</sub> as one such case.<sup>62</sup>

In addition to the comments above, the Panel offers the following line-by-line comments on Section 3.4.1 of the draft CIB:

ACC-61 Ch. 3

- Lines 975-978: NIOSH’s description of the Heinrich, *et al.* (1995) study in connection with the Bermudez, *et al.* (2004) study fails to demonstrate that in mice, cell proliferation leads to a minor pulmonary effect, while in rats, it leads to a major pulmonary effect.

ACC-62 Ch. 3

- Lines 980-981: The draft CIB states, “[b]oth fine and ultrafine TiO<sub>2</sub> are fibrogenic and carcinogenic in the lungs of chronically exposed rats. Pulmonary interstitial fibrosis developed in rats exposed to 50 or 250 mg/m<sup>3</sup> fine TiO<sub>2</sub> 6 hr/day for 2 years.”<sup>63</sup> The first statement is misleading because it fails to acknowledge overload concentrations or that lung tumors were produced in rats exposed only to 250 mg/m<sup>3</sup> -- where only one tumor was a carcinoma -- the rest were adenomas and proliferative keratin cysts. The statement about pulmonary interstitial fibrosis fails to indicate that the fibrosis was mild to minimal and was a normal reaction to extreme dust overload.

ACC-63 Ch. 3

- Lines 988-990: The use of the term “adenocarcinomas” is inaccurate for the Lee, *et al.* (1985) study, and only one tumor was a squamous cell carcinoma.

<sup>60</sup> Pub. L. No. 101-549, § 303(a) (Nov. 15, 1990).

<sup>61</sup> Volume 2 at 65.

<sup>62</sup> *Id.* (Table 4-2).

<sup>63</sup> Draft CIB at 38.



G. Section 3.4.2 (Lung Overload)

ACC-64 Ch. 3

NIOSH's review of the scientific literature pertinent to lung overload ignores completely two studies that the Panel believes are highly critical: Nikula, *et al.* (1997)<sup>64</sup> and Nikula, *et al.* (2001).<sup>65</sup> NIOSH should revise the CIB to consider these studies.

ACC-64  
cont.  
(Ch. 3)

The Nikula, *et al.* (1997) study compared the anatomical pattern of particle retention and the lung tissue response of rats and monkeys exposed chronically (for 24 months) to high occupational concentrations of poorly soluble particles. The study found that rats (versus monkeys) retained a greater portion of particles in alveolar ducts, while monkeys (versus rats) retained a greater portion of particles in interstitium. In addition, rats, but not monkeys, were found to have significant alveolar epithelial hyperplastic, inflammatory, and septal fibrotic responses to the retained particles. The authors concluded as follows:

There was no significant difference in the relative amount of retained particulate material between diesel exhaust-exposed monkeys and rats. Within each species, the sites of particle retention and lung tissue responses were the same for diesel soot, coal dust, and the combined material. Rats retained a greater portion of the particulate material in lumens of alveolar ducts and alveoli than monkeys. Conversely, monkeys retained a greater portion of the particulate material in the interstitium than rats. Rats, but not monkeys, had significant alveolar epithelial hyperplastic, inflammatory, and septal fibrotic responses to the

<sup>64</sup> Nikula KJ, Avila KJ, Griffith WC, Mauderly JL (1997). Lung tissue responses and sites of particle retention differ between rats and cynomolgus monkeys exposed chronically to diesel exhaust and coal dust. *Fund. Appl. Toxicol.* 37:37-53.

<sup>65</sup> Nikula KJ, Vallyathan V, Green FH, Hahn FF (2001). Influence of exposure concentration or dose on the distribution of particulate material in rat and human lungs. *Environ. Health Perspect.* 109:311-318.



retained particles. These results suggest that intrapulmonary particle retention patterns and tissue reactions in rats may not be predictive of retention patterns and tissue responses in primates exposed to poorly soluble particles at concentrations representing high occupational exposures.<sup>66</sup>

ACC-64 cont'.  
(Ch. 3)

The Nikula, *et al.* (2001) study used morphometry to assess particle retention in histologic sections from rats and humans. Rats were exposed to diesel exhaust for 24 months at concentrations of 0.35, 3.5, or 7.0 mg soot/m<sup>3</sup>, and nonsmoking coal miners were used in the study. The study authors found that retained particle distribution within the lungs was markedly different for rats and humans. They concluded:

These results show that chronically inhaled diesel soot is retained predominately in the airspaces of rats over a wide range of exposures, whereas in humans, chronically inhaled particulate material is retained primarily in the interstitium. In humans, the percentage of particles in the interstitium is increased with increased dose (exposure concentration, years of exposure, and/or lung burden). This difference in distribution may bring different lung cells into contact with the retained particles or particle-containing macrophages in rats and humans and may account for differences in species response to inhaled particles.<sup>67</sup>

ACC-64 cont'.  
(Ch. 3)

Due to these omissions, NIOSH appears to have misinterpreted the apparent paradox in lung responses between rats and humans. Indeed, the pulmonary clearance of dusts in humans and monkeys is significantly slower when compared to rats. One might assume that this leads to a greater degree of particle overload. The pulmonary response of humans and monkeys to inhaled diesel exhaust and coal dust is significantly different from rats, however. First, the

<sup>66</sup> Nikula, *et al.* (1997).

<sup>67</sup> Nikula, *et al.* (2001).

ACC-64 cont.  
(Ch. 3)

distribution of inhaled dusts in humans and nonhuman primates is different from rats. In humans and primates, there is a much greater tendency to interstitialization, whereas in rats, more of the dust is constrained to the alveolar compartment. Second, as the Nikula, *et al.* (1997) and Nikula, *et al.* (2001) studies have demonstrated, the rat lung response is much more reactive and inflammogenic when compared to the response of human and primate lungs. Despite the fact that there may be a much greater dust burden in humans and primates relative to rats, this does lead to a rat-type lung overload response. This likely is the reason why pathologists have not observed in humans any dust-related (silica and asbestos excepted) lung tumors in the absence of smoking. Thus, NIOSH has erred in making the case that humans exposed to overload concentrations of particles may develop lung tumors and should revise the draft CIB to reflect accurately the available scientific data.

In addition to the comments above, the Panel offers the following line-by-line comments on Section 3.4.2:

ACC-65  
Ch. 3

- Lines 1006-1007: NIOSH states that “the lung tumor response of PSLT can be predicted by the particle surface area dose without the need to account for overloading.”<sup>68</sup> This statement is inaccurate for two reasons: (1) the development of lung tumors in rats is threshold mediated; and (2) particle overload is a prerequisite for the development of lung tumors in rats exposed to low solubility/low toxicity dusts.

ACC-66  
Ch. 3

- Lines 1016-1017: The statement that “mice and hamsters are known to give false negatives in bioassays for some human carcinogens” is misleading.<sup>69</sup> No examples are provided, and it is unclear whether NIOSH is referring to true carcinogenic agents or to studies with particles. Absent clarification, the existing statement does not explain the fact that other

<sup>68</sup> Draft CIB at 39.

<sup>69</sup> *Id.*

than the rat, none of the rodent species or the large mammalian species develop lung tumors in response to extreme particle overload.

ACC-67 Ch. 3

- Lines 1020-1022: NIOSH asserts that “evidence from known human carcinogens, such as asbestos and crystalline silica, suggests that rats are no more sensitive to the[] [carcinogenic effects of TiO<sub>2</sub>] than humans.”<sup>70</sup> The Panel believes that this assertion is flawed. Neither asbestos nor crystalline silica falls into the class of low toxicity, low solubility particles. Crystalline silica is well known as a cytotoxic dust that produces sustained inflammation, fibrosis (silicosis), alveolar proteinosis, and, in some cases, lung tumors. Asbestos is similarly known to be a fibrogenic and mesotheliogenic fiber. To compare these cytotoxic dusts to TiO<sub>2</sub> is not germane to the argument that rats and humans may have similar-type responses to TiO<sub>2</sub> particles. Additionally, no data suggesting that rats are no more sensitive to carcinogenic effects than humans is offered.

#### H. Section 3.4.3 (Dose Metric)

ACC-68 Ch. 3

The dose metric discussion in Section 3.4.3 again indicates an insufficient understanding of the fundamental species differences between the rat and other rodent species as well as large mammalian species. In addition, the Panel urges NIOSH to incorporate in the CIB a better understanding of the relationship between BAL fluid indicators of inflammation and tissue responses.<sup>71</sup> In the mouse, sustained pulmonary inflammation does not lead to significant adverse lung tissue response, while in the rat, it leads to epithelial proliferation, fibroproliferative responses, and septal fibrosis.

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<sup>70</sup> *Id.*

<sup>71</sup> See Bermudez, *et al.* (2002, 2004).

ACC-69 Ch. 3

Additionally, on lines 1051-1052, NIOSH should make clear that the situation described -- where a "sufficient particle surface area dose of fine TiO<sub>2</sub> would be expected to be carcinogenic"<sup>72</sup> -- is one where gross overload exists.

I. Section 3.5.1 (Lung Tissue Responses)

ACC-70 Ch. 3

In the first paragraph of Section 3.5.1, the draft CIB, as described in Section 3.4.2 above, uses selective logic and fails to recognize the fundamental differences between the manner in which humans and rats respond to inhaled dusts. Moreover, no human and animal studies in which "respirable TiO<sub>2</sub> persisted in the lung" are cited by NIOSH. While the lung clearance response in humans is slower than it is in rats, NIOSH does not recognize that the lung inflammatory response in humans to dust concentrations is relatively muted, while the response in rats is reactive. Overall, NIOSH errs in not considering adequately the two Nikula, *et al.* studies cited above, and NIOSH should revise the draft CIB to reflect such a consideration of these studies.

ACC-71 Ch. 3

On line 1074, NIOSH references "[t]he one case of life-threatening lipoproteinosis seen in a worker with high pulmonary deposition of TiO<sub>2</sub>," and states that it "was more severe than seen in any exposed laboratory animals, although alveolar lipoproteinosis was also observed in TiO<sub>2</sub>-exposed rats."<sup>73</sup> Without evidence that the worker had not been exposed

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<sup>72</sup> Draft CIB at 41.

<sup>73</sup> *Id.* at 42.



to silica or any other particle, this statement is unjustified and misleading. In addition, the comparison to rats exposed for two years to 250 mg/m<sup>3</sup> of TiO<sub>2</sub> is inappropriate.

ACC-72 Ch. 3

Finally, on lines 1082-1084, it is not clear whether NIOSH is referring to the alveolar metaplasia in the three human patients who had a common exposure to TiO<sub>2</sub> (and any other substances). Absent this, there is an insufficient basis to justify conducting a comparative risk assessment for rats and humans.

J. Section 3.5.2 (Role of Chronic Inflammation in Lung Disease)

ACC-73 Ch. 3

NIOSH improperly includes silica and asbestos in its paradigm to justify the potential risk assessment comparisons between rats and humans. The epidemiological data for TiO<sub>2</sub> workers simply do not justify a risk assessment. In humans, silica exposure has been shown to result in chronic inflammation, fibrosis (silicosis), and ultimately potential lung tumors. TiO<sub>2</sub> exposure does not result in chronic inflammation, however, and there is no epidemiological evidence of fibrosis and, ultimately, lung tumors.

ACC-74 Ch. 3

Figure 3-3 compares the tumor incidences between the pigment-grade and ultrafine TiO<sub>2</sub> studies. While those studies allow for lung burden by taking into account the different strains of rat used, there is no reference to the differences in study termination time. Time of termination of a study is an important factor when comparing incidences of particle-induced tumors. The lung tumors seen from particulate exposures are ones of old age, and an extension beyond the normal termination time of two years usually results in a large increase in



ACC-74 cont.  
(Ch. 3)

these tumors. The Lee, *et al.* (1985) study ended at two years, whereas the Heinrich, *et al.* (1995) ultrafine TiO<sub>2</sub> study lasted for up to 30 months (six months of non-exposure after the two-year exposure period). Nikula covered this issue in a paper published in 2000,<sup>74</sup> where the author observed in the discussion of strain differences that some caution is needed when comparing some of the studies' data with the data from other studies, given that the study durations differed (25.5 months versus 30 months). With a potential for a significant increase in lung tumor incidences during the final six months of a 30-month study, care is needed in interpreting different tumor incidences among studies when the termination times of those studies differ significantly.

ACC-75 Ch. 3

Figure 3-3, as well as Figure 3-4, specifically the lung tumor-proportion data reflected in those figures, also should be modified to reflect new data published by Warheit and Frame.<sup>75</sup>

V. NIOSH SHOULD REVIEW ALL OF THE SCIENTIFIC DATA RELEVANT TO THE HUMAN HEALTH EFFECTS OF COAL MINE DUST, INCLUDING EPIDEMIOLOGY STUDIES

ACC-76  
Overall

In the draft CIB, NIOSH cites at least 12 separate references based on human or animal exposure to coal mine dust to provide "additional support for the determination that the rat is a reasonable animal model with which to predict human tumor response for other particles,

<sup>74</sup> See Nikula KJ (2000). Rat lung tumors induced by exposure to selected poorly soluble nonfibrous particles. *Inhal. Toxicol* 12:97-119.

<sup>75</sup> See *supra*, footnote 52.

such as TiO<sub>2</sub>.<sup>76</sup> The primary examples of the use of studies of coal mine dust effects include the following:

ACC-76 cont'.  
(Overall)

■ **Lung Overload (lines 1008-1012):** "In addition, lung clearance of particles is slower in humans than in rats, by approximately an order of magnitude, and some humans (e.g., coal miners) may be exposed to concentrations resulting in doses that would be considered overloaded in rats. Thus, the doses that cause overloading in the rat may be relevant to estimating disease risk in workers with high dust exposures."<sup>77</sup>

■ **Role of Chronic Inflammation in Lung Disease (lines 1103-1108):** "In humans, chronic inflammation has been associated with non-neoplastic lung diseases in workers with dusty jobs. Rom [1991] found a statistically significant increase in the percentage of PMNs in BALF of workers with respiratory impairment who had been exposed to asbestos, coal, or silica (4.5% PMN in cases versus 1.5% PMNs in controls). Elevated levels of PMNs have been observed in the BALF of miners with simple coal workers' pneumoconiosis (31% of total BAL cells versus 3% in controls).  
...<sup>78</sup>

ACC-76 cont'.  
(Overall)

■ **Use of Coal Dust Data (Figure 3-4):** Relationship between Particle Surface Area Dose in the Lungs of Rats after Chronic Inhalation to Various Types of Poorly Soluble Low Toxicity (PSLT) Particles and Tumor Proportion.<sup>79</sup>

ACC-76 cont'.  
(Overall)

■ **Mechanistic Considerations (lines 1524-1539):** "The mechanism of action of TiO<sub>2</sub> is relevant to a consideration of the associated risks because, as discussed earlier, the weight of evidence suggests that the tumor response observed in rats exposed to fine and ultrafine TiO<sub>2</sub> results from a secondary genotoxic mechanism involving chronic inflammation and cell proliferation, rather than via genotoxicity of TiO<sub>2</sub> itself. This effect appears related to the physical form of the inhaled particle (i.e., particle surface area) rather than the chemical compound itself. In this

<sup>76</sup> Draft CIB at 94.

<sup>77</sup> *Id.* at 39 (citation omitted).

<sup>78</sup> *Id.* at 43 (citations omitted).

<sup>79</sup> *Id.* at 48.

way, TiO<sub>2</sub> behaves in a similar manner to other PSLT particles, such as barium sulfate, carbon black, toner, and coal dust.”<sup>80</sup>

ACC-76 cont.  
(Overall)

- **Basing the REL on Rat Tumor Data (lines 1922-1933):** “NIOSH has considered the evidence suggesting that rats may be an inappropriate model for human lung cancer after exposure to particulates and has concluded that the rat is a reasonable model for predicting human lung cancer risks. Although there is not extensive evidence that the overloading of lung clearance, as observed in rats . . ., occurs in humans, lung burdens consistent with overloading doses in rats have been observed in some humans with dusty jobs (e.g., coal miners).”<sup>81</sup>

ACC-76 cont.  
(Overall)

The Panel supports NIOSH’s use of the coal mine dust data in this manner. The Panel concurs that rats and humans respond similarly to all PSLT particles based on the surface area of the particles. Given the similarity of response to coal mine dust and TiO<sub>2</sub>, however, all of the scientific data relevant to the human health effects of coal mine dust, including the human epidemiology studies, are relevant as well. In Section 2 of the draft CIB, NIOSH critiques four TiO<sub>2</sub> occupational epidemiology studies but disregards the relevant studies of lung cancer among coal miners.

ACC-76 cont.  
(Overall)

In addition, NIOSH references one of its own publications in support of the use of international definitions for respirable dust.<sup>82</sup> That publication, NIOSH Publication No. 95-106 (*Criteria for a Recommended Standard: Occupational Exposure to Respirable Coal Mine Dust*), which is not referenced elsewhere in the draft CIB, contains the following discussion of the

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<sup>80</sup> *Id.* at 63.

<sup>81</sup> *Id.* at 93 (citation omitted).

<sup>82</sup> *Id.* at 4.

epidemiological evidence for lung cancer due to coal mine dust exposure that should be included in the final CIB:

ACC-76 cont.  
(Overall)

Most studies have reported that mortality from lung cancer is lower than expected among coal miners when compared with general population rates, although some studies have reported elevated lung cancer mortality among coal miners. Mortality from lung cancer was not associated with cumulative exposure to respirable coal mine dust in the two studies that evaluated this relationship. In a study of lung cancer by histologic type, Vallyathan et al. [1985] found little difference in the pathologic features of lung cancer in coal miners and in men from the general population who smoke cigarettes. Vallyathan et al. [1985] also found no relationship between lung cancer and years in coal mining.<sup>83</sup>

Publication 95-106 further states that "SMRs for lung cancer . . . have generally been lower than expected among coal miners."<sup>84</sup>

ACC-76 cont.  
(Overall)

An additional reference that should be included in the final CIB is the International Agency for Research on Cancer's (IARC) *Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 68: Silica*, which contains the following summary of the epidemiological evidence regarding coal mine dust and lung cancer:

There have been no epidemiological investigations on cancer risks in relation to coal dust *per se*. There is, however, a large body of published literature concerning cancer risks potentially associated with employment as a coal miner, including a small number of exposure-response associations with coal mine dust.

<sup>83</sup> NIOSH, *Criteria for a Recommended Standard: Occupational Exposure to Respirable Coal Mine Dust* (Sept. 1995), at 64 (citations omitted), available at <http://www.cdc.gov/niosh/95-106.html>.

<sup>84</sup> *Id.* (citations omitted).



ACC-76 cont'.  
(Overall)

...

The evidence from occupational cohort studies for an association between coal mine dust and lung cancer has not been consistent; some studies revealed excess risks, whereas others indicated cohort-wide lung cancer deficits. There is no consistent evidence supporting an exposure-response relation for lung cancer with any of the customary dose surrogates, including duration of exposure, cumulative exposure or radiographic evidence of pneumoconiosis.

...

ACC-76 cont'.  
(Overall)

...

There is *inadequate evidence* in humans for the carcinogenicity of coal dust.<sup>85</sup>

ACC-77  
(Overall)

In addition to epidemiologic studies of coal mine dust and lung cancer among coal miners, the Panel believes that epidemiologic studies among workers exposed to other PSLT particles also are relevant to TiO<sub>2</sub> risk assessment and should be included in the final CIB. The inclusion of relevant epidemiologic studies of workers exposed to all PSLT particles would significantly increase the statistical power of this line of evidence, which would increase the confidence that the REL for fine TiO<sub>2</sub> is safe for all workers.

<sup>85</sup>

IARC, *Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 68: Silica* (last updated May 20, 1997) at Section 5 (emphasis in original), available at <http://www-cie.iarc.fr/htdocs/monographs/vol68/coal.htm>.

VI. NIOSH SHOULD RELY UPON THRESHOLD MODELING APPROACHES IN ITS QUANTITATIVE RISK ASSESSMENT THAT ARE NOT DRIVEN BY TUMOR RESPONSES AT VERY HIGH DOSES AND NIOSH SHOULD NOT IGNORE EVIDENCE FROM MORE RELEVANT LEVELS OF EXPOSURE

A. The Quantitative Risk Assessment Is Erroneously Driven by Tumor Responses at Very High Doses and Should Instead Rely Upon Threshold Models and Bayesian Model Averaging (BMA)

ACC-78 Ch. 4

In the draft CIB, NIOSH states that the "plausible mechanism of action for TiO<sub>2</sub> in rats can be described as the accumulation of TiO<sub>2</sub> in the lungs, overloading of lung clearance mechanisms, followed by increased pulmonary inflammation and oxidative stress, cellular proliferation, and, at higher doses, tumorigenesis."<sup>86</sup> The draft CIB also states that these effects are better described by particle surface area than mass dose, that the observed inflammatory response is consistent with a threshold mechanism, and that the best-fitting dose-response curves for the tumorigenicity of TiO<sub>2</sub> are nonlinear.<sup>87</sup> Despite these conclusions, NIOSH derived the RELs using risk assessment methodology developed for use with a genotoxic carcinogen that has no threshold.<sup>88</sup> Threshold models are needed to reflect mechanism of action conclusions; linear extrapolation from the 1/10 benchmark dose (BMD) and linearized multistage approaches are not appropriate for this purpose in this case. The Panel thus provides the following specific comments on the limitations of NIOSH's tumor modeling approach for TiO<sub>2</sub>:

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<sup>86</sup> Draft CIB at 64.

<sup>87</sup> *Id.*

<sup>88</sup> *Id.* at 68.

ACC-79 Ch. 4

- The Panel urges NIOSH to consider applying a threshold modeling approach. The threshold seen and modeled for pulmonary inflammation is clearly apparent in the tumorigenicity data shown in Figure 3-4 of the draft CIB.<sup>89</sup> Peter Morfeld of the University of Cologne has successfully fitted a threshold model to the animal carcinogenicity data in Figure 3-4 using an approach similar to that described in Appendix B.<sup>90</sup> Morfeld's reanalysis of Fig 3-4 of the NIOSH TiO<sub>2</sub> document yielded a threshold at 0.32 m<sup>2</sup>/g (0.95-CI: 0.13, 1) analyzing the eight TiO<sub>2</sub> experiments only, and 0.18 m<sup>2</sup>/g (0.95-CI: 0.063, 0.32) when analyzing all 32 experiments (including carbon black, talc, etc.). The methodology used is described in Appendix B of the NIOSH document (the results are based on the likelihood profile). Morfeld applied no weights in this aggregated reanalysis. The thresholds are clearly significant and NIOSH missed this issue because it applied only non-threshold models. Morfeld's findings point at rather high thresholds for both fine and ultrafine TiO<sub>2</sub>, when transformed into mg/m<sup>3</sup> (cf. Tables 4.5 and 4.6 of the NIOSH paper). Morfeld also has applied the methodology to tumor prevalence data from another study of rats exposed to a range of low and high surface area dusts.<sup>91</sup> The application of a better fitting threshold model would not result in the same problems observed with NIOSH's current model, that is, a model that fits in the lower and upper ranges but not in the middle, where the points are below the curve.

ACC-80 Ch. 4

- Linear extrapolation from the 1/10 BMD is not an appropriate approach to rely upon in the draft CIB because the risk estimates are driven entirely by tumor response at high doses. The risk estimate and upper bound would be almost identical if just the high dose tumor responses had been used to perform the calculation.<sup>92</sup> Thus, linear extrapolation from the BMD effectively provides the same answers as the linear model would, which is the worst fitting model in Table 4-4 of NIOSH's analysis.

ACC-81 Ch. 4

- The linearized multistage model is also very sensitive to the high dose response (see Lovell and Thomas, 1996) and should not be relied upon by NIOSH. Using the upper confidence interval of the linear term (the linearized upper bound on risk) to obtain an upper bound on risk

<sup>89</sup> *Id.* at 48.

<sup>90</sup> Personal Communication with Dr. Peter Morfeld.

<sup>91</sup> Morfeld P, *et al.* (2006). Dose-response and threshold analysis of tumor prevalence after intratracheal instillation of six types of low- and high-surface-area dusts in a chronic rat experiment. *Inhal Toxicol* (in press; appended as Attachment 4).

<sup>92</sup> See Draft CIB at 86 (Fig. 4-4).

effectively ignores the data at the more relevant low doses. The best fitting multistage model is one that can be as close to a threshold model as possible (*i.e.*, a zero linear term and a zero quadratic term), and NIOSH must not ignore this fact and calculate the linearized upper bound on risk.

ACC-82 Ch. 4

- The Panel also urges NIOSH to consider nonlinear models such as the multistage, Gamma and Weibull model, that best model the low (and more relevant) dose behavior. In the case of the multistage model, the lower confidence limit for the 1 in 1,000 excess risk dose should be obtained directly from the model (*i.e.*, not using the upper confidence limit for the slope term as in the linearized multistage approach) as it is for the Weibull and Gamma models. A lower limit dose obtained from this approach for the multistage model is not supplied in Table 4-5 of the draft CIB,<sup>93</sup> but would be expected to be much closer to the dose from the Gamma (0.042 m<sup>2</sup>/g) and Weibull (0.036 m<sup>2</sup>/g) models than the linearized multistage estimate of 0.014 m<sup>2</sup>/g.

ACC-83 Ch. 4

- Although NIOSH notes positive aspects of the Bayesian model averaging (BMA) approach, the BMA is provided little weight in the draft CIB. Specifically, NIOSH correctly notes that "BMA provides an approach for summarizing the risk estimates from the various models, which differ in the low-dose region of interest for human health risk estimation."<sup>94</sup> NIOSH further states that BMA also "provides an approach for addressing the uncertainty in choice of model in the BMD approach."<sup>95</sup> The Panel urges NIOSH to factor in the estimates from the BMA approach more favorably in the CIB than they are currently presented. The Panel believes that BMA may be a useful approach to address uncertainties in model assumptions, but there must be appropriate prior weightings of models and the averaging must include threshold models.

ACC-84 Ch. 4

- NIOSH notes that their "rat-based risk estimates cannot be reasonably be dismissed from use in predicting the excess risk of lung cancer in humans exposed to TiO<sub>2</sub>" on the basis of comparing one set of rat-based MLE excess risk estimates for lung cancer to the 95 percent UCL of excess risk from the epidemiologic studies (Appendices E and F).<sup>96</sup> The Panel notes that the threshold model and the majority, if not all, of the modeling approaches used by NIOSH give MLE rat-based excess risk estimates for

<sup>93</sup> *Id.* at 76.

<sup>94</sup> *Id.* at 59.

<sup>95</sup> *Id.*

<sup>96</sup> *Id.* at 69.



ACC-84 cont'.  
(Ch. 4)

lung cancer that are lower than the 95 percent UCL of excess risk from the epidemiologic studies and also cannot be reasonably dismissed on that basis. In addition, NIOSH states that "If the sensitivity of the rat response to inhaled particulates differs from that of humans, then the excess risks derived from the rat data would be expected to differ from the excess risks estimated from the human studies."<sup>97</sup> That will not be the case, however, if one compares excess risk in the region of the dose response curves where neither species shows any evidence of effect, *i.e.*, in the region below the threshold.

ACC-84 cont'.  
(Ch. 4)

The following chart provides a summary of the most plausible risk estimates from rat tumor modeling for fine TiO<sub>2</sub> that should be addressed in the draft CIB. The extrapolation from m<sup>2</sup>/g rat lung to mg/m<sup>3</sup> is the same as used in the draft CIB:

	Best estimate mg/m <sup>3</sup>	Lower confidence limit mg/m <sup>3</sup>
Threshold (all dusts model) <sup>a</sup>	45 (25)	18 (9)
Bayesian Model Averaging	8.7 <sup>b</sup>	6.5 <sup>b</sup>
Nonlinear models <sup>c</sup> (1 in 1,000)	31 - 39	5 - 6

- a Source: Dr. Peter Morfeld. The results in this chart were presented by Dr. John Tomenson at NIOSH's February 27, 2006, public meeting in Cincinnati, Ohio, regarding the draft CIB.
- b Will increase if threshold models included, and given appropriate prior probability.
- c Multistage, Weibull and Gamma models.

<sup>97</sup> *Id.*

B. NIOSH Ignores Epidemiology Data from More Relevant Levels of Exposure in Its Quantitative Risk Assessment and Should Revise the CIB To Reflect These Data

ACC-85 Ch. 4

In Section 4.1.1 of the draft CIB, NIOSH states: "For quantitative risk assessment, dose-response data are needed, either from human studies or extrapolated to humans from animal studies. The epidemiologic studies on lung cancer have not shown a dose-response relationship in TiO<sub>2</sub> workers [Fryzek, *et al.* (2003); Boffetta, *et al.* (2004)]. However, dose-response data are available in rats, for both cancer (lung tumors) and early, noncancer (pulmonary inflammation) endpoints."<sup>98</sup> In Section 4.4 of the draft CIB, NIOSH further states that "the epidemiologic studies lacked the power to detect an excess risk of 1/1000."<sup>99</sup> While the Panel understands that the epidemiologic studies may not have sufficient power to detect a standardized mortality ratio (SMR) for lung cancer of 1.02 (equivalent to an excess risk of 1/1000 for lung cancer), this does not mean that a risk assessment based on an effect seen in rats at exposures equivalent to 150 mg/m<sup>3</sup> in humans is scientifically defensible. NIOSH should not favor rat data over human data simply because there is no evidence of dose response in the human studies. Instead, the Panel urges NIOSH to rely upon the human studies in its risk assessment as part of a weight of evidence process instead of only using the negative epidemiologic data to test a hypothesis derived from implausible animal models, a position which is scientifically indefensible.

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<sup>98</sup> *Id.* at 50.

<sup>99</sup> *Id.* at 65.

## VII. NIOSH'S PROPOSED RELs ARE NOT SCIENTIFICALLY DEFENSIBLE

ACC-86 Ch. 5

In Section 5 of the draft CIB, NIOSH sets forth proposed RELs of 1.5 mg/m<sup>3</sup> for fine TiO<sub>2</sub> and 0.1 mg/m<sup>3</sup> for ultrafine TiO<sub>2</sub> as time-weighted average concentrations for up to 10 hours a day during a 40-hour work week.<sup>100</sup> While the Panel, as explained in Section I of these comments, supports NIOSH's determination that there is insufficient evidence to designate TiO<sub>2</sub> as a "potential occupational carcinogen," the Panel has identified several flaws in NIOSH's analysis that has resulted in unacceptably low proposed RELs. These errors discussed in detail above -- particularly NIOSH's arbitrary selection of risk assessment models -- contribute to proposed RELs that are not scientifically defensible. The Panel thus urges NIOSH to incorporate the Panel's comments discussed above, reevaluate the studies relevant to TiO<sub>2</sub> use threshold modelling in its quantitative risk assessment, and propose scientifically defensible RELs.

## VIII. NIOSH HAS FAILED TO PROVIDE INDUSTRY WITH A CONFIRMED METHOD(S) FOR THE ANALYSIS OF TiO<sub>2</sub> IN THE WORKPLACE SUFFICIENT TO SUPPORT THE PROPOSED RELS

ACC-87 Ch. 6

Under the provisions of the 1970 Occupational Safety and Health Act of 1970 (Public Law 91-596), NIOSH must provide suitable procedures for the analysis of workplace standards. As further discussed in NIOSH Publication No. 95-117, any proposed method must meet certain standards of accuracy and reliability.<sup>101</sup> In this regard, NIOSH has developed

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<sup>100</sup> *Id.* at 94.

<sup>101</sup> Kennedy, E.R.; Fischbach, T.J.; Song, R; Eller, P.M.; Shulman, S.A.: "Guidelines for Air Sampling and Analytical Method Development and Evaluation" DHHS(NIOSH) Publication No. 95-117 (1995).

standard procedures for such method validations. In the draft CIB, there is not a suitable method or methods, which has undergone validation testing, and which is suitable to support the proposed exposure limits. NIOSH recognizes the need for an analysis method based on particle surface area, but admits such a method is not available. Certain interim methods and sampling strategies are proposed but NIOSH provides no documentation as to the accuracy, reproducibility, or reliability of such methods as applied to  $\text{TiO}_2$ . In addition, the Panel feels that the proposed scheme for characterizing workplace exposures to  $\text{TiO}_2$  is confusing and possibly unworkable, especially for certain smaller producers. Until a suitable and confirmed method is available for the analysis of  $\text{TiO}_2$  in the workplace, the Panel urges NIOSH to remove recommendations for workplace exposure analyses.

#### CONCLUSION

The Panel appreciates this opportunity to provide its comments, and urges NIOSH to revise the draft CIB to reflect the changes and issues noted herein.

Attachments



**Comments on the draft NIOSH CURRENT  
INTELLIGENCE BULLETIN:  
Evaluation of Health Hazard and Recommendations  
for Occupational Exposure to Titanium Dioxide**

John Tomenson PhD, Dip Stat Cantab, BSc  
Consultant Epidemiologist/Biostatistician  
Causation Ltd, UK

Representing the Titanium Dioxide Panel of the American  
Chemistry Council

## Aim of presentation

- To draw attention to the strengths of all 3 cohort studies (the CIB evaluation focuses too much on “*methodologic and epidemiologic limitations*”)
- To draw attention to the limitations of the quantitative risk assessment which is driven by tumor responses at very high doses and ignores the evidence from more relevant levels of exposure

# Evaluation of Human Studies

## 1. Boffetta et al (2004)

- Study covers 2/3 of the total 22,000 subjects, but no methodological limitations are listed.
- CIB Summary states "*Nonmalignant respiratory disease was not increased significantly (i.e.,  $p < 0.05$ ) in any of the studies*".

In fact, deficits of nonmalignant respiratory disease in all 3 studies including the 202 obs versus 228 exp male deaths in this study.

- CIB comments about lack of power of studies to detect possible TiO<sub>2</sub> pneumoconiosis deaths and lack of reporting of such deaths (line 719) but only mentions the two US studies.

The Boffetta study had much greater power, and is certain to have commented on an unusual pattern of pneumoconiosis deaths given the evident interest in a possible association between TiO<sub>2</sub> exposure pleural plaques and thickening (see discussion of pleural cancer by Boffetta et al).

## **Evaluation of Human Studies**

### **1. Boffetta et al (2004) Low Power?**

Lines 3141-50 argue that a significant dose-response relationship for TiO<sub>2</sub> exposed and lung cancer would not be expected to be observed in the European study because the upper confidence limit on excess risk at the median cumulative exposure is estimated to be quite low.



# Power of Boffetta study

- Cumulative exposure in the highest quartile group is much more relevant (mid point estimated to be 56.5 and 78.1 mg/m<sup>3</sup> years i.e. 29 and 39 times higher than the median cumulative exposure value)
- 56.5 and 78.1 mg/m<sup>3</sup> years equate to average lifetime exposures of 1.26 and 1.74 mg/m<sup>3</sup> and Table E-2 indicates that the upper confidence limits on excess risk at these concentrations correspond to relative risks of 1.5 (using the appropriate model).
- The CIB correctly states that Boffetta et al. (2004) does not provide information on study power, but the full report of the European study (Boffetta et al, 2003) does discuss the power of the study and states that "*in the internal analysis, the power of the study to detect (at  $\alpha$  level of 0.05) a relative risk of 1.7 in the highest versus the lowest quartile of cumulative exposure was 90% ... and 1.5 was 74%*".

**Hence there was reasonable power to detect a dose response**

## Evaluation of Human Studies

### 2. Fryzek et al (2003)

- The CIB states that “*company records from the early period were destroyed or lost for the companies*”. Fryzek states “it is possible that some company records from the early periods in the plants may have been destroyed or lost. Although we found no evidence to support such an assumption ...”

## Evaluation of Human Studies

### 2. Fryzek et al (2003) cont

- The CIB states “*the RRs may have been artificially low*” and “*questionable modeling methods [Beaumont et al. 2004]*”. However, comments by Beaumont related only to analyses in one table and Fryzek clearly shows that the effect of the possible bias raised by Beaumont is negligible.
- It is unclear why the CIB draws attention to a non significant hazard ratio of 1.3 in the medium cumulative exposure group but doesn't mention the hazard ratio of 0.7 in the high cumulative exposure group.

## Evaluation of Human Studies

### 3. Chen and Fayerweather (1988)

- The CIB states that serious limitations of the study by Fayerweather and Chen (1988) precluded any conclusions (line 567).

Many of the limitations listed (e.g. possible confounding by asbestos) are less relevant to the mortality component of the study and do **not** invalidate the lung cancer findings (SMR = 0.52).

- For example, the CIB states that the “study reported the number of observed deaths for the period 1935–1983; the source for deaths prior to 1957 is not clear”.  
The investigators clearly state that they used the SSA and NDI to obtain vital status information not available in the DuPont registry and there is no evidence of under ascertainment of lung cancer deaths.



## **Conclusions from epidemiologic studies**

- No evidence of exposure effect in over 20,000 workers exposed since 1930s in US and Europe
- No evidence of effect in highest cumulative exposure group of the 2 large multi company studies
  - a) In European study, equivalent mean lifetime exposures ranged from 0.3 – 3.2 mg/m<sup>3</sup> fine TiO<sub>2</sub> in highest exposure group
  - b) Range not known for US multi company study, but probably similar to European. Highest exposed group had mean exposure of 6.2 mg/m<sup>3</sup> total dust over last half of study period
- Studies not informative about ultrafine

## **Quantitative Risk Assessment**

### **Key mechanistic conclusions (section 4.3)**

- NIOSH has determined that a plausible mechanism of action for TiO<sub>2</sub> in rats can be described as the accumulation of TiO<sub>2</sub> in the lungs, overloading of lung clearance mechanisms, followed by increased pulmonary inflammation and oxidative stress, cellular proliferation, and, at higher doses, tumorigenesis
- These effects are better described by particle surface area than mass dose
- The observed inflammatory response is consistent with a threshold mechanism
- The weight of evidence suggests that the tumor response observed in rats exposed to fine and ultrafine TiO<sub>2</sub> results from a secondary genotoxic mechanism involving chronic inflammation and cell proliferation, rather than via genotoxicity of TiO<sub>2</sub> itself.

## **Lung tumor modeling approaches used to generate risk estimates**

- Benchmark dose (BMD) modeling with linear extrapolation (1/10 dose divided by 100)
- Linearized multi-stage modeling

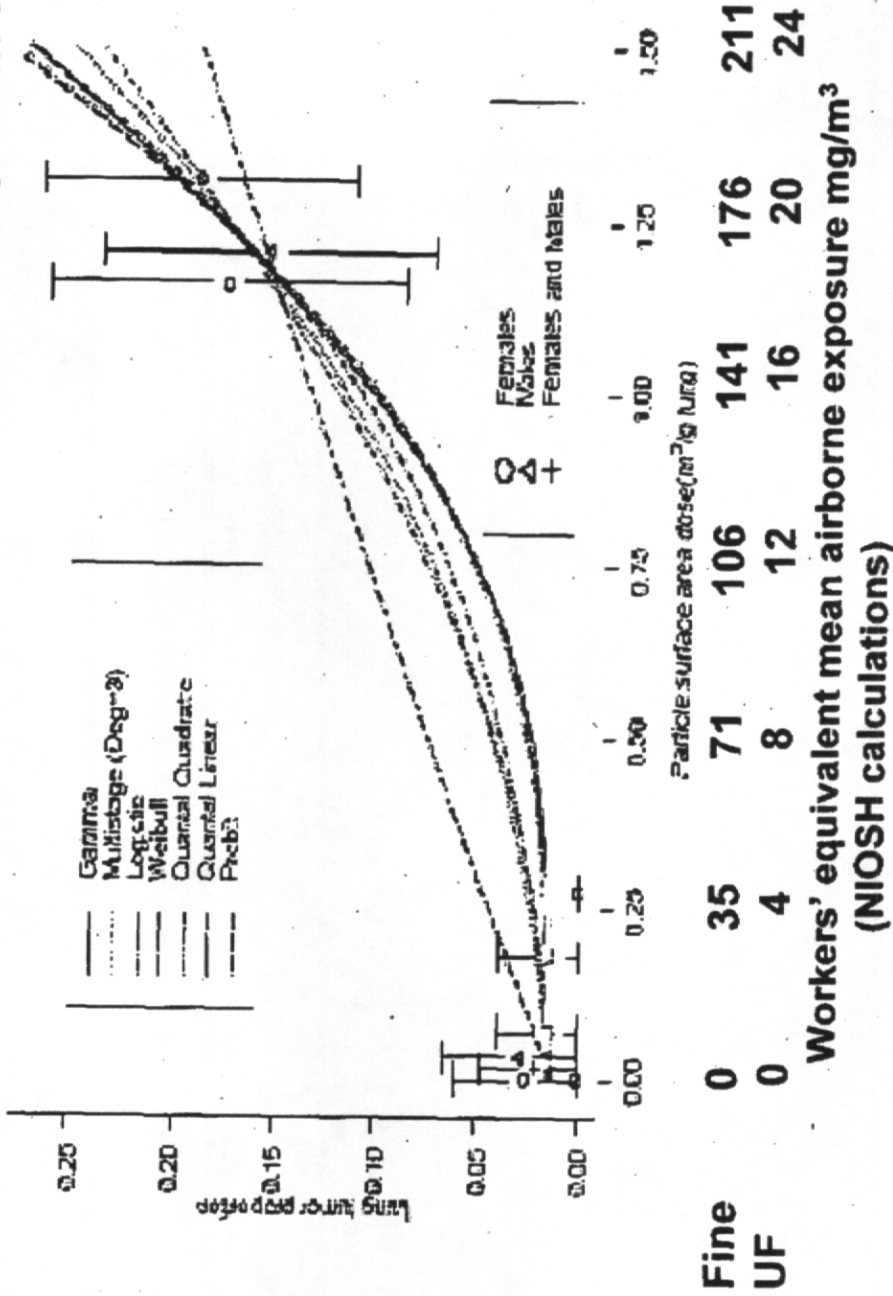
## **Usual approach for a genotoxic carcinogen with no threshold - why use for TiO<sub>2</sub>?**

- Bayesian model averaging (BMA) of all model estimates

**Potentially better approach, but results ignored**

# Why does the rat model lead to RELs of 1.5 mg/m<sup>3</sup> fine and 0.1 mg/m<sup>3</sup> UF?

Fig 4-4 with equivalent mean worker exposure



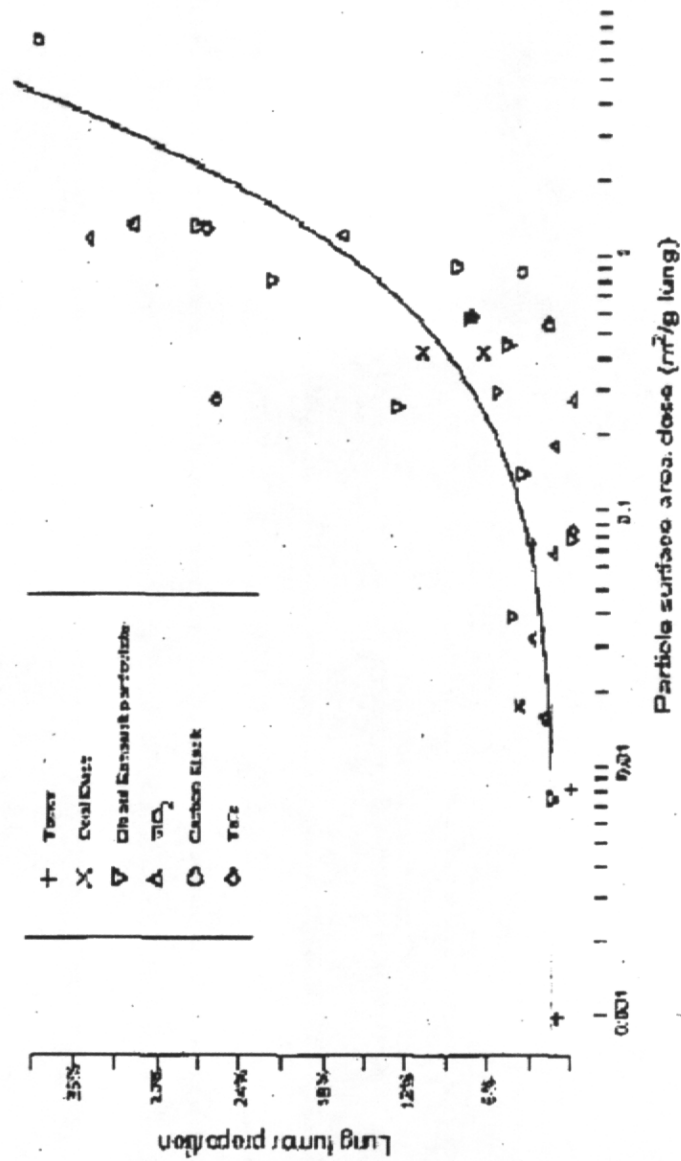


# **Limitations of tumor modeling approach**

## **1. No Threshold**

- The mechanistic conclusions suggest that NIOSH should have used a threshold modeling approach
- NIOSH notes that the best-fitting dose-response curves for the tumorigenicity of TiO<sub>2</sub> are nonlinear (e.g., multistage model is cubic with no linear term), but the threshold seen and modeled for pulmonary inflammation is also clearly apparent in the tumorigenicity data shown in Fig 3-4
- Morfeld (personal communication) has successfully fitted a threshold model to the data in Fig 3-4

Fig 3-4 Relationship between particle surface area dose and tumor proportion in rats for various PSLT dusts



### Threshold model

All dusts      Threshold estimate = 0.18 m<sup>2</sup>/g (95% CI 0.063 – 0.32)  
 TiO<sub>2</sub>          Threshold estimate = 0.32 m<sup>2</sup>/g (95% CI 0.13 – 1.00)

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## **Threshold modeling approach of Morfeld**

“The methodology used is described in Appendix B of the NIOSH document (the results are based on the likelihood profile). No weights were applied in this aggregated re-analysis. The thresholds are clearly significant.” (Peter Morfeld, University of Cologne)

See also Morfeld et al. (2006) Dose-response and threshold analysis of tumor prevalence after intratracheal instillation of six types of low- and high-surface-area dusts in a chronic rat experiment. *Inhalation Toxicology* (in press)

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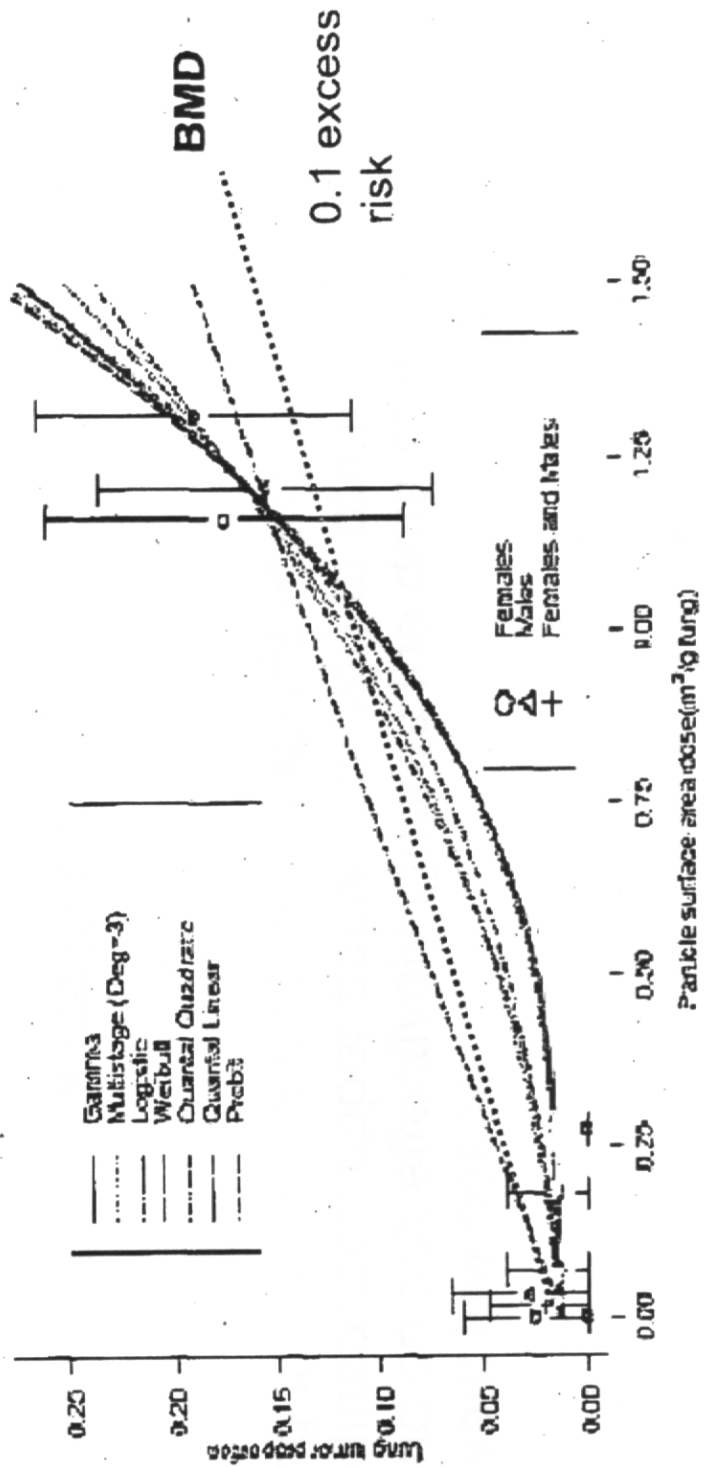
## **Comments on tumor modeling approaches**

### **2. Benchmark dose (BMD)**

- Essentially model (and science) free
- Risk estimate and upper bound would be almost identical if just the high dose tumor responses had been used to perform the calculation
- BMD effectively gives the same answer as the quantal linear model – easily the worst fitting model



# BMD driven entirely by tumor response at high doses



Fine 0 35 71 106 141 176 211  
Workers' equivalent mean airborne exposure mg/m<sup>3</sup>  
(NIOSH calculations)

## Limitations of tumor modeling approaches

### 5. Bayesian model averaging (BMA)

- The CIB correctly notes that *“BMA provides an approach for summarizing the risk estimates from the various models, which differ in the low-dose region of interest for human health risk estimation. BMA also provides an approach for addressing the uncertainty in choice of model in the BMD approach.”*
- Nevertheless, the BMA is given little weight by the CIB.
- However, it is surprising that the 3 best fitting models have easily the lowest posterior probabilities - what prior probabilities were used?

## Summary of most plausible risk estimates from rat tumor modeling for fine TiO<sub>2</sub>

	Best estimate mg/m <sup>3</sup>	Lower conf limit mg/m <sup>3</sup>
Threshold (all dusts model)	45 (25)	18 (2 mg/m <sup>3</sup> UF) (9)
BMA (1 in 1000)	8.7 <sup>a</sup>	6.5 <sup>a</sup>
Nonlinear <sup>b</sup> (1 in 1000)	31 - 39	5 - 6

<sup>a</sup> Will increase if threshold models included, and given appropriate prior probability

<sup>b</sup> Multistage, Weibull and Gamma models

## Limitations of Quantitative Risk Assessment approach

### – use of epidemiology data

- In section 4.4. NIOSH states that “the epidemiologic studies lacked the power to detect an excess risk of 1/1000”.  
They do not have sufficient power to detect an SMR for lung cancer of 1.02, but does an effect seen in rats at exposures equivalent to 150 mg/m<sup>3</sup> in human indicate power?
- The CIB states that “*For quantitative risk assessment, dose-response data are needed, either from human studies or extrapolated to humans from animal studies. The epidemiologic studies on lung cancer have not shown a dose-response relationship in TiO<sub>2</sub> workers [Fryzek et al. 2003; Boffetta et al. 2004]. However, dose-response data are available in rats ...*”

It seems odd to favor the rat data over human because there is no evidence of dose response in the human studies



## **Limitations of Quantitative Risk Assessment approach – use of epidemiology data cont.**

- The main use made of the negative epidemiologic data is to test an hypothesis derived from implausible animal models
- However, a finding of no difference in excess risks from the rat and human model at 1.5 mg/m<sup>3</sup> cannot be interpreted as meaning that the rat has the same sensitivity as man (and that predictions can be made using the rat model – see lines 3044-9).
- In fact, no evidence of an exposure effect in either species at that level.

## Overall conclusions

- No evidence of an exposure effect in over 20,000 workers exposed since the 1930s in US and Europe
- Strong evidence from human and animal studies of no effect at low levels of exposure, but human data provides limited information about ultrafine
- Strong evidence that rat is far more sensitive than mice, hamsters and primates
- Threshold models are needed to reflect mechanism of action conclusions (BMD and linearized multistage are not appropriate)
- BMA may be a useful approach to deal with uncertainty in model assumptions but must have sensible prior weightings and include threshold models

**Rat threshold model indicates that the lower limit for the critical dose of ultrafine may be as high as 2 mg/m<sup>3</sup>. Hence, REL of 1.5 mg/m<sup>3</sup> would be protective for fine and ultrafine exposures.**

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**NIOSH Public Comment Meeting**  
**February 27, 2006**

**John P. Gibbs, M.D.**  
**Representing the ACC TiO<sub>2</sub> Panel**

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# How Many Workers are Exposed to Throughout the Respiratory Route to TiO<sub>2</sub> in the Workplace?



**Nov 22 DRAFT NIOSH CURRENT INTELLIGENCE BULLETIN:  
Evaluation of Health Hazard and Recommendations for  
Occupational Exposure to Titanium Dioxide**

“The National Occupational Exposure Survey (NOES), conducted from 1981—1983, estimated that **2.7 million workers** (2.2 million male, 0.5 million female) are potentially exposed to TiO<sub>2</sub> (CAS Number 13463-67-7) in 42 standard industrial classifications (SICs) and 246 occupational groups [NIOSH 1983].”

**Nov 22 DRAFT NIOSH CURRENT INTELLIGENCE BULLETIN:  
Evaluation of Health Hazard and Recommendations for  
Occupational Exposure to Titanium Dioxide**

'The survey observed the use of a "specific agent" or tradename product known to contain the specific agent"

Included:

108,654 exposed to textile mill products

165,824 exposed to electric and electronic equipment

192,970 exposed to machinery except electrical

80,854 exposed to electric, gas and sanitary services

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The manufacturing steps which generate dust occur at the beginning and toward the end of the processes. The remaining operations take place in closed systems or in the liquid phase.

Industry estimates place the number of pigment plant workers routinely (once per day) exposed to TiO<sub>2</sub> dust at about 2,700 individuals, worldwide.

No reliable estimates of the number of individuals involved in compounding of downstream products is available. However, exposure levels in this step are expected to be at or below those encountered in TiO<sub>2</sub> production operations.

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The first step in all downstream uses (paints, coatings, plastics, rubber, ink, foodstuffs, etc) is incorporation into an organic or inorganic matrix.

From this point forward to the end-user, and beyond, titanium dioxide is enclosed within this matrix and there is virtually no exposure to TiO<sub>2</sub> dusts –to workers, consumers or the environment.

The universe of exposed individuals is limited to workers in the “white” end of TiO<sub>2</sub> plants plus those workers involved in the initial compounding of downstream products.



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## Conclusion

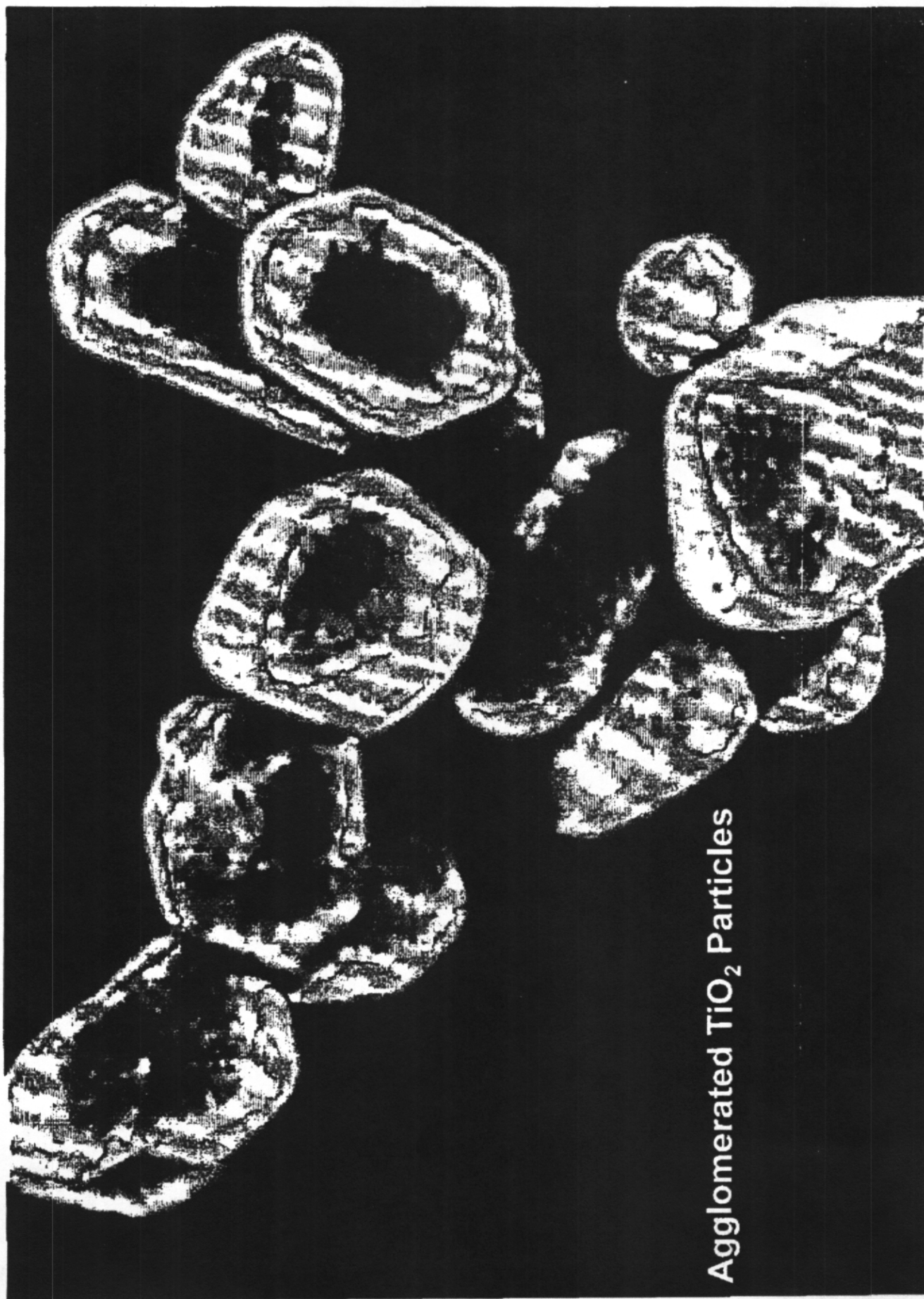
The 1981-83 National Occupational Exposure Survey Grossly Overestimates the Number of Workers in the U.S. with Respiratory Exposure to TiO<sub>2</sub>!

**Nov 22 DRAFT NIOSH CURRENT INTELLIGENCE BULLETIN:**  
**Evaluation of Health Hazard and Recommendations for**  
**Occupational Exposure to Titanium Dioxide**

*“Data are particularly needed on the airborne particle size distributions and exposures to ultrafines in specific operations or tasks.”*

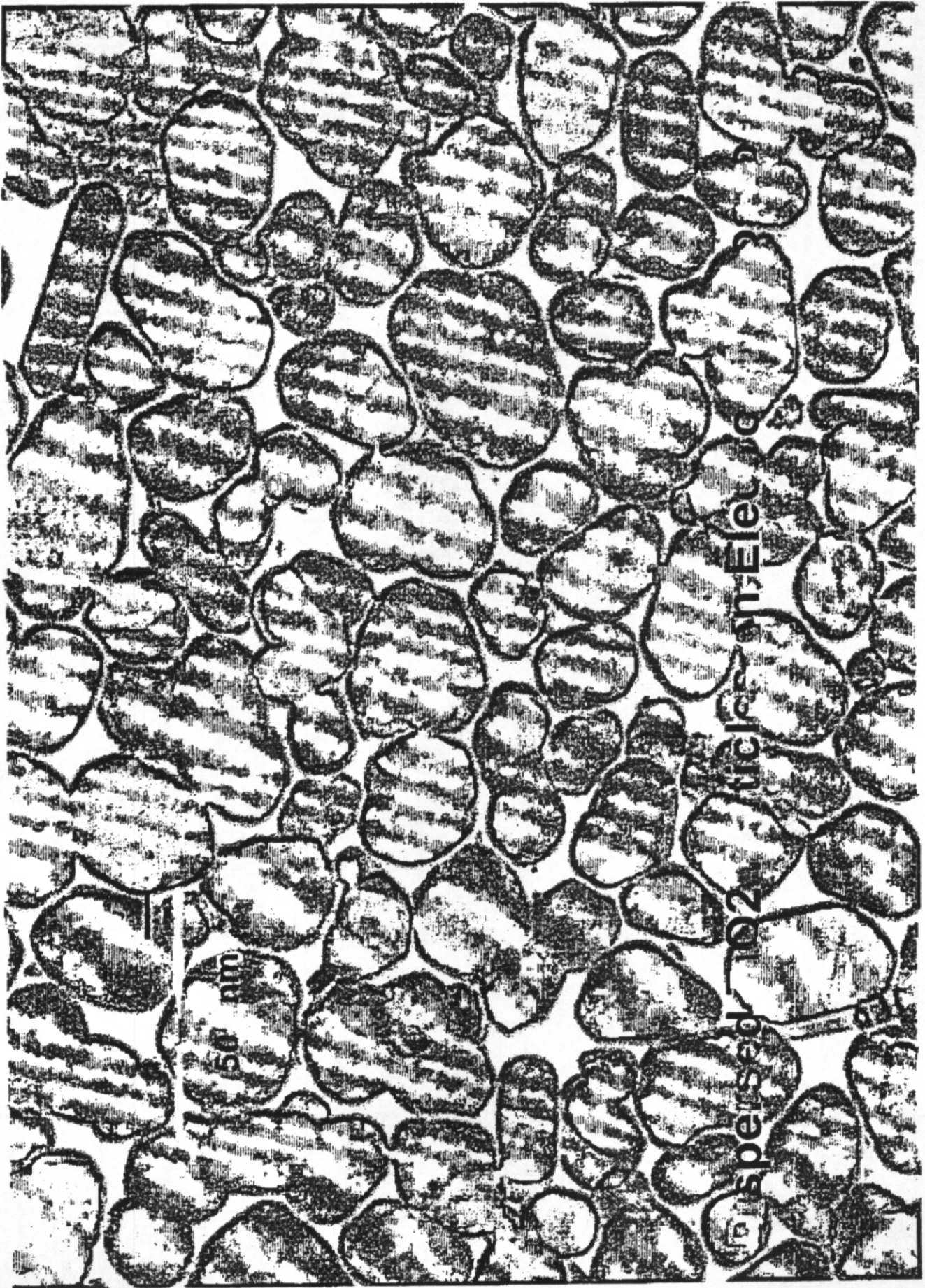
*‘No data have been published on occupational exposures to ultrafine TiO<sub>2</sub>.’*

*Limitations of the Fryzek study include “no information about ultrafine exposures”*

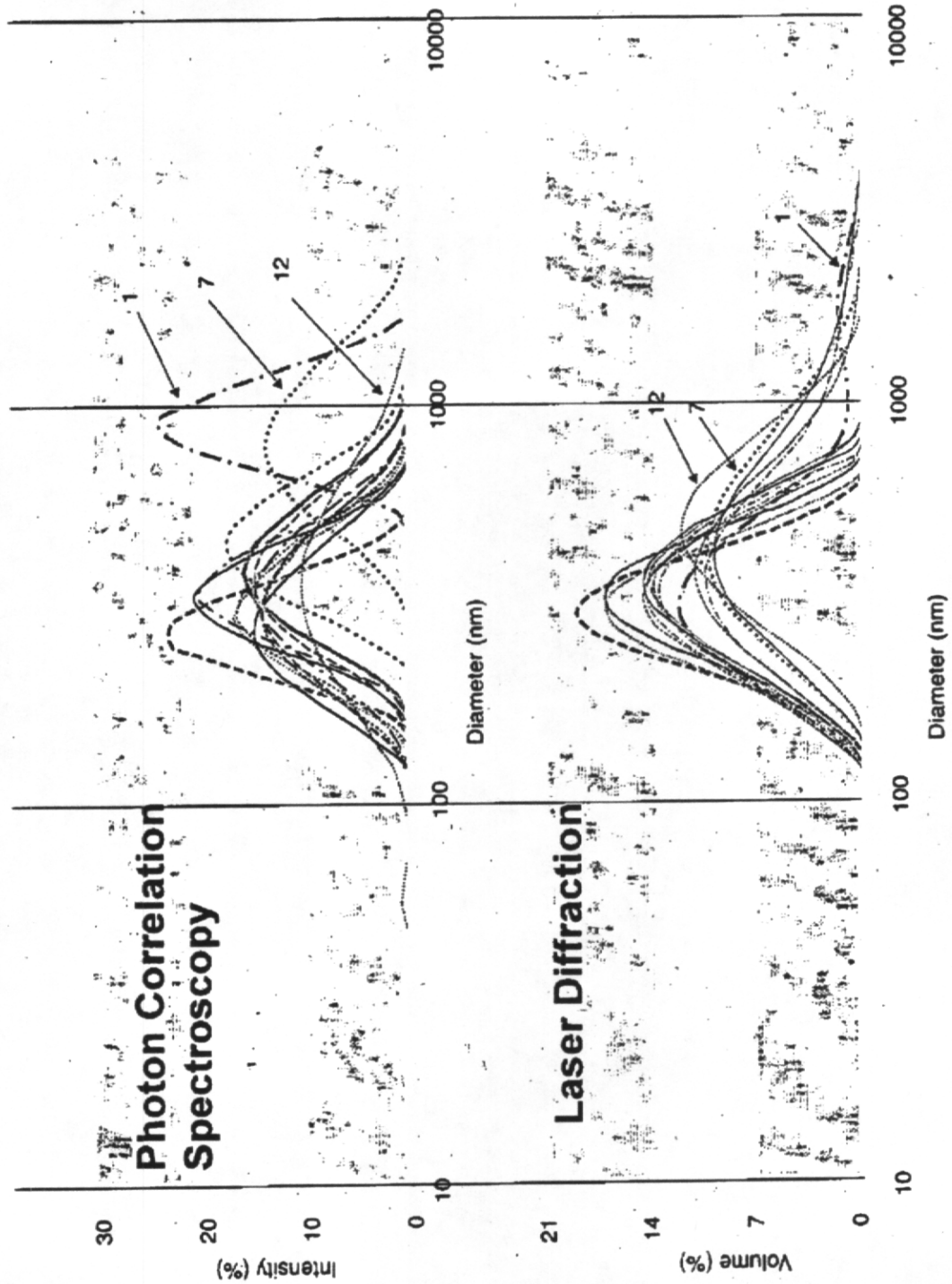


Agglomerated  $\text{TiO}_2$  Particles









Comparison of Primary Particle Size Distributions as Analyzed PCS and by Laser Diffraction

# Other Considerations

- Practical lower limit of particle size reduction with pigmentary size TiO<sub>2</sub> by fluid energy grinding is ~0.1 micron -- *physics*
- Energy requirements increase in proportion to the total surface area of the particles – *economics*
- Particles < 0.1 micron do not reflect visible light – *not effective as pigment*
- Ultrafine TiO<sub>2</sub> represents < 0.1% of the world wide TiO<sub>2</sub> Market

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## Conclusion

Significant ultrafine TiO<sub>2</sub> exposure is not likely to be present during the manufacturing of pigment grade (fine) TiO<sub>2</sub> using conventional technology!

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# Are Coal Dust and Other PSLT Particulate Exposures Relevant?



**Nov 22 DRAFT NIOSH CURRENT INTELLIGENCE BULLETIN:**  
**Evaluation of Health Hazard and Recommendations for**  
**Occupational Exposure to Titanium Dioxide**

NIOSH cites at least 12 separate references based on human or animal exposure to **coal dust** in the draft CIB in order to provide "*additional support for the determination that the rat is a reasonable animal model with which to predict human tumor response for other particles, such as TiO<sub>2</sub>.*"

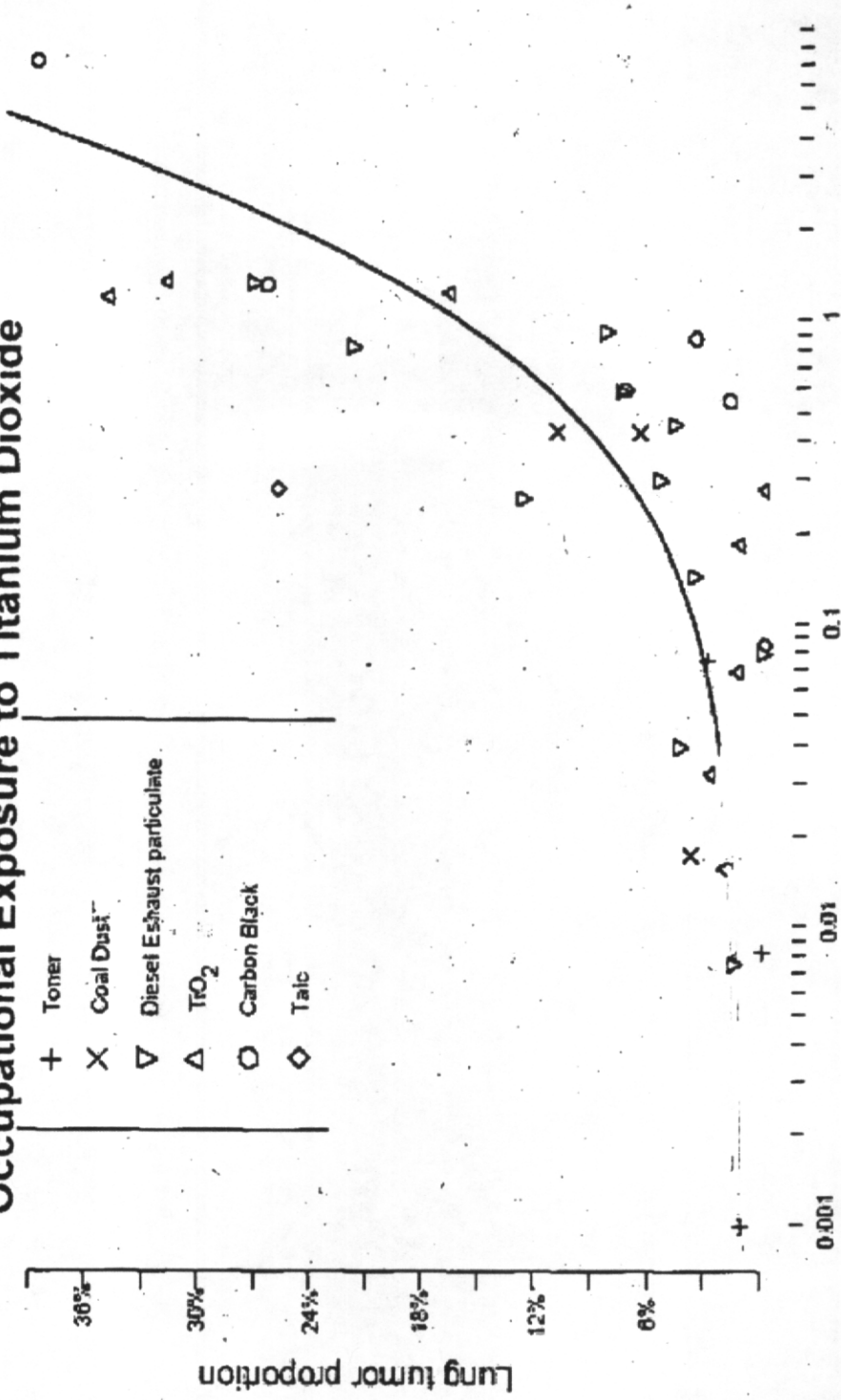
**Nov 22 DRAFT NIOSH CURRENT INTELLIGENCE BULLETIN:  
Evaluation of Health Hazard and Recommendations for  
Occupational Exposure to Titanium Dioxide**

*"In addition, lung clearance of particles is slower in humans than in rats, by approximately an order of magnitude..., and some humans (e.g., coal miners) may be exposed to concentrations resulting in doses that would be considered overloaded in rats. Thus, the doses that cause overloading in the rat may be relevant to estimating disease risk in workers with high dust exposures." (1008 - 1012)*

**Nov 22 DRAFT NIOSH CURRENT INTELLIGENCE BULLETIN:  
Evaluation of Health Hazard and Recommendations for  
Occupational Exposure to Titanium Dioxide**

*"In humans, chronic inflammation has been associated with non-neoplastic lung diseases in workers with dusty jobs. Rom [1991] found a statistically significant increase in the percentage of PMNs in BALF of workers with respiratory impairment who had been exposed to asbestos, coal, or silica (4.5% PMN in cases versus 1.5% PMNs in controls). Elevated levels of PMNs have been observed in the BALF of miners with simple coal workers' pneumoconiosis (31% of total BAL cells versus 3% in controls) ]..." (1103-1108)*

**Nov 22 DRAFT NIOSH CURRENT INTELLIGENCE BULLETIN:  
 Evaluation of Health Hazard and Recommendations for  
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**Figure 3-4**  
 Particle surface area dose (m<sup>2</sup>/g lung)



**Nov 22 DRAFT NIOSH CURRENT INTELLIGENCE BULLETIN:  
Evaluation of Health Hazard and Recommendations for  
Occupational Exposure to Titanium Dioxide**

*“The mechanism of action of TiO<sub>2</sub> is relevant to a consideration of the associated risks because, as discussed earlier, the weight of evidence suggests that the tumor response observed in rats exposed to fine and ultrafine TiO<sub>2</sub> results from a secondary genotoxic mechanism involving chronic inflammation and cell proliferation, rather than via genotoxicity of TiO<sub>2</sub> itself. This effect appears related to the physical form of the inhaled particle (i.e., particle surface area) rather than the chemical compound itself. In this way, TiO<sub>2</sub> behaves in a similar manner to other PSLT particles, such as barium sulfate, carbon black, toner, and coal...” (1523- 1539)*

**Nov 22 DRAFT NIOSH CURRENT INTELLIGENCE BULLETIN:  
Evaluation of Health Hazard and Recommendations for  
Occupational Exposure to Titanium Dioxide**

*“NIOSH has considered the evidence suggesting that rats may be an inappropriate model for human lung cancer after exposure to particulates and has concluded that the rat is a reasonable model for predicting human lung cancer risks. Although there is not extensive evidence that the overloading of lung clearance, as observed in rats..., occurs in humans, lung burdens consistent with overloading doses in rats have been observed in some humans with dusty jobs (e.g., coal miners)..” (1922-1933)*



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**Criteria for a Recommended Standard: Occupational  
Exposure to Respirable Coal Mine Dust**

*“Most studies have reported that mortality from lung cancer is lower than expected among coal miners when compared with general population rates ... although some studies have reported elevated lung cancer mortality among coal miners... Mortality from lung cancer was not associated with cumulative exposure to respirable coal mine dust in the two studies that evaluated this relationship... SMR’s for lung cancer ... have generally been lower than expected among coal miners.”*



## IARC MONOGRAPH VOL 68

*“There is ... a large body of published literature concerning cancer risks potentially associated with employment as a coal miner, including a small number of exposure-response associations with coal mine dust...”*

*The evidence from occupational cohort studies for an association between coal mine dust and lung cancer has not been consistent; some studies revealed excess risks, whereas others indicated cohort-wide lung cancer deficits.*

*There is no consistent evidence supporting an exposure-response relation for lung cancer with any of the customary dose surrogates, including duration of exposure, cumulative exposure or radiographic evidence of pneumoconiosis...”*

## Recommendation

In addition to epidemiological studies of coal mine dust and lung cancer among miners, epidemiological studies among workers exposed to other PSLT particles are also relevant to TiO<sub>2</sub> risk assessment and should be included.

The inclusion of relevant epidemiological studies of workers exposed to all PSLT particles would significantly increase the statistical power of this line of evidence.

This would increase the confidence that the REL for fine TiO<sub>2</sub> is safe for all workers and may even provide confidence in a higher REL.

**Comments on the draft NIOSH  
Current Intelligence Bulletin:  
Evaluation of Health Hazard and  
Recommendations for Occupational  
Exposure to Titanium Dioxide**



David B. Warheit, Ph.D., DABT, FATS  
DuPont Haskell Laboratory  
Representing the ACC TiO<sub>2</sub> Panel  
NIOSH Taft Auditorium-Cincinnati  
February 27, 2006

# General Conclusions I

- General document and pertinent literature review is for the most part, comprehensive
- However, many of the summaries are either misrepresented or the results misinterpreted.
- The authors ignore the critically relevant studies by Nikula et al., (1997, 2001) which demonstrate the fundamental differences in lung responses to low solubility dusts when comparing pulmonary responses of rats to humans and nonhuman primates.



## General Conclusions II

- The authors draw the erroneous conclusion that since humans have slow dust clearance response, leading to particle overload, the human response might be similar to the rat response, possibly leading to lung tumors.
  - At least 2 fundamental weaknesses to this argument:
    - 1) the epidemiology data is negative for lung cancer;
    - 2) the lung response of humans is different from rats – both in clearance kinetics, and with regard to inflammatory and pathological responses.
- Thus, the basis for conducting the risk assessment models is flawed.

## General Conclusions III

- The authors put forth a weak and nonrelevant model suggesting that the human lung could respond to overload concentrations by citing the effects of humans to inhaled silica and asbestos. It is well known that the pulmonary responses to asbestos and silica differ from the responses to poorly soluble particulates (including TiO<sub>2</sub> particles) – with no known epidemiological relationship to lung cancer and no known evidence, from human lung pathology studies that, in the absence of smoking, exposure to poorly soluble particulates like coal dust or TiO<sub>2</sub> lead to lung cancer in humans.

## **General Conclusions IV**

- Rats are uniquely sensitive to developing lung responses to poorly soluble particulates at particle overload concentrations. This response does not occur in ANY other species.

# General Conclusions V

- Current Mode of Action Scenario for Development of Lung Tumors in Rats exposed to Overload concentrations of PSPs
  - In rats → chronic exposure to  $\text{TiO}_2$  → Particle Overload → sustained inflammation → epithelial cell proliferation, septal fibrosis and fibroproliferative effects → metaplasia → mutations → lung tumors
- In humans → chronic exposure to PSP → Particle Overload → low degree of inflammation → little or no Fibrosis → no Mutations → No lung tumors



## General Conclusions VI

Poor Justification for the suggested RELs for pigment grade (1.5 mg/m<sup>3</sup>) or ultrafine TiO<sub>2</sub> particles (0.1 mg/m<sup>3</sup>) (John Tomenson)

- Throughout the CIB document, the authors fail to adequately characterize the crystal structures and particle sizes (physical characteristics) used by the investigators in the various studies.
- This is important because the document assumes that all of the ultrafine TiO<sub>2</sub> particles are similar or identical to the ultrafine P25 TiO<sub>2</sub> particles used in the Heinrich and Bermudez studies. In fact, not all ultrafine TiO<sub>2</sub> particles have the same crystal structure or particle size as P25 (80% anatase: 20% rutile)

## General Conclusions VII

- Particle overload/surface area issues in Rat lung inflammatory/tumor responses are unique to that species and are not relevant for Humans.
- The Epidemiological evidence in humans exposed to TiO<sub>2</sub> particles is negative. In addition, there is no histopathological evidence that exposure to PSPs including TiO<sub>2</sub> produce lung tumors in humans.
- Ultrafine TiO<sub>2</sub> particles are comprised of different crystal structures (anatase or rutile) and different particle sizes and the suggestion that P25 is representative for all ultrafine TiO<sub>2</sub> particle-types is flawed.

## **Background – Important publications on Particle Effects in the Rat Lung**

- Lee et al., Tox Appl Pharm. 79:179-192, 1985.
- Heinrich et al., Inhal Toxicol 7:533-556, 1995.
- Hext – Human & Exper Toxicol 13:700-715, 1994
- Warheit et al., Toxicol Appl Pharmacol 145: 10-22, 1997
- Carlton – Fundam Appl Toxicol 23:304-307, 1994
- Levy – In: Toxic and Carcinogenic Effects of Solid Particles, 1994
- Boorman et al. – Toxicological Pathology 24: 564-573, 1996

## **Important publications on Particle Effects in the Rat Lung (Cont)**

- Warheit and Frame – JOEM, 2006 in press
- Vu – Inhalation Toxicol 8 (suppl) 181-191, 1996.
- PCRARM, Presidential Commission on Risk Assessment and Risk Management (1997)
- Nikula et al., Fundam. Appl Toxicol 37: 37-53, 1997.
- Nikula et al. Environ Health Perspec 109: 311-318, 2001.
- Warheit et al. Toxicological Sciences, in press 2006





## **Important publications on Particle Effects in the Rat Lung (Cont)**

- Tran et al., *Inhal Toxicol* 12:1113-1126, 2000.
- Bermudez et al., *Toxicol Sci.* 70:86-97, 2002.
- Bermudez et al., *Toxicol. Sci.* 77:347-357, 2004

## **Important Epidemiological publications on Exposure Effects in TiO<sub>2</sub> Workers**

- Chen and Fayerweather – J Occup Med 30:937-942, 1988.
- Boffetta et al., Scand J Work Environ Health 27:227-232, 2001.
- Fryzek et al, J Occup Environ Med 45:400-409, 2003
- Boffetta et al., (Cancer Causes and Control (2004)

# Inhalation Toxicity studies- fine and ultrafine TiO<sub>2</sub> particles

- **Lee et al.**, (1985) fine TiO<sub>2</sub> ~ 300 nm
  - M and F rats – 0, 10, 50 and 250 mg/m<sup>3</sup> for 2 yrs
  - 10 mg/m<sup>3</sup> - minor effects
  - 50 mg/m<sup>3</sup> - various effects + fibrosis + no tumors
  - 250 mg/m<sup>3</sup> – various effects + fibrosis + ~ 25 % benign tumors + PKC
- **Heinrich et al.**, (1995) ultrafine TiO<sub>2</sub> P-25 (10-40 nm)
  - F Wistar rats – DEEP 7 mg/m<sup>3</sup>, CB 11.6 mg/m<sup>3</sup>, P-25 10 mg/m<sup>3</sup> – 2 yrs + 6 months
  - Lung Tumors: DEEP 22/100; CB 39/100; P-25 32/100

## **Hext – Current Perspectives on Particulate Induced Pulmonary Tumours**

- Chronic exposure to insoluble particulates can lead to the development of pulmonary tumors in rats but not in other rodent species.
- Prerequisite – overloading of normal alveolar macrophage mediated mechanisms.
- Inflammation → epithelial hypertrophy and/or hyperplasia and squamous metaplasia.
- Persistence of these effects leads to lung tumors.



**Warheit et al. – Inhalation of high concentrations of low toxicity dusts results in impaired pulmonary clearance mechanisms and persistent inflammation**

- Male rats exposed to TiO<sub>2</sub> or carbonyl iron particles for 4 weeks at 5, 50 and 250 mg/m<sup>3</sup> and evaluated through 6 months postexposure.
- Exposures to 250 mg/m<sup>3</sup> produced sustained inflammation, enhanced proliferation of pulmonary cells, impairment of particle clearance, deficits in macrophage function and macrophage aggregates at sites of particle deposition.

**Carlton – “Proliferative Keratin Cyst” – a lesion in the lungs of rats following chronic exposure to para-aramid fibrils**

- Workshop of pathologists to reach a diagnostic descriptive consensus on cystic keratinizing pulmonary lesions produced in rats by para-aramid fibrils and TiO<sub>2</sub> particles.
- All participants agreed that the cystic lesions were not malignant neoplasms. A majority considered the lesions to be nontumorous “proliferative keratin cysts” (PKC). A minority (3/13) considered the lesions to be benign tumors.

**Levy – Squamous lesions associated with chronic exposure by inhalation of rats to p-aramid fibrils and to titanium dioxide: Findings of a pathology workshop**

- Report of the same workshop – implications of the PKC for humans.
- None of the pathologists had observed these lesions in humans.
- These lesions generally considered to be unique to rats.

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**Boorman et al. Classification of cystic  
keratinizing squamous lesions of the rat  
lung: Report of a workshop**

- Workshop of pathologists reached a consensus on classification of these unique pulmonary tissues responses in response to particle overload exposures in the rat lung.



## **Warheit and Frame - Characterization and reclassification of TiO<sub>2</sub>- related pulmonary lesions (JOEM, in press 2006)**

- **OBJECTIVE:** Utilizing current diagnostic criteria, the manuscript summarized the microscopic review of 16 proliferative squamous lesions, previously diagnosed as cystic keratinizing squamous cell carcinoma, in the lungs of rats from a two-year inhalation study with pigment-grade titanium dioxide particles.
- **RESULTS:** Unanimous agreement was reached as to the diagnosis of each of the lesions. Two of the lesions were diagnosed as squamous metaplasia and one as a poorly-keratinizing squamous cell carcinoma. The remaining 13 lesions were diagnosed as non-neoplastic pulmonary keratin cysts

## **Vu – Use of hazard and risk information in risk management decisions: Solid particles and fibers under EPA's TSCA and EPCRA**

- Since the enactment of EPCRA, EPA has received many petitions to delist chemicals from the TRI. After a careful review of pertinent health information on TiO<sub>2</sub>, (particles 1-3 μm diameter) EPA issued a final rule deleting this substance from the list of toxic chemicals under section 313 of Title III of SARA.
- With regard to human health and the environment, EPA has determined that TiO<sub>2</sub> poses a low risk of acute respiratory effects.

## Vu - continued

- TiO<sub>2</sub> is of low acute toxicity by inhalation.
- There is insufficient evidence of chronic respiratory effects, carcinogenicity, and heritable mutations.
- The single positive result at the time of the EPA review (Lee et al., 1985), in which an increase in lung tumors was observed, occurred in rats exposed via inhalation to high concentrations that may have overwhelmed clearance mechanisms of the lung.
- Along with the negative carcinogenic responses from multiple studies by various routes of exposure + the negative mutagenicity data leads to an overall weight of evidence determination that there is not sufficient evidence to show that TiO<sub>2</sub> will cause or can reasonably be expected to cause cancer in humans (USEPA, 1988).

## **PCRAM – Presidential Commission on Risk Assessment and Risk Management (1997) Final Report, Volume 2**

- “There are ...cases ... where rodent tumor responses have been shown to be irrelevant to humans or may occur at doses far exceeding any recognized human exposures...”
- The PCRAM specifically identified  $\text{TiO}_2$  as one such chemical because observed rodent tumor responses associated with exposure to  $\text{TiO}_2$  are not relevant to human risk.



**Nikula et al., - Lung tissue responses and sites of particle retention differ between rats and Cynomolgus monkeys exposed chronically to diesel exhaust and coal dust.**

- Study compared the anatomical pattern of particle retention and the lung tissue response of rats and monkeys exposed chronically (24 months) to high occupational concentrations of poorly soluble particles

## **Nikula-1 (cont)**

- Rats retained greater portion of particles in alveolar ducts vs. monkeys
- Monkeys retained greater portion of particles in interstitium vs. rats.
- Rats but not monkeys had significant alveolar epithelial hyperplastic, inflammatory and septal fibrotic responses to the retained particles.
- Authors concluded that particle retention patterns and tissue reactions in rats may not be predictive for primates at high conc.

**Nikula et al. Influence of exposure conc. or dose on the distribution of particulate material in rat and human lungs**

- Study used morphometry to assess particle retention in histologic sections from rats and humans.
- Rats exposed 24 months to DEEP at 0.35, 3.5 or 7 mg soot/m<sup>3</sup>
- Humans – nonsmoking coal miners.
- Retained particle distribution within the lungs markedly different in rats vs. humans.

## Nikula-2 (cont)

- In rats - chronically inhaled diesel soot is retained in alveolar regions.
- In humans - chronically inhaled particulate matter is retained primarily in interstitium.
- In humans - percentage of particles in the interstitium ↑ with ↑ dose
- Difference in distribution may account for species differences in lung response to particles.



## Species Comparisons of Pulmonary Effects of Particle Overload in Rats vs Large Mammals

Classical attributes and sequelae of lung overload in rats	Rats	Dog, Monkey, and Man
Chronic pulmonary inflammation	Yes	Not certain
Hyperplasia of macrophages and epithelial cells	Yes	Not certain
Altered pulmonary clearance (overwhelms) macrophage mediated clearance	Yes	Probably not
Large pulmonary burdens of particles	Yes	Probably not
Increased interstitialization of deposited particles	Yes	Yes
Increased translocation of particles from lung to thoracic lymph nodes	Probably	Probably
Interstitial lung disease (fibrosis)	Yes	Yes but less severe
Production of lung tumors	Yes	No

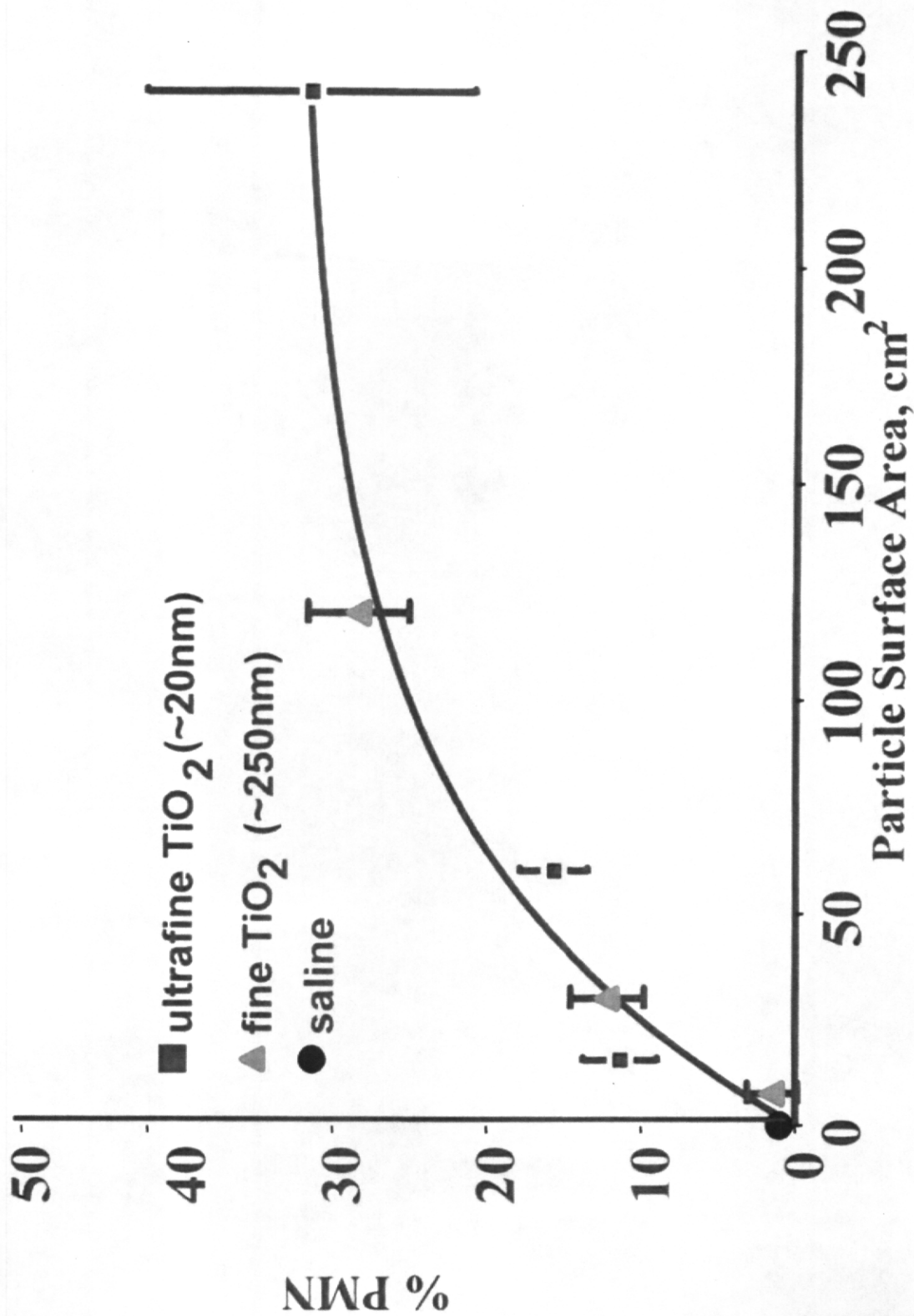
## **Tran et al., Inhalation of poorly soluble particles.**

### **II. Influence of particle surface area on inflammation and clearance.**

- Tested volumetric overload hypothesis- which predicts the impairment of particle clearance in terms of particle volume
- Evaluated exposures to  $\text{TiO}_2$  and  $\text{BaSO}_4$ .
- Concluded that inflammation and translocation best described when the lung burden was expressed as total particle surface area.

# Percent of PMN in BAL 24 hrs After Instillation of TiO<sub>2</sub> in Rats

*Correlation with Particle Surface Area- Oberdorster, 1994*







## **CIIT Inhalation Toxicity studies- fine and ultrafine TiO<sub>2</sub> particles**

Bermudez et al., " Pulmonary Responses of Mice, Rats, and Hamsters to Subchronic Inhalation of Ultrafine Titanium Dioxide Particles" - 2004

- F rats, mice and hamsters exposed for 13 weeks to 0.5, 2.0 and 10 mg/m<sup>3</sup> – and evaluated over 1 yr pe.
- **In summary, there were significant species differences in lung responses to uftiO<sub>2</sub>- rats more severe inflammation, progressive epithelial and fibroproliferative lesions.**

**Bermudez et al., 2002**

- Pigment grade TiO<sub>2</sub> study – 0, 10, 50 and 250 mg/m<sup>3</sup>
- The 10 mg/m<sup>3</sup> effect in rats exposed to uftiO<sub>2</sub> was similar to the 50 mg/m<sup>3</sup> pigment-grade and not the 250 mg/m<sup>3</sup> pigment.

## **Take home points regarding the lung toxicity of fine and ultrafine TiO<sub>2</sub> particles**

- Pulmonary lesions were most severe in rats, where progressive epithelial- and fibroproliferative changes were observed in the 250 mg/m<sup>3</sup> group. These epithelial proliferative changes were also manifested in rats as an increase in alveolar epithelial cell labeling in cell proliferation studies. Associated with these foci of epithelial proliferation were interstitial particle accumulation and alveolar septal fibrosis.

## Take home points - II

- In summary, there were significant species differences in pulmonary response to inhaled pigment grade TiO<sub>2</sub> particles. Under conditions in which the lung pigment grade TiO<sub>2</sub> burdens were similar and likely to induce pulmonary overload, rats developed a more severe and persistent pulmonary inflammatory response than either mice or hamsters.

## Take home points – III

- Rats also were unique in the development of progressive fibroproliferative lesions and alveolar epithelial metaplasia in response to 90 days of exposure to a high concentration of pigment grade  $\text{TiO}_2$  particles.



# Conclusions on Toxicology Studies in Rats with TiO<sub>2</sub> and PSPs

- Chronic exposures to overload concentrations of 250 but not 50 mg/m<sup>3</sup> pigment-grade TiO<sub>2</sub> in rats produced benign lung tumors.
- Rats are uniquely sensitive to overload concentrations of poorly soluble particles and develop proliferative keratin cysts.
- Other rodent species do not develop lung tumors to high doses of PSP particle-types.
- The distribution and cellular responses to inhaled dusts in larger mammals is different when compared to rats.

# Epidemiology Studies with Worker Exposure to TiO<sub>2</sub> Particles

- 1) Chen and Fayerweather; (1988) Epidemiologic study of workers exposed to titanium dioxide.
- 2) Boffetta et al., (2001) Exposure to titanium dioxide and risk of lung cancer in a population-based study from Montreal
- 3) Fryzek et al. (2003) A cohort mortality study among titanium dioxide manufacturing workers in the United States.

## **Epidemiology studies (cont.)**

- Boffetta et al., (2004) – Mortality among workers employed in the titanium dioxide production industry in Europe.
- **The four epidemiology studies of large population cohorts in different parts of the world were negative for lung cancer in TiO<sub>2</sub>-exposed workers.**



**Pulmonary Bioassay  
Studies with Fine and  
Nanoscale TiO<sub>2</sub>  
Particulates**

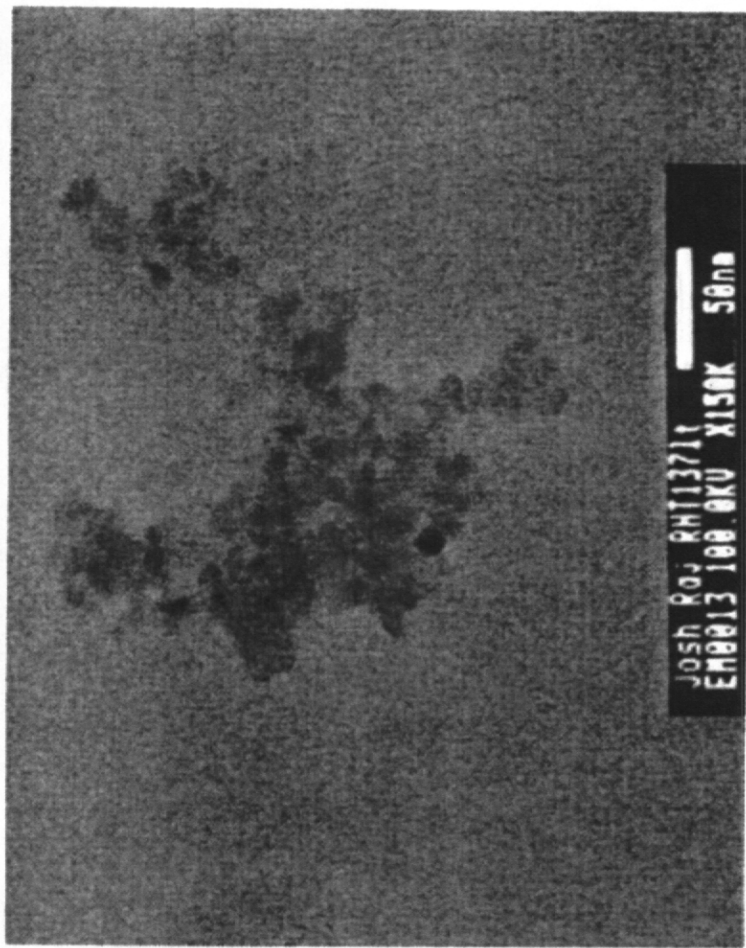


## **New Information - Particle Surface indices do not always correlate with Pulmonary Inflammation in Rats**

- Pulmonary Instillation Studies with Nanoscale TiO<sub>2</sub> Rods and Dots in Rats: Toxicity is not dependent upon Particle Size and Surface Area – Warheit et al., in press, **Toxicological Sciences, 2006.**

# TiO<sub>2</sub> Nano Dots

TiO<sub>2</sub> Dots ("RHT-137")



# TiO<sub>2</sub> Nano Rods

TiO<sub>2</sub> Rods ("Chem E.F.")



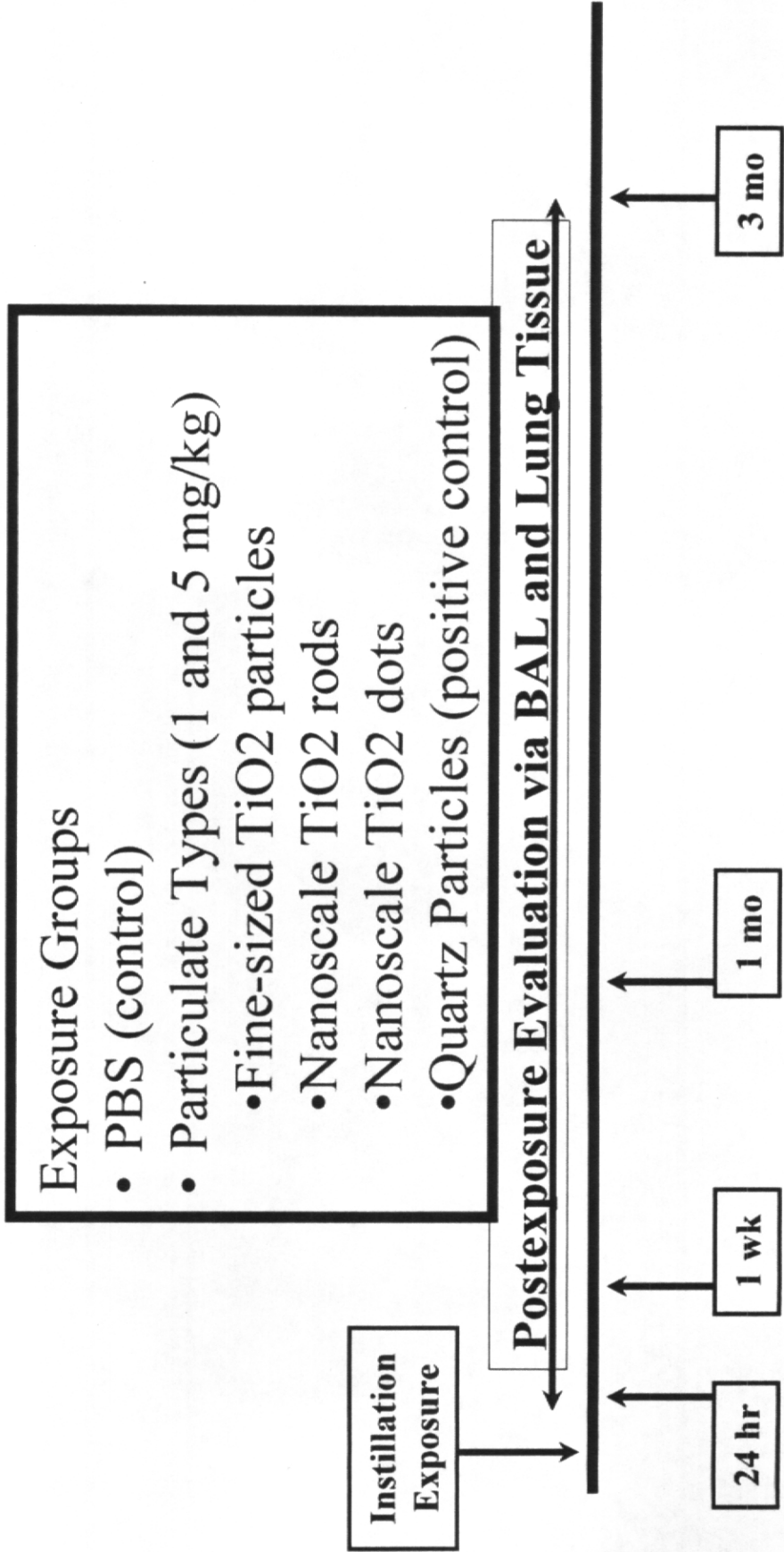
200 nm

**TiPure® R-100**



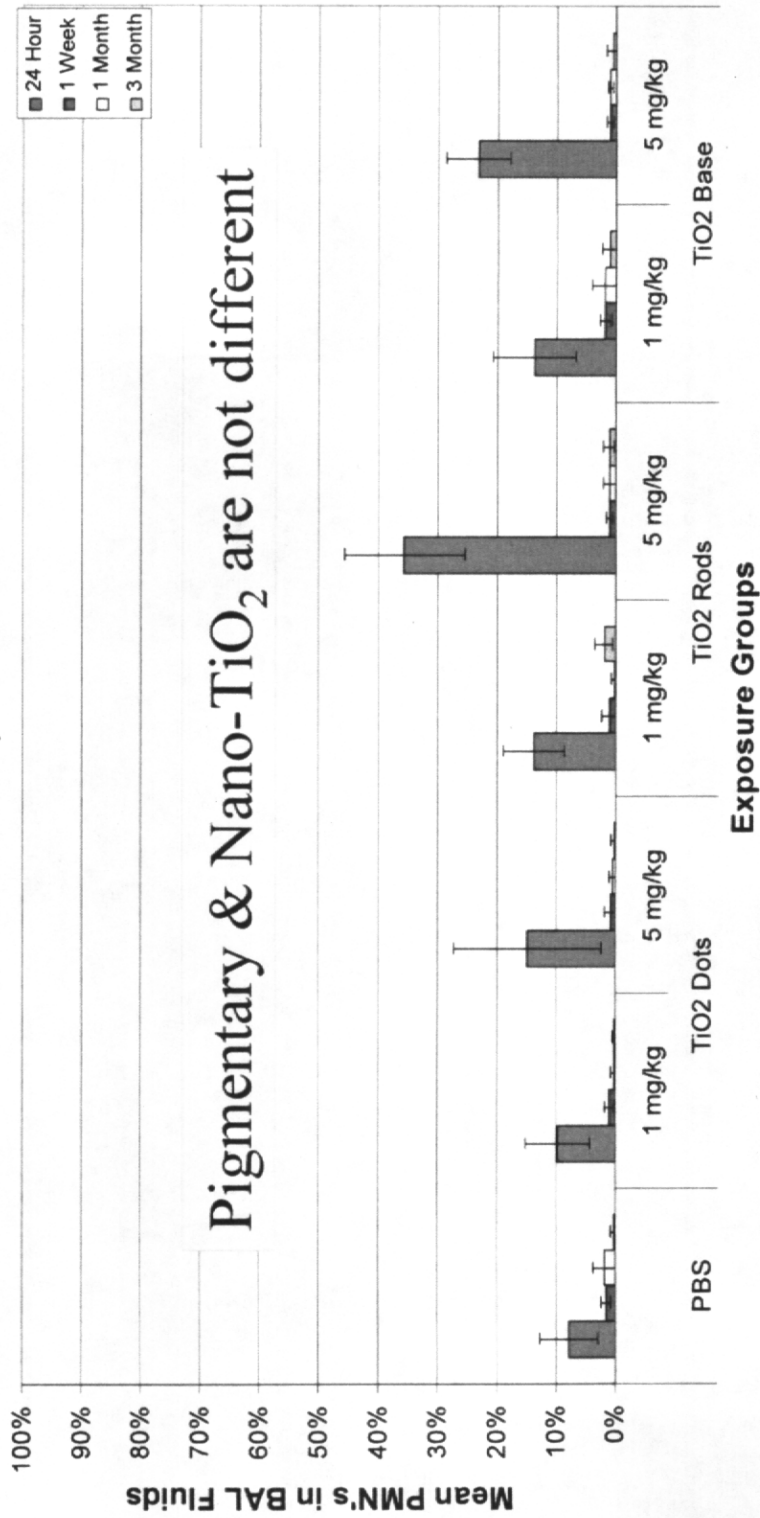


# Protocol for Nanoscale TiO<sub>2</sub> Pulmonary Bioassay Study

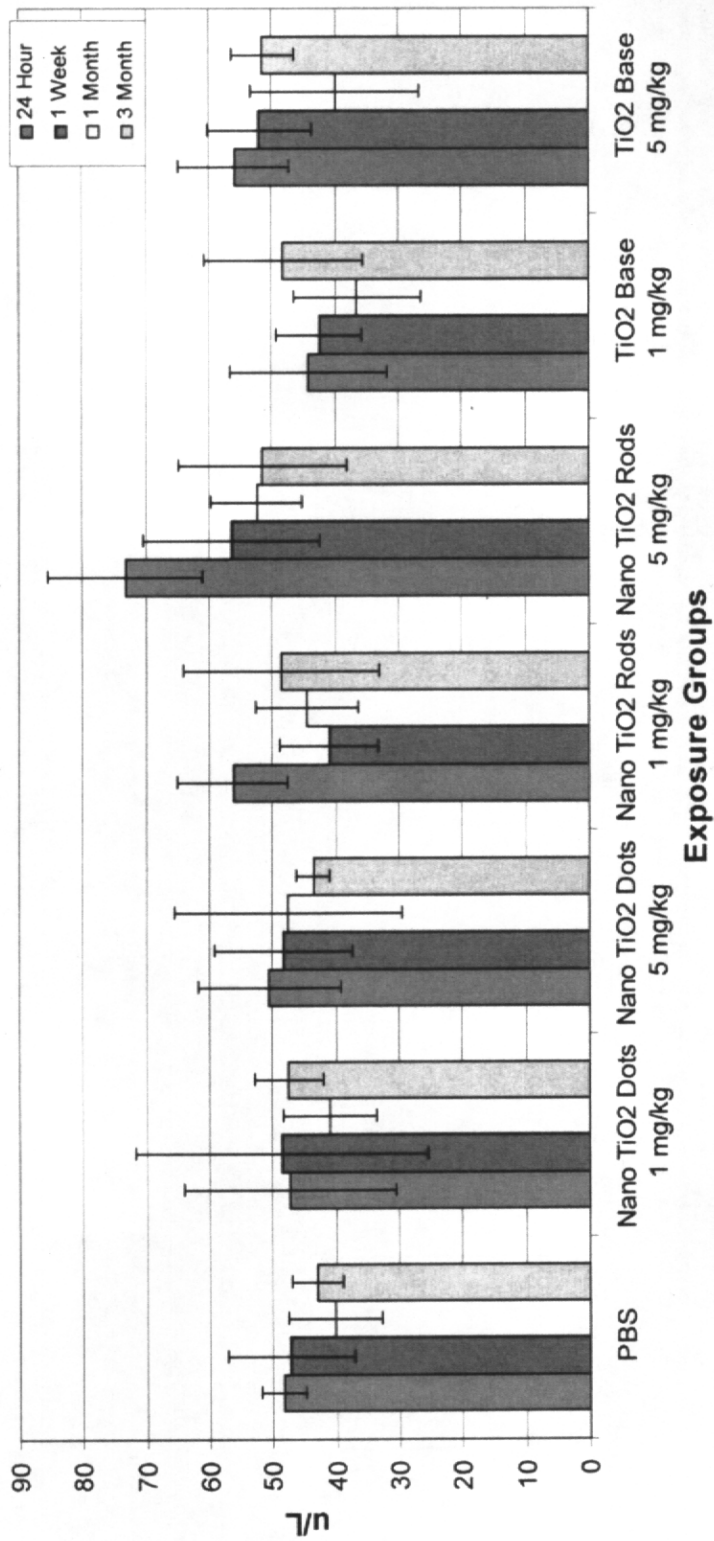


# Collaborative Studies with Rice University: TiO<sub>2</sub>

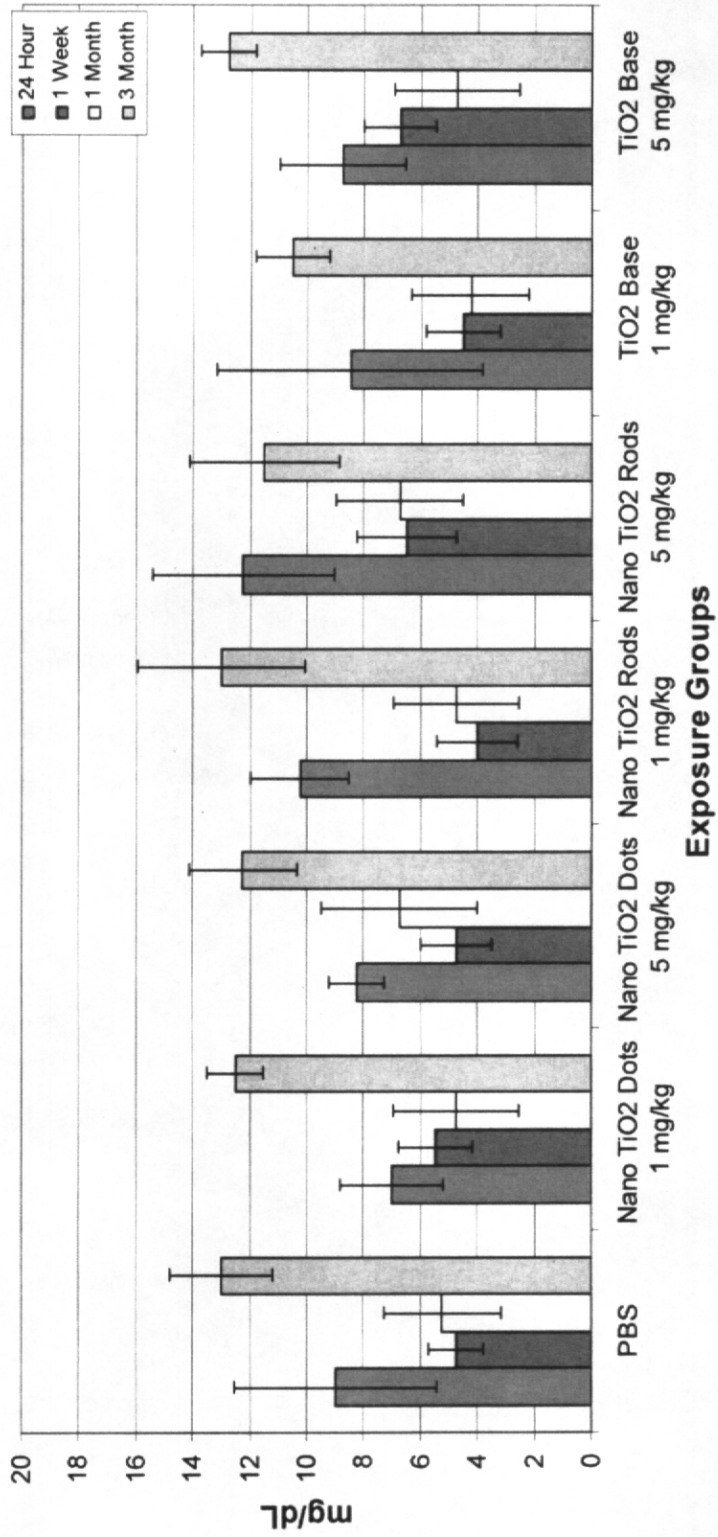
Percent Neutrophils in BAL Fluids of Rats Exposed to TiO<sub>2</sub> Particles, Nano-rods, and Nano-dots



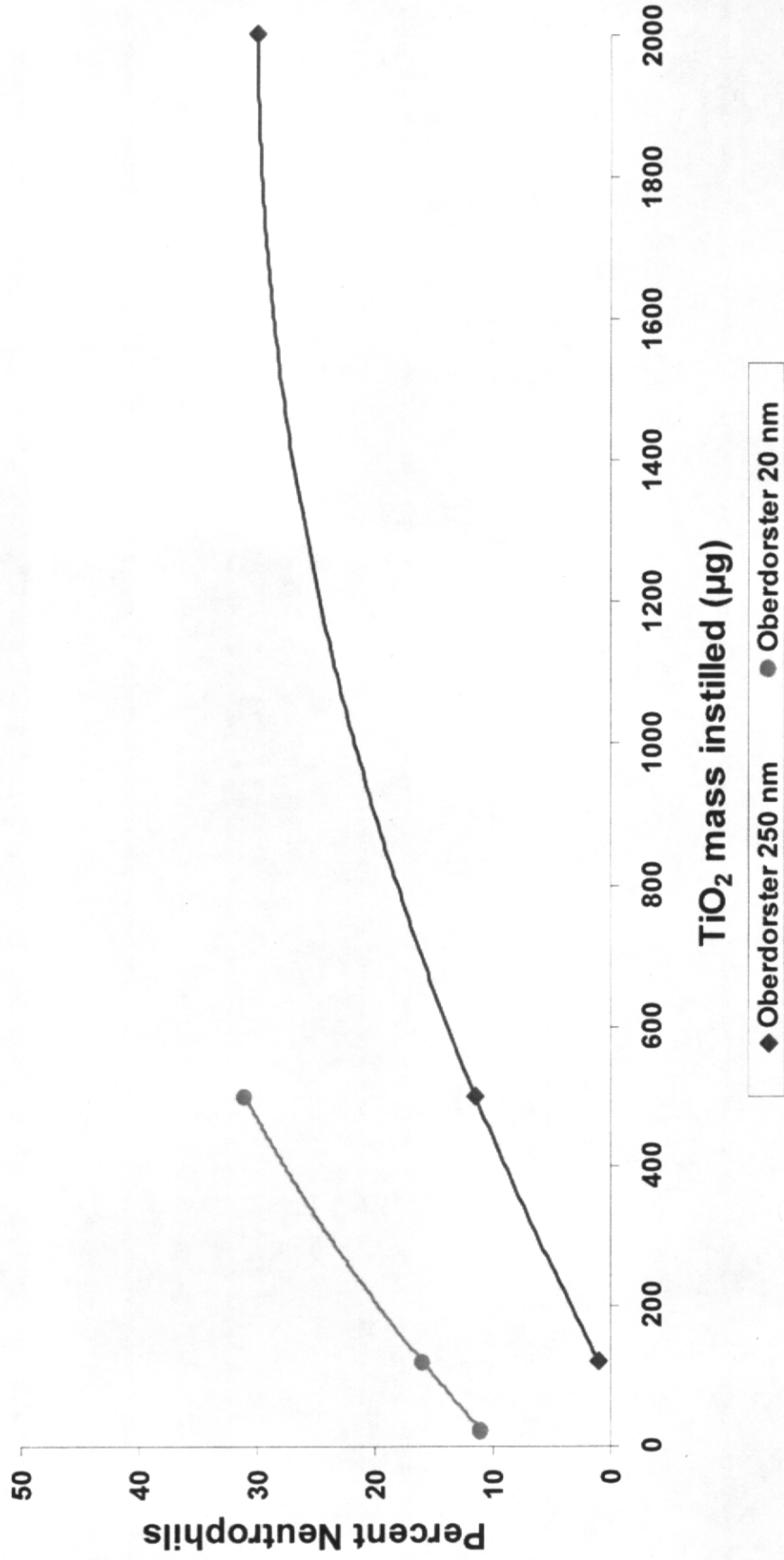
## BAL Fluid LDH Values In Rats Exposed to TiO<sub>2</sub> Particles, Nano-rods, and Nano-dots



## BAL Fluid MTP Values In Rats Exposed to TiO<sub>2</sub> Particles, Nano-rods, and Nano-dots

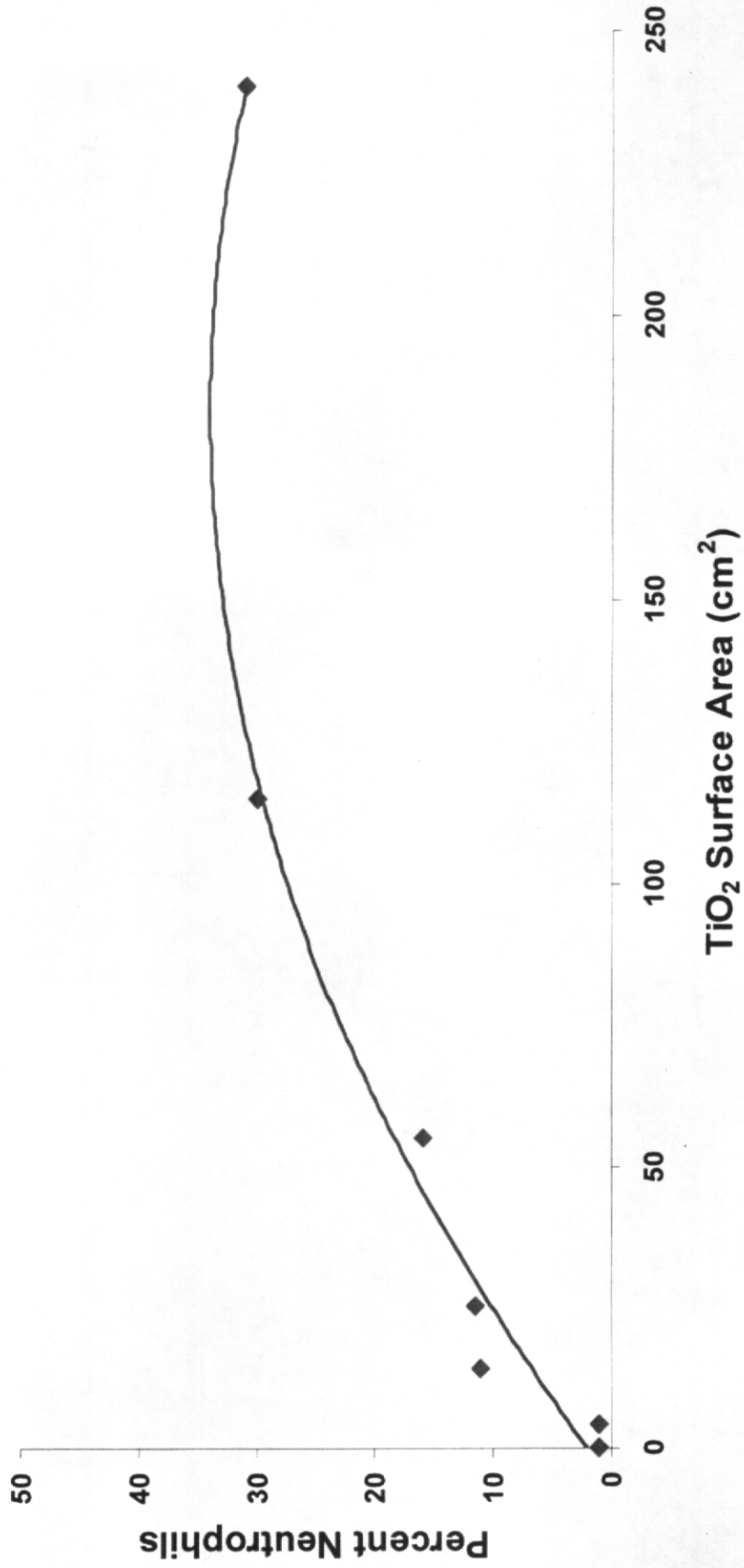


# Relationship of Pulmonary Inflammation to $\text{TiO}_2$ Particle Mass dose at 24 hrs PE (Oberdorster<sup>3</sup> EHP, 2005)

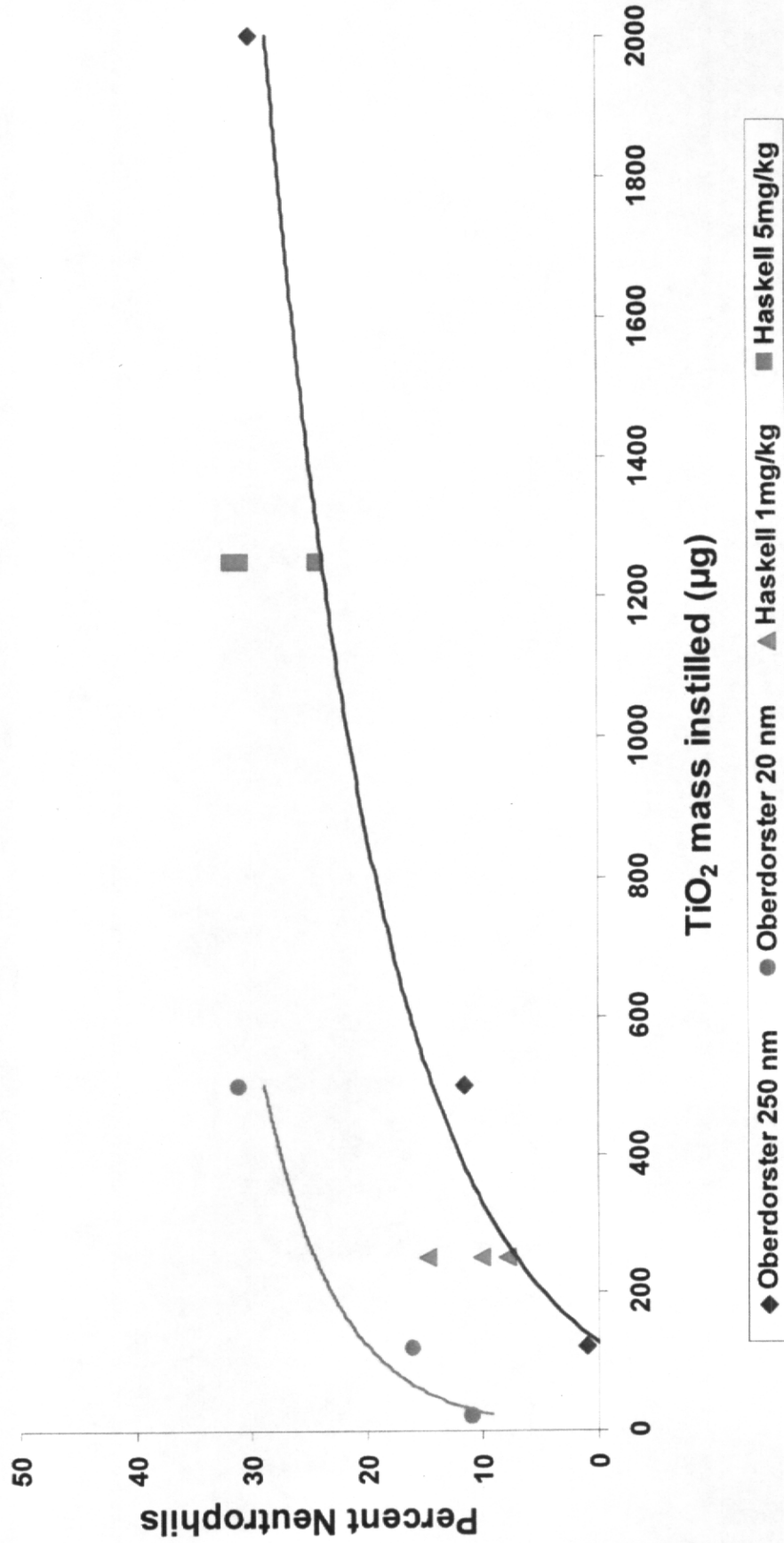




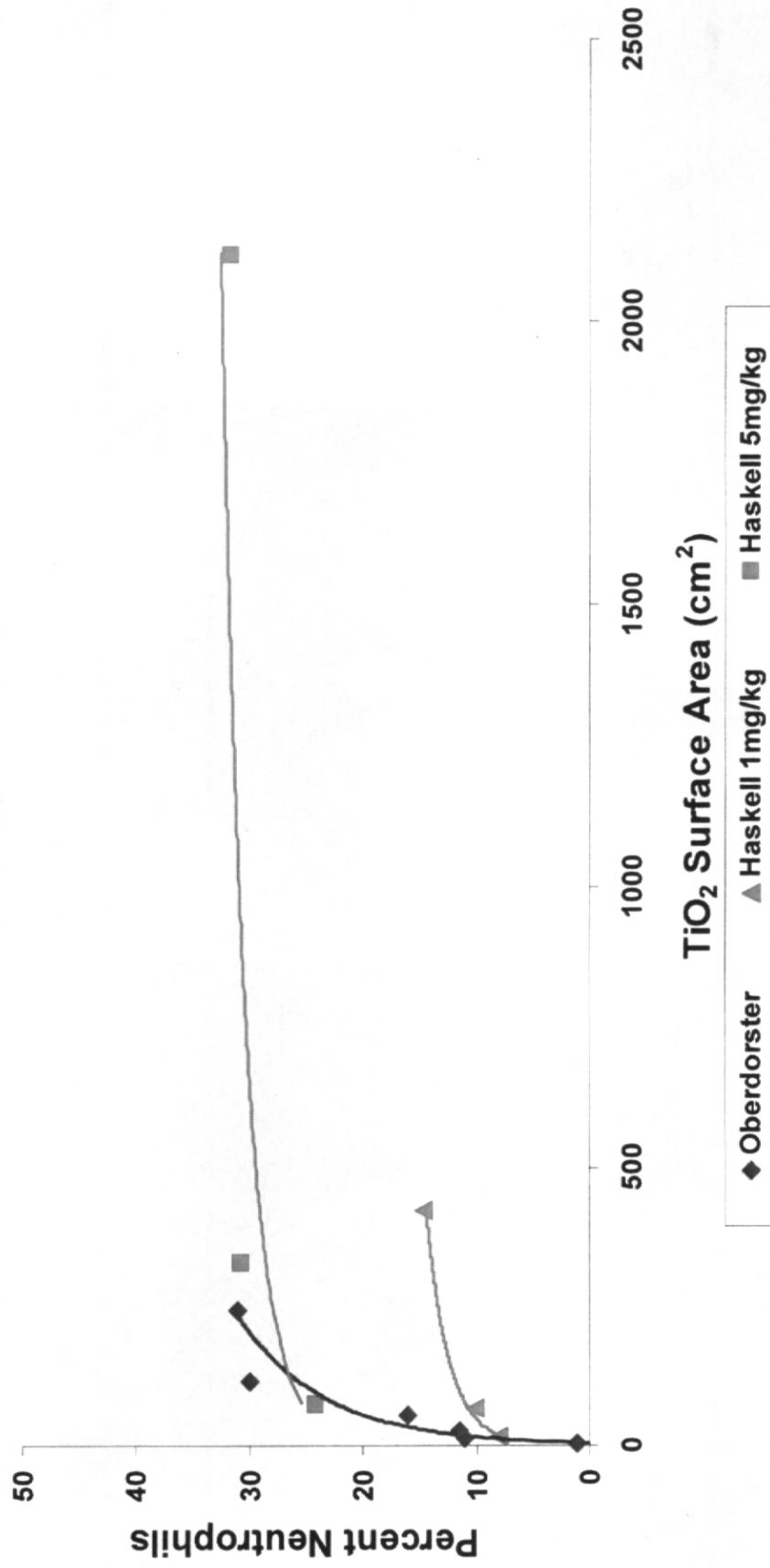
# Relationship of Pulmonary Inflammation to TiO<sub>2</sub> Particle Surface Area at 24 hrs PE Oberdorster<sup>3</sup> (EHP, 2005)



**Relationship of Pulmonary Inflammation to TiO<sub>2</sub>  
Particle Mass dose at 24 hrs PE  
(Oberdorster<sup>3</sup> EHP, 2005) + (Haskell)**



# Relationship of Pulmonary Inflammation to TiO<sub>2</sub> Particle Surface Area at 24 hrs PE (Oberdorster<sup>3</sup> EHP) + (Haskell)





# Summary of Results and Significance

- These results provide the first example of nanoscale particle-types which are not more cytotoxic or inflammatory to the lung compared to larger-sized particles of similar composition. Furthermore, these findings run counter to the postulation that surface area is a major factor associated with the pulmonary toxicity of nanoscale particle-types.



## **Summary of Results and Significance relative to TiO<sub>2</sub> CIB**

- The results of this study and other hazard studies demonstrate that the P25 ultrafine TiO<sub>2</sub> particles utilized in the Heinrich et al., and Bermudez et al. studies are not representative for all ultrafine or Nano TiO<sub>2</sub> particle-types. Therefore the recommendation of an exposure limit of 0.1 mg/m<sup>3</sup> becomes problematic.



# Summary Conclusions - I

- General document and pertinent literature review is for the most part, comprehensive
- However, many of the summaries are not properly interpreted.
- The authors seem to de-emphasize the critically relevant studies by Nikula et al., and Bermudez et al.
- The authors draw the erroneous conclusion that since humans have slow dust clearance response, leading to particle overload, the human response might be similar to the rat response, possibly leading to lung tumors. Thus the corresponding risk assessment models are inappropriate.

## **Summary Conclusions - II**

- Rats are uniquely sensitive to developing lung responses to poorly soluble particulates at particle overload concentrations. This response does not occur in ANY other species.

# Summary Conclusions - III

- Current Mode of Action Scenario for Development of Lung Tumors in Rats exposed to Overload concentrations of PSPs
- In rats → chronic exposure to  $\text{TiO}_2$  → Particle Overload → sustained inflammation → epithelial cell proliferation, septal fibrosis and fibroproliferative effects → metaplasia → mutations → lung tumors
- In humans → chronic exposure to PSP → Particle Overload → low degree of inflammation → little or no Fibrosis → no Mutations → No lung tumors

## Summary Conclusions - IV

- Poor Justification for the suggested RELs for pigment grade (1.5 mg/m<sup>3</sup>) or ultrafine TiO<sub>2</sub> particles (0.1 mg/m<sup>3</sup>) (John Tomenson)
- Throughout the CIB document, the authors fail to adequately characterize the crystal structures and particle sizes (physical characteristics) used by the investigators in the various studies.

## Summary Conclusions - V

- Epidemiology results from 4 extensive studies are negative for lung cancer in TiO<sub>2</sub> workers.
- Ultrafine TiO<sub>2</sub> particles are comprised of different crystal structures (anatase or rutile) and different particle sizes and the suggestion that P25 is representative for all ultrafine TiO<sub>2</sub> particle-types is inappropriate.
- Acknowledgment by other federal agencies and commissions that TiO<sub>2</sub> is a low toxicity dust and therefore has been de-listed by USEPA from their TRI listing.