NIOSH Response to Comments submitted to NIOSH Docket 033 by the American Chemistry Council Titanium Dioxide Panel, March 31, 2006

http://www.cdc.gov/niosh/docket/pdfs/NIOSH-033/Submissions/0033-033106-ACC%20TIO2_submission.pdf

RESPONSES

ACC-1: overall statement about outdated NOES data.
Response: See response to comment ACC-11.

ACC-2: overall statement regarding NIOSH's consideration of the epidemiology studies.
Response: ACC's comments were considered and our responses are provided in this response to comments document.

ACC-3: Some of the draft CIB conclusions are erroneous, based on misrepresentations or misinterpretations of some of the animal studies and fail to consider several studies that are critically important.... In particular ... two important studies by Nikula et al.
Response: The Nikula et al. 1997 and 2001 pertain to coal dust and diesel exhaust particulate; however, discussion of these studies was added to Chapter 3 in the context of particle kinetic mechanisms in rat and human lungs. The statements in Chapter 3 of the draft CIB have been verified in the references cited, as shown in responses to ACC #36-75. Minor errors were found and corrected. Additional clarification and explanation have been provided.

ACC-4: NIOSH should review all the scientific data relevant to the human health effects of coal mine dust.
Response: NIOSH has determined that this document should focus on data directly relevant to TiO_2. A comprehensive review of coal mine dust health effects data is beyond the scope of this document.

ACC-5: The Panel urges NIOSH to use threshold models to reflect mechanism of action conclusions instead of benchmark dose (BMD) modeling and linearized multistage approaches.
Response: See response to ACC-78 and ACC-79, below.

ACC-6: NIOSH's proposed RELs are not scientifically defensible.
Response: NIOSH expanded its threshold analysis from that done in the public comment draft to include data supplied by the Hamner Institute. These analyses did not support a threshold for inflammation. Therefore, in the final analysis, NIOSH relied on model averaging of the cancer dose-response relationship for its final risk estimates.

ACC-7: NIOSH has failed to provide industry with a confirmed Method(s) for the analysis of TiO_2 in the workplace sufficient to support the proposed RELs.

Response: NIOSH is recommending the use of Method 0600 for the respirable mass analysis of fine and ultrafine TiO_2. This method is recommended as a surrogate for surface area measurements and should be adequate for monitoring workplace exposures to TiO_2 as long as the size distribution of the aerosol is known and remains constant. NIOSH provides a sampling and analytical strategy that can be used to help ascertain the particle size and identification of the aerosol to ensure that measurements taken with Method 0600 provide representative exposure concentrations to TiO_2. NIOSH Method 0600 has been validated in the laboratory and field for many types of metals and therefore the method should be expected to attain the same accuracy and reliability for the measurement of TiO_2.

ACC-8: 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.
Response: NIOSH notes that after the National Academies review of this Bulletin, OMB has withdrawn the Proposed Risk Assessment Bulletin. NIOSH uses the highest standards of objectivity, transparency and integrity as a routine practice in its risk assessments. NIOSH is also in full compliance with the later-issued OMB Risk Assessment memo.

ACC-9: There are studies that are highly relevant to this analysis that are not discussed in the CIB, while other studies that are discussed are not afforded proper attention.
Response: While the CIB is not intended to be an exhaustive review of the literature relevant to occupational exposure to TiO_2, the Institute strives to fully review and consider all pertinent scientific data. To that end, NIOSH has expanded its review of the scientific literature supporting this CIB (see chapter 3). NIOSH also seriously considers all peer review and public comments supplied during the public comment period.

ACC-10: The panel supports NIOSH's decision to remove its designation of TiO_2 as a "potential occupational carcinogen."
Response: In consideration of the peer review and public comments received on this topic and after careful reconsideration of the scientific literature, NIOSH has retained the designation "potential occupational carcinogen" for ultrafine TiO_2 but concludes there are insufficient data to similarly classify fine TiO_2. Please see chapter 3 and 4 of the CIB for a fuller discussion of these issues. In addition, NIOSH also notes that after the draft CIB was published, IARC determined that TiO_2 is a Group 2B carcinogen, possibly carcinogenic to humans.

ACC-11: request to delete NOES estimate of workers or revise discussion to include NOES deficiencies.
Response: Deleted NOES estimate (lines 361-367). Revised text to include ACC's unreferenced estimate given in comment ACC-11. Next paragraph: added U.S. Geological Survey's 2007 estimate of 4,300 workers employed in the U.S. plants.

ACC-12: request to alter RELs to refer to TiO_2 as "free and unbound" as compared to when TiO_2 is tightly bound in final products, such as paint, plastics, sunscreens.
Response: There is no need to qualify the REL by saying "free and unbound" because the sampling strategy (Figure 6-1) requires that when there is a question about the

constituents of a material then electron microscopy is used to distinguish TiO_2 from other contaminants.

ACC-13: regarding request to add "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_2 since the 1930s."
Response: Assuming that "over 20,000 workers" represents the combined total number of workers in the various epidemiology studies, a statement about health risks of combined cohorts would be best supported by a combined analysis. To our knowledge, one has not been conducted and published. No change.

ACC-14: ACC states that aerosols of TiO_2 will agglomerate and in the pigment industry a significant fraction of the exposure is to respirable agglomerated particles.
Response: NIOSH agrees that a substantial amount of aerosolized TiO_2 will probably agglomerate depending on surface treatment, relative humidity, sample aging, and other factors. The statement in Chapter 6 has been modified to indicate that exposures to TiO_2 will be comprised of respirable particles and agglomerates.

ACC-15: ACC states that it does not believe fine TiO_2 can be micronized into an ultrafine particle fraction and asks that the statement be deleted or referenced.
Response: This statement has been removed.

ACC-16: Request for addition of word "fine" so that lines 506-507 read: "A few epidemiologic studies have evaluated the carcinogenicity of fine TiO_2 in humans; they are described here and in Table 2-1."
Response: The epidemiologic studies evaluated exposure to TiO_2 dust (or TiO_2 as dust, mist, or fumes) and did not report whether it was fine or ultrafine. No change.

ACC-17: Request for addition of word "fine" so that lines 716-717 read: "Overall, these studies provide no clear evidence of elevated risks of lung cancer mortality or morbidity among those workers exposed to fine TiO_2 dust."
Response: The epidemiologic studies evaluated exposure to TiO_2 dust (or TiO_2 as dust, mist, or fumes) and did not report whether it was fine or ultrafine. No change.

ACC-18: Request for revision of lines 726-728 to read: "In addition to the methodologic and epidemiologic limitations of the studies of workers exposed to fine TiO_2, there are no studies available of workers exposed to ultrafine TiO_2."
Response: The epidemiologic studies did not report that the exposure was to fine TiO_2. The studies evaluated exposure to TiO_2 dust (or TiO_2 as dust, mist, or fumes). No change.

ACC-19: This comment is an introduction to the next seven comments from the Panel; all pertain to the Chen and Fayerweather [1988] study which had several components and part of comment states "…NIOSH neglects to point out that the limitations cited do not apply to each and every one of the study components."
Response: The draft does not "dismiss" any component of the study; however, it does point out the 'serious limitations' of this study. Deleted phrase "…preclude any conclusions…" from line 568 and deleted "serious" to coincide with text of the other

studies' limitations text and comment in Table 2-1. Revised text to clarify which components are affected by each limitation, when possible (see responses to ACC-20 through ACC-26). Added ascertainment proportions for vital status and death certificates to study description.

ACC-20: Lines 568-569 of the draft state that the study is limited because it is unclear whether quantitative exposure data for respirable TiO_2 existed after 1975. Comment says that "exposure classification committees evaluated the exposure of each TiO_2- exposed job" and that "The clear implication is that quantitative exposure data existed after 1975."
Response: The study makes an implication and is not specific. Re-worded and combined this limitation with limitation 2 about lack of information about the exposure data. Draft already has sentence about the committees. Deleted "if any" from line 524.

ACC-21: Lines 570-573 states that certain details about exposure measurement were not reported. Comment states that few studies provide that level of detail and that it is reasonable to assume that the authors were "describing total dust."
Response: the limitation provides examples of descriptive information that would be useful in understanding the exposure data and its collection and use. Most studies do report at least some of those items; this one did not. The authors did not state that it was total dust. No change.

ACC-22: Line 573 states that duration of exposure was not described and comment says that quartiles for exposure duration were provided and show that only 25 percent of the cohort was exposed >4 years, "which the Panel concurs is a limitation of the study".
Response: Re-worded the limitation. Workers, deaths, cases per exposure quartile not described.

ACC-23: Lines 573-574 state that other chemicals and asbestos could have acted as confounders. Comment requests that "NIOSH should note that this limitation does not explain reduced lung cancer mortality."
Response: Asks for speculation about direction of results if confounding was present. No change.

ACC-24: Lines 574-575 state that the incidence and mortality data were not described in detail and the healthy worker effect may have affected incidence and mortality. Comment says it is "highly unlikely to have concealed an exposure-related effect on lung cancer mortality".
Response: Comment considered. No change.

ACC-25: Lines 575-576 state that chest X-rays were not available for retired and terminated workers. Comment states that this fact does not invalidate the cross-sectional component and it is irrelevant to the mortality component.
Response: The lack of post-employment X-rays does not "invalidate" the study, but the prevalence of dust exposure-related respiratory disease in that group is an important question that this study could not answer. Moved limitation to the chest X-ray paragraph (lines 529-530).

ACC-26: Lines 576-578 states that company registries were the only apparent source for some information and comment states that this may be true of incidence component but with respect to the mortality component, there was 94% ascertainment of death certificates.
Response: Added 94% ascertainment to study description. "Information concerning deaths among active and pensioned employees was obtained from the DuPont Mortality Registry" [Chen and Fayerweather 1988]. Added "incidence and mortality" before "information" in the limitation.

ACC-27: requesting revision of line 621 regarding destruction of company records and Fryzek et al. [2003] study.
Response: Line revised as suggested; study authors quoted. Moved from limitations to preceding paragraph.

ACC-28: requests revision of Table 2-1's comment about "questionable modeling methods" and more explanation in text of data analyses conducted by Fryzek et al. in response to letter to editor from Beaumont et al. [2004].
Response: Text and table revised.

ACC-29: states that hazard ratio for "medium" cumulative exposure [Fryzek et al. 2004a,b] is in the draft and asks that hazard ratio for "high" cumulative exposure group be added.
Response: Added.

ACC-30: requests revision of lines 704-705, lack of exposure-response relationship in Boffetta et al. [2004], second point in sentence.
Response: Revised text as suggested; quoted Boffetta et al. [2004].

ACC-31: about heterogeneity by country in Boffetta et al. 2004.
Response: Added: "…heterogeneity by country, which the authors thought should be explained by chance and differences in effects of confounders (see next item), rather than factors of TiO_2 dust exposure,…"

ACC-32: 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. 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.
Response: Information checked and Appendix C revised in accordance with the reviewer's comment.

ACC-33: requests additions to section 2.3 (epi summary) of 1) result from Boffetta et al. [2004] study of lower than expected deaths from nonmalignant respiratory disease, and 2) that Boffetta et al. would have discussed pneumoconiosis deaths in the same manner that they focused on pleural plaques and thickening.
Response: Added the requested result to text description and section 2.3.

Regarding request 2), cannot speculate about what Boffetta et al. would have included in their paper. Added to summary that Boffetta et al. discussed pleural cancer deaths and quoted authors' sentence that mortality data may not be very sensitive to risks of chronic respiratory disease.

ACC-34: Asks for revision because "Contrary to what NIOSH indicates in the draft CIB, the Boffetta, et al. (2004) study has reasonable power to detect a dose response…"(comment continues for two paragraphs).
Response: This comment was helpful and we have revised the document accordingly.

ACC-35: requests deletion of a specific case report of a worker fatality described in lines 477-479 because of "insufficient information on the role that TiO_2 played".
Response: The report is part of published information describing cases of adverse health effects (Poison Control Centers Annual Report 2001). Case reports may lack detail, but can provide information for further investigation. Revised these lines to include: 1) name and purpose of the surveillance database that contained the fatality abstract, 2) a sentence that NIOSH has no further information, and 3) that the abstract does not indicate whether an autopsy was conducted.

ACC-36: Many of the animal studies … have been misrepresented or misinterpreted by NIOSH. For example, discussion of two studies by Bermudez et al. does not describe rat unique lung response compared to mouse or hamster and that it is likely the responsible mechanism for lung tumor development in rats.
Response: Several specific differences in the rat vs. mouse and hamster lung responses in the Bermudez et al. studies were cited in the draft CIB. This discussion has been revised to clarify these findings.

ACC-37: The draft CIB ignores a number of studies that are extremely critical. In particular … NIOSH has failed to consider two important studies by Nikula et al. …
Response: Nikula et al. 1997 and 2001 did not study TiO_2 but coal dust and diesel exhaust particulate. However, NIOSH has added discussion of these studies in Section 3.4.2 in the context of particle kinetic mechanisms in rat and human lungs.

ACC-38: 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….
Response: Other than the Nikula et al. studies (which did not investigate TiO_2, but have been added for the mechanistic information), the reviewer has not provided any other studies that NIOSH did not include. In response to the reviewer's two points: (1) Appendix C of the draft CIB provides a quantitative analysis showing that the rat-based risk estimates for TiO_2 are not inconsistent with the human study results; and (2) the reviewer has not provided any references to support their claim that the rat and human lung responses are different. Cited in Section 3.5.2 of the draft CIB are several studies

that show that the rat and human lung responses to inhaled particles are qualitatively similar in several steps, including impaired lung clearance, pulmonary inflammation inflammation, oxidative damage, and cell proliferation. The draft CIB also explains that although the data are limited for quantitative comparison of rat and human dose-response relationships to inhaled particles, the data that are available (e.g., crystalline silica and diesel exhaust particles) suggest that the rat is no more sensitive to these effects than humans. Additional references have been added to provide more information on this topic.

ACC-39: In Section 3.1.1 in the draft CIB, NIOSH states that TiO_2 may have genotoxic potential under some conditions. This conclusion is not representative of the large majority of studies .... [the reviewer cites an unpublished report on the opinion of a scientific group regarding TiO_2 in cosmetic and nonfood products. The affiliation of the group and the source of the request to review TiO_2 are not listed in the report].
Response: The studies cited in Section 3.1.1 are based on a literature search of articles published after 1989 (these prior studies are summarized in IARC 1989, as cited in Section 3.1.1). Many of the references cited in the unpublished report (referenced in ACC comments) appear to be unpublished company studies. Of the published studies, only two were published after 1989 (Myhr et al 1991 and Tripathy et al. 1990) (a third study, Nakagawa et al. 1997 is already cited in the draft CIB). The Myhr et al. and Tripathy et al. studies, which tested many substances including TiO_2, were reviewed and added to Section 3.1.1. The summary was modified slightly to state that the scientific literature suggests TiO_2 may be genotoxic under some conditions, but not mutagenic in the assays used. The mechanism of the genotoxicity (DNA damage) appears to involve the production of reactive oxygen species, as explained in the revised section.

ACC-40: Studies cited in Section 3.21 and elsewhere in CIB fail to identify the crystal structure of the TiO_2 particles.
Response: Additional information, where available, was added for the particle characteristics in the studies cited.

ACC-41: In lines 815-821, the reviewer requests NIOSH to state that the fine TiO_2 studied was rutile, and to mention that the purpose of the Warheit et al 1997 study was to show that inhalation of high concentrations of low toxicity dust caused impaired lung clearance and persistent inflammation in rats, a non-chemical specific response to particle overload.
Response: Revised to include this information.

ACC-42: Additional physical characterization of the ultrafine TiO_2 in Baggs et al. 1997 should be added.
Response: Additional available information was added.

ACC-43: On line 832, change 52 to 32, provide additional physical characterization information, and add authors' conclusions.
Response: Information checked and revised as needed.

ACC-44: Draft CIB has inadequate physical characterization of the fine TiO_2 and summary of key findings in Warheit et al. 2005.
Response: Information checked and revised as needed.

ACC-45: NIOSH states on lines 866-867 that "[i]haling 50 or 250 mg/m^3 fine TiO_2 for 13 weeks caused histopathological changes consistent with alveolar epithelial cell hypertrophy and hyperplasia in all species [Everitt et al. 2000]. This study summary is "erroneous" and NIOSH should "correct" the draft CIB using text from Bermudez et al. 2000.
Response: Lines 866-867 in the draft CIB are not erroneous and are based directly on Everitt et al. 2000, p. 282: "In all three species, high particulate burdens were associated with significant intraluminal inflammatory changes characterized by proliferative changes of the alveolar epithelium....These lesions consisted primarily of alveolar type II cell hypertrophy and hyperplasia." The discussion of the studies reported by Everitt et al. [2000] and Bermudez et al. [2002, 2004] has been revised to provide additional information and clarification.

ACC-46: On lines 866-822, NIOSH misrepresents the findings of Bermudez et al. 2002, which concluded that there are significant rodent species differences in lung responses to particle overload, and that the rat develops a unique adverse response....
Response: This summary is based on results cited in Bermudez et al. 2002. Several differences in the rodent species responses to inhaled TiO_2 are described in this section of the draft CIB, for example, "In rats, but not mice and hamsters, these foci of alveolar epithelial hypertrophy became increasingly more prominent with time, even after cessation of exposure, and in the high dose rats progressed to bronchiolization of alveoli (metaplasia) and fibrotic changes with focal interstitialization of TiO_2 particles (Bermudez et al. 2002)." Additional information has been added describing the lung particle clearance and pulmonary responses in these rodent species.

ACC-47: "NIOSH also errs by failing to discuss in Section 3.2.3 the Bermudez et al. 2004 study" of ultrafine TiO_2.
Response: Bermudez et al. 2004 was discussed in Section 3.4 of the draft CIB, but was inadvertently omitted from Section 3.2.3. It has been added to that section as well.

ACC-48: "In sum, NIOSH misinterprets the conclusions of ... Bermudez et al. (2002) ... and Bermudez et al. (2004)."
Response: This comment repeats the previous comments.

ACC-49: Line 887: "ultrafine TiO_2" in Heinrich et al. (1995) study should be better characterized in terms of size and crystal structure.
Response: Table 4-4 provides complete information provided in the Heinrich study, including the size of airborne particles (MMAD and GSD) and primary particles, and the crystal structure (80% anatase, 20% rutile). Particle characterization provided in the publications has been added in Chapter 3 as well.

ACC-50: Line 890: the word "carcinomas" should be replaced with "tumors" inasmuch as most of the described carcinomas likely were keratin cysts.

Response: The reviewer does not provide any basis for their assumption about the tumor types reported in that study. However, the suggested change was made because titanium tetrachloride is not discussed further in this document, and "tumors" is a broader term which includes carcinomas.

ACC-51: 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 [specific text was included].
Response: These lines in the draft CIB provide an accurate summary of the findings by Boorman et al. (1996). The additional paper (now published) by Warheit and Frame (2006) has been added to the paragraph.

ACC-52: Lines 915-924: Clarify exposure regimen and description of ultrafine TiO_2 in Heinrich et al. (1995).
Response: Done.

ACC-53: Lines 928-930: NIOSH should state that under the conditions of the study, exposure to ultrafine TiO_2 particles in mice was negative.
Response: This information is already provided on lines 928-930 of the draft CIB: "This exposure did not produce [elevated] tumors in NMRI...."

ACC-54: Lines 928-930: A section summary of pulmonary effects should be provided.
Response: A brief summary was added.

ACC-55: "NIOSH inexplicably omits other negative oral toxicity studies in TiO_2. For example, Bernard et al. ..."
Response: The Bernard et al. 1990 study is on TiO_2-coated mica; however, it is now briefly mentioned. A follow-up literature search on titanium dioxide and oral toxicity resulted in one additional (acute) oral toxicity study of TiO_2, by Wang et al. 2007, which was published after the draft CIB. It has also been added to Chapter 3.

ACC-56: The statement "on line 950 '[b]oth fine and ultrafine TiO_2 are capable of eliciting pulmonary inflammation in the rat'....is overly broad and inaccurate because any particle in sufficient doses can elicit pulmonary inflammation." Statement does not distinguish short-term and long-term pulmonary inflammation, and does not specify particle sizes and crystal structure of fine and ultrafine TiO_2.
Response: This introductory sentence in Section 3.4 of the draft CIB is accurate, and this section goes on to provide additional specific information regarding the rat lung responses to ultrafine and fine TiO_2 at short and long-term exposures. Additional information on particle size and crystal structure has been added where available, and the discussion has been revised to summarize and interpret the findings of the preceding sections.

ACC-57: NIOSH misrepresents and misinterprets the Bermudez et al. (2004) study, which found significant species differences in lung responses to ultrafine TiO_2.... [re: Section 3.4.1].

Response: Comparison of the rodent species lung responses to TiO_2 has been described in the draft CIB. The findings cited in Section 3.4.2 of the draft CIB are from these reference sources:

Lines 958-962: "Rats and mice inhaling 10 mg/m^3 ultrafine TiO_2 had impaired clearance after ~3 months of exposure, which persisted with or without exposure cessation. In contrast, no impaired clearance was seen in hamsters" – from pp. 347 and 350 of Bermudez et al. [2004] and from p. 543 in Heinrich et al. [1995]. [This sentence has been revised to clarify which findings are from each study].

Lines 962-967: "Rats and mice inhaling 10 mg/m^3 ultrafine TiO_2 had significantly elevated BALF cells; macrophage and neutrophils returned to control levels in rats at 13 and 26 weeks post-exposure, but remained elevated in mice through 52 weeks post-exposure" – from p. 351 and Figure 3 of Bermudez et al. [2004].

Lines 969-975: Altered proliferation of alveolar epithelium was observed in both rats and mice inhaling 10 mg/m^3 ultrafine TiO_2; cell replication was significantly increased at 13 and 26 weeks post-exposure in mice, and at end of exposure in rats (exposed to 2 and 10 mg/m^3), persisting at 4 and 13 weeks post-exposure (10 mg/m^3) – from p. 353 and Table 4 of Bermudez et al. [2004]. [On line 971 of draft CIB, "fine" TiO_2 was corrected to "ultrafine."]

ACC-58: The Maronpot et al. (2004) study requires much more detailed explanation. The data do not support the conclusion that "the pulmonary adenomas and adenocarcinomas seen in TiO_2-exposed rats are similar to pulmonary neoplasms in humans." The draft CIB ignores the guidance given in the ILSI document, wherein fundamental distinctions are made between the lung tumors observed in humans and those observed in rats.

Response: In contrast to the reviewer's interpretation of the ILSI [2000] report, the ILSI findings are consistent with the NIOSH discussion of rat and human lung tumors. According to ILSI [2000], in the Section entitled "What are the similarities and differences between rat lung tumors and lung tumors in humans?": "There are histopathologic similarities and differences between the lung cancer cell types observed in rats and humans.... The major cell types of human lung cancer are adenocarcinoma, squamous-cell carcinoma [and two types not seen in rats].... [M]ost cancers in rats exposed to PSPs are adenocarcinomas or squamous-cell carcinomas of the alveolar ducts. Furthermore, it is noteworthy that recently there has been a worldwide increase in the human lung adenocarcinomas in the bronchoalveolar region.... Therefore, alveolar adenocarcinomas should not be dismissed as being irrelevant to the human condition...."

Maronpot et al. [2004] and ILSI [2000] provides similar analyses. In the section entitled "Comparative Neoplastic Pathology," Maronpot et al. point out that some of the apparent difference in the bronchioloalveolar carcinoma incidences in rodents and humans can be explained by differences in terminology. They suggest a more accurate comparison would be to combine the adenocarcinomas and bronchioloalveolar carcinomas in humans, which would significantly reduce the apparent difference. Both ILSI and Maronpot et al. discuss the influence of cigarette smoking, which contributes

considerably to the differences in human vs. rodent tumor types. Maronpot et al. suggest that if the smoking-related tumor types were eliminated from the comparison, then the "major tumor subtypes in humans would be adenocarcinomas and bronchioloalveolar carcinomas, which would correspond very closely to the types of lung tumors occurring in rodents."

Citation of the ISLI reference and additional discussion based on the ILSI and Maronpot et al. articles has been added to this section.

ACC-59: The draft CIB should consider in Section 3.4.1 the forthcoming Warheit and Frame study....
Response: That paper has been added to Section 3.4.1

ACC-60: 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 (1997).... The Commission identified TiO_2 as a case where "rodent tumor responses have been shown to be irrelevant to humans or may occur at doses far exceeding any recognized humans exposures including workplace exposures."
Response: With regard to the statement that the rat lung tumor response is "irrelevant to humans," see NIOSH response to ACC-58. The statement that "doses far exceeding any recognized humans exposures including workplace exposures," would not necessarily apply to ultrafine TiO_2, given that (1) the current OSHA PEL for TiO_2 is 15 mg/m^3 (regardless of particle size), and (2) a statistically significant increase in adenocarcinoma and squamous cell carcinoma was observed in rats exposed to 10 mg/m^3 ultrafine TiO_2 (Heinrich et al. 1995).

ACC-61: Line 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.
Response: The reviewer's comment does not take into account the inconsistency in the cell proliferation and tumor findings for mice in the Heinrich et al. and Bermudez et al. studies, nor the difference in mouse strains used in those two studies. While both rats and mice had elevated alveolar cell proliferation in Bermudez et al. 2004; only rats had elevated lung carcinomas in Heinrich et al. 1995. Those results in mice are unexpected since cell proliferation is an important step in tumor development. A possible explanation for this apparent discrepancy is that the different strains of mice used in those two studies (B3C3F1/CrlBR in Bermudez et al and NMRI in Heinrich et al.) may have had different proliferative and tumorigenic lung responses to TiO_2. This information cannot be determined from those studies, however, because cell proliferation and tumor data were not both collected in the same study and mouse strain. This additional information has been added.

ACC-62: Lines 980-981: ... This statement is misleading because it fails to acknowledge overload concentrations or that the lung tumors were produced in rats exposed only to 250 mg/m^3.... 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.

Response: The reviewer is incorrect that lung tumors were produced in rats "exposed only to 250 mg/m^3." Rats exposed to 10 mg/m^3 ultrafine TiO_2 developed a statistically significant increase in the incidence of adenocarcinomas and squamous cell carcinomas (Heinrich et al. 1995, Table 10, p. 545). These rats also developed "slight to moderate interstitial fibrosis" (p. 544, Heinrich et al. 1995). An exposure concentration of 10 mg/m^3 of ultrafine TiO_2 is considerably lower than the mass doses of fine TiO_2 associated with overloading of lung clearance, and similar to potential occupational exposures (e.g., OSHA PEL is 15 mg/m^3 TiO_2, regardless of particle size).

ACC-63: Lines 988-990: The use of the term "adenocarcinomas" is inaccurate for the Lee et al. (1985) study…

Response: This sentence summarizes the tumor types observed in rats exposed to TiO_2 from all the chronic inhalation studies. Detailed information on the tumor types observed in each study was provided earlier (Section 3.3.1 of the draft CIB), and a statement has been added to refer the reader to that section (now Section 3.2.5).

ACC-64 (1): NIOSH's review of the scientific literature on lung overload "ignores completely" the Nikula et al. 1997 and 2001 studies….

Response: Although the Nikula et al. 1997 and 2001 studies pertain to coal dust and diesel exhaust particulate, and not to TiO_2, these studies have been added to Chapter 3 in the context of particle kinetic mechanisms in rat and human lungs.

ACC-64 (contd-2): The Nikula et al. (1997) study compared the anatomical pattern of particle retention and tissue response of rats and monkeys exposed chronically (for 24 months) to high occupational concentrations of poorly soluble particles…. Differences in particle retention pattern and responses in the lungs were noted between rats and monkeys.

Response: It is incorrect to state that the exposure concentration of 2 mg/m^3 is a "high occupational concentration of poorly soluble particles." By comparison, the TiO_2 PEL is 15 mg/m^3, and the PNOR PEL is 5 mg/m^3. Thus, the Nikula et al. 1997 findings based on only 2 mg/m^3 may not be relevant to workers exposed to higher dust concentrations over a working lifetime. In addition, the 2 year exposure is relatively short compared to a monkey's lifetime or to a human-equivalent working lifetime.

ACC-64 (contd-3): The Nikula et al. (2001) study used morphometry to assess particle retention in histological sections from rats and humans. Rats exposed to diesel exhaust particulate (DEP) for 24 months at 0.35, 3.5, or 7.0 mg/m^3 were compared to nonsmoking coal miners. The authors of that study found that rats retained a higher proportion of particles in the alveolar lumen than in the interstitium, whereas coal miners retained more particles in the interstitium. The differences in particle retention patterns may account for differences in lung response in rats and humans.

Response: Nikula et al. [2001] report differences in the percentage of particles observed in the alveolar vs. interstitial region of the lungs in rats exposed to DEP vs. miners exposed to coal dust. This study did not report lung responses. Inference is also difficult

because two different particle types (DEP vs. coal dust) were compared in lungs of rats and humans, and because the no lung dose data were available in humans.

ACC-64 (contd-4): Due to these omissions, NIOSH appears to have misinterpreted the apparent paradox in lung responses between rats and humans…. "The pulmonary response of humans and monkeys to inhaled diesel exhaust and coal dust is significantly different from rats"….
Response: Given the differences in particle size, surface area, and surface reactivity between diesel exhaust and coal dust, and the limited lung dose data in the Nikula et al. 1997 and 2001 studies, the reviewer's comparison is not necessarily valid. Other studies have shown that rats and humans have qualitatively similar responses to inhaled poorly soluble particles (reviewed in Section 3.5.2 of the draft CIB).

ACC-65: 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." 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.
Response: The reviewer has misinterpreted that sentence. The point is that the rat pulmonary inflammation and lung tumor responses to both fine and ultrafine TiO_2 is well described statistically using the same dose-response relationship, regardless of whether the dose had overloaded lung clearance. This sentence has been clarified to avoid confusion. With regard to the reviewer's "two reasons": (1) no basis is provided for the statement that rat lung tumors are threshold mediated; and (2) the statement that "particle overload is a prerequisite…" does not account for the elevated tumor response in rats exposed to 10 mg/m^3 ultrafine TiO_2, which is considerably lower than the mass doses of fine TiO_2 associated with overloading of lung clearance in rodents.

ACC-66: Lines 1016-1017: The statement that "mice and hamsters are known to give false negatives in bioassays for some human carcinogens" is misleading. No examples are provided....none of the rodent species or the large mammalian species develop lung tumors in response to extreme particle overload.
Response: A reference has been provided for this statement (Mauderly 1997), and the sentence revised to clarify that it refers to inhaled particles that have been classified as human carcinogens with limited or sufficient evidence.

ACC-67: Lines 1020-1022: NIOSH asserts that "evidence from known carcinogens, such as asbestos and crystalline silica suggests that rats are no more sensitive to the [carcinogenic effects of TiO_2] than humans." The Panel believes that this assertion is flawed…. Additionally, no data suggesting that rats are no more sensitive to carcinogenic effects than humans is offered.
Response: This sentence has been revised to include references of the qualitative and quantitative comparisons of the rat and human lung responses to inhaled particles.

ACC-68: 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....
Response: Section 3.4.3 of the draft CIB deals with dose metric, and therefore a discussion of the relationship between inflammation and other lung responses is not relevant here. Additional information regarding species responses to particles in the lungs has been added in the appropriate section (Section 3.5 in revised CIB).

ACC-69: Lines 1051-1052: NIOSH should make clear that the situation described – where a "sufficient particle surface area dose of fine TiO_2 would be expected to carcinogenic" – is one where gross overload exists.
Response: Additional information has been added to clarify that for fine TiO_2, elevated lung tumors occurred at a mass dose associated with overloading of lung clearance, while for ultrafine TiO_2, elevated lung cancer in rats was observed at a mass dose below that associated with particle mass-based overloading. Some evidence suggests the impaired clearance in rats exposed to ultrafine TiO_2 may involve mechanisms other than high-dose overloading, such as altered alveolar macrophage function (phagocytosis or chemotaxis) (Renwick et al. 2001, 2004) related to the increased surface area of ultrafine particles (Tran et al. 1999).

ACC-70: In the first paragraph of Section 3.5.2, 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_2 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.
Response: The reviewer provides no evidence to support the statement that humans and rats have "fundamental differences" in response to inhaled dust, or that "the lung inflammatory response in humans to dust concentrations is relatively muted." Section 3.5.2 of the draft CIB cites several studies of workers in dusty jobs showing significant pulmonary inflammation. Studies cited in that section also show that the many of the human and rat responses to inhaled particles are qualitatively similar, including the role of pulmonary inflammation in the development of particle-related lung diseases in workers. Case studies of TiO_2 workers have reported lung responses indicative of inflammation, including alveolar proteinosis and interstitial fibrosis (also cited in Section 3.5.2 of draft CIB). As stated earlier, the Nikula studies (which described diesel exhaust particulate and coal dust) have been added to Chapter 3 in the context of the kinetic mechanisms of particle retention in rats and humans.

ACC-71: Line 1074: Reviewer disagrees with comparison of the lipoproteinosis observed in a worker with high pulmonary deposition of TiO_2 and that observed in rats exposed to TiO_2, and considers the statement to be "unjustified and misleading" "without evidence that the worker had not been exposed to silica or any other particle."
Response: This finding is from Keller et al. 1995, who measured titanium levels in a painter's lung tissue that were "among the highest recorded." The "titanium-containing

particles were consistent with titanium dioxide" and were the major type of particle found in the patient's lungs.

ACC-72: Lines 1082-1084: Not clear whether NIOSH is referring to the alveolar metaplasia in the three human patients who had a common exposure to TiO_2 (and any other substances). Absent this, there is an insufficient basis to justify conducting a comparative risk assessment for rats and humans.
Response: NIOSH cites studies describing alveolar metaplasia in three human patients with inhalation exposure to TiO_2 (lines 1079-1081) and rats (lines 1081-1082). On lines 1082-1084, NIOSH recognizes that a detailed evaluation of this response in rats and humans has not been performed. In addition to these limited data of alveolar metaplasia in both rats and humans exposed to TiO_2, Section 3.5 of the draft CIB cites studies showing similarities in the human and rat lung responses to inhaled poorly soluble particles such as TiO_2. Expert advisory panels have concluded that chronic inhalation studies in rats are the most appropriate tests for predicting the inhalation hazard and risk of fibers to humans [Vu et al. 1994], and that in the absence of mechanistic data to the contrary, it is reasonable to assume that the rat model can identify potential carcinogenic hazards of poorly-soluble particles to humans [ILSI 2000].

ACC-73: 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_2 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_2 exposure does not result in chronic inflammation, however, and there is no epidemiological evidence of fibrosis, and ultimately, lung tumors.
Response: The data available for quantitative comparison of dose-response relationships in humans and rodents exposed to inhaled poorly soluble particles and fibers are limited and include the two examples cited. Another example, which has been added to this section, is diesel exhaust particulates. These various poorly-soluble materials elicit some of the same responses in the lungs, in particular chronic inflammation, which appears to play an important role in subsequent cancer and noncancer responses, as described in Section 3.5. The epidemiological data of TiO_2 workers do not show an elevated lung tumor response, although the rat-based risk estimates for TiO_2 are also not inconsistent with the human study results, as shown in Appendix C of the draft CIB.

ACC-74: Re: Figure 3-3.... Study termination time is not taken into account. "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 these tumors." ... Nikula et al. 2000 discussed termination time with regard to interpreting study results.
Response: The exposure duration in each of these studies was two years, although as noted, the rats in the Lee et al. 1985 study were killed at the end of exposure, while those in the Heinrich et al. 1995 study were killed 6 months post-exposure. This increases the likelihood that either exposure- or age-related tumors would be more likely to be observed in the Heinrich et al. study than the Lee et al. study. The reviewers' comment that the tumors observed in the Heinrich study are "ones of old age" ignores the statistically significant increase in adenocarcinoma and squamous cell carcinoma in that

study (i.e., the unexposed or control rats did not experience this elevation in lung carcinoma). Additional discussion of study termination time has been added.

ACC-75: 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.
Response: Figure 3-3 already plots the data for either "all tumors" or "tumors excluding the keratinizing cystic tumors," based on the findings of earlier re-analyses of the Lee et al. 1985 tumor data (discussed in Section 3.3.1 of the draft CIB), which had arrived at similar conclusions to those in the Warheit and Frame study). In Figure 3-4 it was not feasible to plot these responses separately because some of the studies did not report those tumor types separately.

ACC-76: A multi-part comment (pp. 38-42) pertaining to the examples cited in the TiO_2 CIB of coal dust and other PSLT data.
Response: Coal dust is one of the examples cited on respiratory disease mechanisms of inhaled poorly soluble low toxicity particles (PSLT), a class of particles that includes TiO_2. This TiO_2 CIB focuses primarily on studies of TiO_2 exposure in humans and animals. However, studies of other PSLT particles are also cited which provide additional scientific evidence of the mechanisms of the PSLT-induced lung diseases. This level of discussion is within the scope of this TiO_2 CIB, whereas expanding the discussion to include a detailed review and evaluation of all human and animal PSLT data, including coal dust, would be beyond the scope of this document.

ACC-77: Request that NIOSH include epidemiology for all PSLT particles in its analysis.
Response: The RELs in this document were based solely on the data collected for TiO_2. Although additional studies on PSLTs might lend support to the proposed mechanism of action and perhaps statistical power to the analyses, the Institute instead decided that the complexity of considering multiple particles in a single document introduced too many variables into the analyses. Therefore, the decision was made to limit this document to TiO_2. The Institute notes that employers are welcome to use the RELs for TiO_2 as a surrogate for other PSLTs where appropriate, if that makes sense for their work situation in the absence of particle and/or chemical specific information.

ACC-78: Threshold models are needed to reflect mechanism of action conclusions.
ACC-79: NIOSH should consider a threshold modeling approach.
Response: NIOSH has considered the use of threshold models for both the rat lung inflammation data and the rat lung tumor data. As discussed in the revised CIB, new data not included in the draft CIB are inconsistent with a threshold model for the inflammatory response. Also, a recently published analysis of the rat tumor data for TiO_2 (Dankovic et al. 2007) has shown that a non-linear (i.e., quantal-quadratic) model for the tumor response cannot be rejected. The quantal-quadratic model does not include a threshold parameter. Therefore NIOSH does not agree that threshold models are needed.

ACC-80: Linear extrapolation from the 1/10 BMD is not an appropriate approach.
Response: This approach is no longer used in the revised CIB.

ACC-81: The linearized multistage model is also very sensitive to the high dose response and should not be relied upon.
Response: The linearized multistage model is no longer used as a basis for risk estimates in the revised CIB. The multistage model used in the model average is not linearized. The upper bound is estimated by bootstrapping.

ACC-82: The Panel also urges NIOSH to consider nonlinear models such as the multistage, Gamma and Weibull model.
Response: The multistage, log-probit and Weibull models, all of which are nonlinear, are all included, with appropriate weighting, as components of the model average now used as a basis for risk estimation in the revised CIB.

ACC-83: The Panel urges NIOSH to factor in the estimates from the BMA approach more favorably in the CIB.
Response: Model averaging is now used as the basis for the risk estimates presented in the revised CIB.

ACC-84: Compare excess risks in the region of the dose response curves where neither species shows any evidence of effect, *i.e.*, in the region below the threshold.
Response: As noted in the response to ACC comments 78 and 79, NIOSH does not agree that a threshold has been demonstrated for TiO_2. However, if such thresholds were demonstrated for both rats and humans, as ACC has posited, then the excess risk for either species, below the threshold, would by definition be zero.

ACC-85: NIOSH should not favor rat data over human data simply because there is no evidence of dose response in the human studies.
Response: NIOSH did not favor rat data over human data a priori. However, the estimates of excess risk based on the rat studies were substantially more precise. If the epidemiological data had sufficient statistical precision to rule out the risks estimated from the rat data, NIOSH would have given precedence to the human data.

ACC-86: The Panel supports NIOSH's determination that there is insufficient evidence to designate TiO_2 as a "potential occupational carcinogen."
Response: NIOSH has maintained the designation "potential occupational carcinogen" for ultrafine TiO_2 but concludes there are insufficient data to similarly classify fine TiO_2.

ACC-87: ACC states that the proposed sampling method recommended by NIOSH has not met prescribed criteria for accuracy and reliability and therefore NIOSH should not be recommending the sampling and analysis of airborne exposures to TiO_2.
Response: NIOSH is recommending the use of Method 0600 for the measurement of airborne respirable particles and agglomerates of TiO_2. This method is being recommended as a surrogate for the measurement of particle surface area which cannot be performed at this time until adequate sampling instruments have been developed and tested. Method 0600 has been field tested and validated for exposures to other respirable (e.g., metal) particles and therefore is expected to meet the same accuracy and reliability requirements for measuring TiO_2 aerosols.