NIOSH Response to Reviewers' Comments on Draft NIOSH Current Intelligence Bulletin

Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide (11/22/05)

This Response to Comments Document (RCD) addresses written comments submitted to NIOSH from the public and a panel of five external peer reviewers during the public comment period. The comments and other information are posted on the NIOSH Internet Docket Office website in Docket 033: http://www.cdc.gov/niosh/docket/

Responses from NIOSH are organized by document chapter; comments not specific to one chapter are in "Overall Comments". Comments are presented "as is".

Comment sources are coded as:
DECOS (Dutch Expert Committee on Occupational Standards): Coenen (Comments from 3 members of DECOS, Dr. P(eter) Boogaard, Prof. Dr. P(aul) Borm, and Dr. G(erard) Swaen, via Gezondheidsraad/Health Council of the Netherlands)
ACC: Bergeson (American Chemistry Council Titanium Dioxide Panel)
NPCA: Irish (National Paint and Coatings Association)
CPMA: Robinson (Color Pigments Manufacturers Association, Inc.)
BD: Forrest (Bacou-Dallox)
BMT: Burdge (BMT Designers and Planners, Inc.)
OBWC: Rourke (Ohio Bureau of Workers Compensation)
AC: Calpin (Analytics Corp.)
EX1 through EX5: Expert Peer Review Panelist 1, 2, 3, 4, or 5

The submission from Causation Ltd. UK (link in table below) does not contain reviewer comments about the document (sent coefficients for analyses) and therefore is not included in this response document.

Submissions from the Public in Order of Receipt
Submission to the docket from Coenen (Gezondheidsraad Health Council of the Netherlands) (4 pages, 185kb)
Submission to the docket from Bergeson (American Chemistry Council Titanium Dioxide Panel) (163 pages, 33,600kb)
Submission to the docket from Irish (National Paint and Coatings Association) (5 pages, 296kb)
Submission to the docket from Robinson (Color Pigments Manufacturers Association, Inc.) (13 pages, 470kb)
Submission to the docket from Forrest (Bacou-Dalloz) (1 page, 26kb)

Submission to the docket from Burdge (BMT Designers and Planners, Inc.) (1 page, 32kb)

Submission to the docket from Rourke (Ohio Bureau of Workers Compensation) (1 page, 40kb)

Submission to the docket from Calpin (Analytics Corp) (1 page, 29kb)

Submission to the docket from Tomenson (Causation Ltd, UK) (5 pages, 29kb)

Review from external reviewer 1 (8 pages, 490kb)

Review from external reviewer 2 (6 pages, 268kb)

Review from external reviewer 3 (10 pages, 570kb)

Review from external reviewer 4 (7 pages, 332kb)

Review from external reviewer 5 (5 pages, 219kb)

Overall Comments:

BMT: To evaluate potential employee exposures to nano-particles air sampling data in traditional units, weight per unit air volume is incorrect. The recommended exposure limit must be related to surface area of the airborne nano-particles.

Response: Ideally, based on the correlation of risk with surface area, NIOSH agrees that it would be better to base the RELs on surface area than mass. However, current technology limits the ability to routinely measure particle surface area in the workplace. Therefore, NIOSH has developed separate RELs for fine and ultrafine TiO_2 particles. Although not an ideal solution, NIOSH has determined that this is workable for routine workplace measurement.

There is still some concern about particles smaller than 100 nm, however. The REL for ultrafine TiO_2 may not be sufficiently protective for commercially-produced nanoparticles of sizes smaller than 100 nm. RELs based on surface area would solve this problem, but the technological problem of no good method for routine workplace measurement would remain. Therefore, NIOSH did not change its recommendations.

BMT: Evaluating exposures to nano-particles in micrograms per cubic meter of air does not adequately indicate the hazard. The hazard evaluation must be related to surface area which can accurately affect the risk from exposure.

Response: The risk assessment is based on the surface area of the particles predicted to be deposited in the lung. Because of the practicalities of dust measurement in the

workplace, rather than base recommendations on surface area, NIOSH recommended separate mass-based exposure limits for fine and ultrafine particles.

DECOS (member 1): The NIOSH draft on TiO_2 (fine, ultrafine) is an innovative effort to link animal data to human epidemiological outcomes, in order to derive exposure standards to both fine and ultrafine TiO_2. As such this report is the first to classify ultrafine TiO_2 along with its fine counterpart. The report concludes that no clear evidence of elevated risks of lung cancer is found in production workers exposed to (fine) TiO_2 dust, and is conform the recent (February 2006) IARC evaluation. The authors then focussed on the animal responses induced by TiO_2, thereby focussing on inhalation studies and the most relevant metric of exposure. The gravimetric standards derived more or less reflect the surface driven inflammatory and carcinogenic animal response induced by both species of TiO_2. In its exercise NIOSH assumes that the tumourigenic effects of TiO_2 exposure in rats are not chemical specific but occur through inflammation as a secondary genotoxic mechanism. Lung tumour prevalence and lung inflammation in the rat are taken as crucial response to derive an equivalent dose in human to derive a recommended exposure limit in human (Figure 4-1). In its BMD model (Figure 4-4) to relate surface area dose to lung tumours, only inhalation studies were used (Lee et al, 1985; Heinrich et al, 1995).

Response: NIOSH concurs with the commenter on this point.

OBWC: With regard to removing any warning about titanium dioxide having carcinogenic properties: either it does, or it doesn't, and we rely on your agency to be straight shooters. If you are proposing a trade-off in the form of removing the warning in exchange for allowing publication of the document, then I request that you don't do it. First of all, it's simply not right. Secondly, when I make recommendations for exposure controls to employers and tell them that the exposure in question may be carcinogenic, they take my advice more seriously.

Response: As detailed in the revised CIB, NIOSH believes that there is sufficient evidence to consider ultrafine TiO_2 as a potential occupational carcinogen. However, the currently available data for fine TiO_2 are insufficient to classify it as a potential occupational carcinogen.

NPCA: The most significant flaw in this document is its failure to produce adequate support for characterizing any observed health effects as peculiarly resulting from exposure to fine and/or ultrafine TiO_2 particulates, rather than to small particulates in general. As a result, we are unconvinced that there is sufficient evidence to ascribe any detrimental health effects to exposure specific to TiO_2 particulates. Although NIOSH has classified TiO_2 as a potential occupational carcinogen in 1988, based on observations that TiO_2 caused lung tumors in rats in a long-term, high-dose bioassay, the International Agency for Research on Cancer (IARC) currently classifies TiO_2 only in Group 3 ("limited evidence of animal carcinogenicity and inadequate evidence for human carcinogenicity"). Given the ambiguous state of the scientific evidence pertaining to the carcinogenicity of TiO_2, it is incumbent upon NIOSH to provide more specific information that would tie any observed health effects to TiO_2 specifically, rather than

merely to fine or untrafine particulates, which is, of course, an entirely different matter. Given the failure to meet this fundamental requirement, it is our view that this study has failed to meet the basic prerequisite for scientific and legal validity, and that in its current state, NIOSH cannot validly rely upon it as a basis for a recommended exposure limit of any kind.

Response: NIOSH recognizes that the carcinogenicity observed in the animal studies may well be an irritant cascade produced by the physical form of TiO_2 and not related to the chemical nature of TiO_2. The Institute's position in the draft CIB was that the data collected for TiO_2 likely had implications for the potential carcinogenicity of *other* poorly soluble, low toxicity particles. However, discussion of all potential exposures to poorly soluble, low toxicity particles was beyond the scope of this document and may be considered separately in future NIOSH deliberations.

NIOSH objects to the characterization that the observed health effects were not tied to TiO_2. In fact, the reported health effects upon which the risk assessment was conducted were observed in animals exposed to fine and ultrafine TiO_2 particles, and *not* to a non-specific mixture of uncharacterized particles. Therefore, it is with confidence that the Institute linked the health effects with exposure to TiO_2.

NIOSH would also note that since the draft CIB was produced, IARC has revised its carcinogen classification for TiO_2. The current classification is Group 2B (possibly carcinogenic to humans.) IARC determined: There is *inadequate evidence* in humans for the carcinogenicity of titanium dioxide. There is *sufficient evidence* in experimental animals for the carcinogenicity of titanium dioxide.

NPCA: Additionally, even assuming for the sake of argument that any observed health effects can be ascribed to TiO_2, the NIOSH CIB insufficiently characterizes the issue of particle size distribution (fine versus ultrafine). Accordingly, it is incumbent upon NIOSH to provide additional information on this point. Since, as noted, the exposure data for nano-sized TiO_2 particles reveals that any relevant health effects derive not from TiO_2 specifically, but from fine and ultrafine particulates in general, all affected parties need clarification about whether this document will ultimately come to represent NIOSH's approach for all inert ultrafine particulates not otherwise addressed by specific occupational exposure standards.

Response: Although NIOSH has determined that the findings made in the TiO_2 CIB likely have implications for exposures to other poorly soluble, low toxicity particles, the Institute has not yet conducted sufficient analysis to make recommendations pertaining to all poorly soluble, low toxicity particulates in the workplace. That analysis is beyond the scope of the current document although NIOSH may address that in future deliberations.

It is unclear how NIOSH could further characterize particle size distribution to address the commenter's concerns. The Institute has provided a sampling protocol that will aid employers in characterizing the particle size distribution for their workplaces. In addition, recognizing that sampling technology is not yet available to routinely measure particle

surface area in the workplace, NIOSH has proposed mass-based RELs, which while not ideal, do much to address concern for the differential potency of fine and ultrafine TiO_2.

NPCA: As an industry that is a significant user of TiO_2, we believe the CIB fails to account for the absence of reported health impacts and other epidemiological evidence of risk to our worker population (and many other similar industries) from these particulates. In our manufacturing environments TiO_2 (as well as many other powders and pigments of varying particle distributions) have historically been evaluated and properly managed to comply with exposure limits for respirable or total dust (particulate). When proper ventilation and/or PPE are used, the lack of health impacts appears to indicate that these existing and available protection methods are already successfully serving to protect human health fully.

Response: NIOSH has addressed the epidemiological evidence in Chapter 2 of the CIB. Additionally, a statistical comparison of the animal and human data was made to determine whether the human data could rule out or call into question the risks estimated from the animal data. Details of this analysis are contained in Appendix F of the draft CIB and Appendix C of the final CIB. Results of that analysis indicated that the existing epidemiological data was not inconsistent with the risks calculated from the animal data.

CPMA: Entire submission (13 pages) relates to overall document and relevance to pearlescent pigments. See:

http://www.cdc.gov/niosh/docket/pdfs/NIOSH-033/Submissions/0033-051506-robinson_submission.pdf

Response: NIOSH has responded to the CPMA comments concurring with ACC in the responses to the ACC comments. Here the responses pertain to the direct CPMA comments only.

pigment revealed no adverse effects.[2] All the acute oral toxicity tests performed to date indicate LD50 values of greater than 5000 mg/kg.[3,4]

Response: Oral toxicity testing is not directly relevant to occupational inhalation exposures, particularly in the case of TiO_2 where the mechanism presumed to operate is inflammation followed by secondary genotoxicity. Therefore, the cited oral LD50 studies are not pertinent in this case. Attempts to get the cited reports from the commenter were unsuccessful, so NIOSH cannot comment further on the details of those reports.

free of impurities. Chronic health effects have not been identified as a result of exposure to pearlescent pigments containing titanium dioxide, this is despite many years of industry use. Any exposure to titanium dioxide in manufacturing processes which use pearlescent pigments would be controlled by existing regulations. Pearlescent special effect pigments used

Response: Anecdotal observation of industry use of a product is not a substitute for an epidemiological study. As described above, NIOSH conducted a statistical comparison of existing epidemiological studies with the animal studies to determine if the human studies could rule out risks as high as observed in the animal studies. This was not the case. Existing regulations for TiO_2 in the workplace allow substantially higher worker exposure than the NIOSH RELs described in the CIB. NIOSH does not concur with the commenter that existing regulations are sufficient to protect workers from exposure to TiO_2 particulates in the workplace, particularly ultrafine TiO_2.

It is our understanding that, after two years as a "high carcinogenicity concern" substance, titanium dioxide remains assigned to a priority candidate list. From this candidate list, NIOSH may determine to prepare a hazard identification document after which titanium dioxide may be assessed by the California Carcinogen Identification Committee. As discussed

Response: NIOSH is unclear as to the meaning of this comment. NIOSH does not maintain a list of "high carcinogenicity concern" substances nor a priority candidate list. NIOSH has prepared this CIB in response to a request from the Titanium Dioxide Panel of the American Chemistry Council (formerly the Chemical Manufacturers' Association) to reevaluate the evidence of carcinogenicity of TiO_2 after its 1988 determination that TiO_2 is a potential occupational carcinogen.

exposed to titanium dioxide. If no significant connection between higher concentration workplace exposures and lung cancer can be determined from four studies, there would appear to be little evidence to support the NIOSH assessment that titanium dioxide exposures pose a high concern warranting review and possible listing in the California Proposition 65 list of carcinogens. Particularly if we consider that ordinary exposures to consumers would be no more than a fraction of that experienced by workers in an epidemiological study.

Response: With regard to the epidemiological evidence, as explained above, NIOSH has evaluated the epidemiology and has conducted a statistical comparison with the animal data. NIOSH does not have a designation of "high concern warranting review and possible listing in the California Proposition 65 list of carcinogens." In addition, NIOSH is concerned solely with occupational exposures and not with exposures to consumers or the environment.

et al. (1978 and Mohr et al. (1984), all involved doses of titanium dioxide which were many times the allowable limit for nuisance dust exposures in the workplace. Such doses of any dust material are known to overwhelm the clearance

mechanisms which the animals use to clear particles from the lungs.

Response: NIOSH has a full discussion of lung overload issues in Chapter 3 of the CIB. NIOSH disagrees with the commenter that the doses in the animal study are irrelevant to predict the risks of occupational exposure for the reasons outlined in Chapter 3.

The additional studies reviewed in the Draft Bulletin indicate that, for both intraperitoneal injection experiments and high dose feeding studies there was no evidence of carcinogenic activity associated with titanium dioxide. Nor do the available studies for mutagenicity indicate that titanium dioxide poses any concern despite numerous studies.

Therefore, the Draft Bulletin fails to justify the NIOSH high level of concern for exposure to titanium dioxide. It is true that titanium dioxide is widely used in thousands of formulations and products. Since titanium dioxide has been used for over fifty years in so many applications without significant concern, and despite a number of workplace studies, there is little evidence which in any way questions the safety of this extremely important compound.

Response: NIOSH concurs with the commenter that TiO_2 has not been shown to be carcinogenic by oral or i.p. administration. However, inhalation of fine and ultrafine TiO_2 in rats clearly demonstrated tumorigenic response. For workers exposed to TiO_2 dust, inhalation is the key route of administration.

The NIOSH Data Draft Bulletin is contradicted by the ACGIH Assessment for titanium dioxide. The ACGIH monograph for titanium dioxide, dated 2001, reviewed the same body of evidence that the NIOSH has described in its Draft Bulletin. ACGIH

Response: NIOSH is aware of the ACGIH assessment of the TiO_2 literature. NIOSH has come to a different conclusion, supported by the discussions in Chapters 2, 3 and 4 of the CIB. TiO_2 is under study by the ACGIH as of January 1, 2009 [ACGIH 2009].

these pigments. As a result, no exposure in use has any potential to approach nuisance dust levels. Labeling or warning language involving extremely high levels of dust which are not possible in use would lead to unwarranted confusion. Similarly,

Response: NIOSH agrees with the commenter that there are applications of TiO_2 which have less potential for inhalation exposure. Those applications would be of much less

concern for health effects – either pulmonary inflammation or carcinogenicity – in exposed workers. It should be noted that NIOSH is not recommending specific hazard warnings or labels for TiO_2-containing products. The Institute refers the commenter to the appropriate sections of the Occupational Safety and Health Administration Hazard Communication Rule (29 CFR 1910.1200) for guidance on hazard labeling issues.

The NIOSH policy identifying potential carcinogens based on only one exposure without regard to dose or controls and without consideration of other existing studies is not scientifically sound. As long as NIOSH works from this definition as a policy, then all of the technical or scientific discussion about the human studies becomes irrelevant to the decision about identification of carcinogens. For example, if there were a perfect epidemiological study with no observed increase in cancer, it would not change the NIOSH position regarding identification of carcinogens because of this policy and a single animal study at extremely high irrelevant doses.

Response: NIOSH believes that the commenter has misunderstood how NIOSH conducts its analyses. In fact, NIOSH conducted a statistical analysis comparing the animal and epidemiologic data in order to specifically address the possibility that the animal and human data were discordant. This is not what the analysis found. NIOSH carefully weighs all the evidence – human as well as animal data – in conducting its hazard assessment, risk analysis and in making its workplace recommendations.

EX1: I am very impressed with the quality of the science reflected in the NIOSH Current Intelligence Bulletin for TiO2. The document is very well written, and presents the elements of the evaluation with clarity and transparency. It is clear that there was a considerable effort by NIOSH to provide as objective a basis as possible for recommendations concerning occupational exposure to TiO2, using the best available scientific information and state-of-the-art analytical methods. The scientists at NIOSH who participated in this effort are to be congratulated for the obvious care and expertise with which the evaluation was conducted.

My primary concern is what appears to be an inconsistency between the qualitative assessment and the quantitative assessment. The qualitative assessment concludes (Executive Summary, p. iii) that the tumorigenic effects of TiO_2 result from a "secondary genotoxic mechanism associated with persistent inflammation," and that "occupational exposures to low concentrations of TiO_2 produce a negligible risk of lung cancer in workers." As a result, the determination is made by NIOSH that "insufficient evidence exists to designate TiO_2 as a 'potential occupational carcinogen' at this time." Based on these conclusions, I would expect that the quantitative risk assessment for TiO_2 would be conducted on the basis of the relevant non-cancer endpoint, inflammation, under the assumption that protecting against the obligatory precursor, chronic inflammation, would also be protective against cancer. Indeed, NIOSH conducts such a quantitative assessment, using dose-response data for PMN counts in BAL fluid.

However, NIOSH actually bases the proposed RELs on an alternative quantitative approach using data on the dose-response for lung tumors from TiO_2 exposures of rats to estimate a human exposure associated with a lung cancer risk of 1/1000. This analysis is based on the same linear dose-response approaches that would be used for genotoxic carcinogens, despite the fact that the mode of action for TiO_2 is described by NIOSH as "the accumulation of TiO_2 in the lungs, overloading of lung clearance mechanisms, followed by increased pulmonary inflammation and oxidative stress, cellular proliferation, and, at higher doses, tumorigenesis," which clearly is not a description of a genotoxic mode of action that would be expected to be linear to low doses. Moreover, the results of the quantitative analysis are not different from what one would obtain if a direct genotoxic mode of action was assumed, and the results are presented in the same way that the risks of a genotoxic carcinogen would be presented. For example, in the Executive Summary (p. iv) the recommended RELs are described as exposures that "over a working lifetime should reduce risks of lung cancer to below 1 in 1000." Even more surprisingly, the Executive Summary (p. v) states that "NIOSH is concerned about the potential carcinogenicity of ultrafine TiO_2" and "recommends controlling exposures as low as feasible below the RELs." These statements are inconsistent with the determination by NIOSH, in the same document, that TiO_2 should no longer be listed as a "potential human carcinogen."

It is my opinion that the conclusions of NIOSH in its qualitative assessment of TiO_2 carcinogenicity are well supported by the extensive animal toxicity/mechanistic data and human epidemiological data on exposure to TiO_2, and that a number of changes should be made to the quantitative analysis in order to bring it into harmony with the qualitative assessment:

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

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

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

I believe that a modified tumor analysis conducted as described above would result in estimates of fine and ultrafine concentrations associated with "negligible" (i.e., <1/10000, rather than 1/1000) risk that would be consistent with the thresholds for inflammation based on the PMN data. The tumor-based estimates should be presented only in this light (i.e., in a corroborative role), and any unsupported assertions ("concerns") regarding the potential carcinogenicity of TiO_2 at low human exposures should be eliminated from the document. Instead, the Executive Summary should re-state the fact that epidemiological

studies of workers exposed to fine TiO_2 at concentrations exceeding the proposed REL have provided no evidence of increased lung cancer.

Response: NIOSH did conduct risk analyses based on the inflammation data. In fact, in the final document, the risk analysis considers the inflammation data of Bermudez et al. (1991) made available to us by the Hamner Institute. However, these analyses showed that the resulting REL would be far below that set based on cancer data. One reason for this may be that the inflammation response is so early in the secondary genotoxicity chain of events that using it as a basis for risk assessment would be overprotective for the risks of real concern (namely, cancer). When further data becomes available that can quantitatively link the risks of inflammation with the risks of cancer, we will be better able to address this with a risk assessment based solely on inflammation, with tumor data used as a supporting analysis.

In addition, we have tried to address the apparent non-linearity in the cancer data (which is consistent with the proposed secondary genotoxicity mechanism of action) by reevaluating the cancer data with Model Averaging methods. The model-averaging method used in the revised CIB is based on non-linear models, as these were the best fitting models for the TiO_2 data. We believe that this approach coupled with the reasons stated above for not basing the risk assessment on inflammation data alone will address the reviewer's concerns about the model reflecting the nonlinearities of the dose-response.

With regard to the reviewer's prediction on the outcome of the modeling, the final numbers in the NIOSH risk assessment were very different from what he describes above. However, we stand by our numbers and our methods as revised in the final document. We also have significant concern for the potential carcinogenicity of nano-sized TiO_2 based on the data from the animal studies.

EX1: *NIOSH Q4: Is the use of particle surface area as a dose metric appropriate for estimating worker risks from inhalation of TiO2?*
At the present time, yes. There are a number of important issues that remain to be clarified. There is reasonable evidence that surface area is the most appropriate dose metric for particles in the fine and ultrafine range, but it is not yet known whether this dose metric is applicable to primary particles with an MMAD on the order of a nanometer. Therefore, there is some uncertainty with regard to its applicability to workplaces involving exposures to true nanoparticles. Even greater uncertainty would exist in the case of nanoparticles whose surface characteristics had been modified to hinder agglomeration.

Response: NIOSH agrees with the reviewer about the concern for even smaller nanoparticles. The analysis in this document assumed an average size of 100 nm. The RELs adopted in this document may well not be protective against exposure to even smaller particles which have greater surface area. However, there is no animal or human data which would allow us to evaluate the protectiveness of the RELs against smaller particle classes. In addition, the practicalities of routinely measuring exposure to these

particles in an industrial setting and differentiating between different size classes becomes much more difficult with smaller sizes of particles to be analyzed.

EX1: *NIOSH Q 5: Are there additional relevant studies or methods that NIOSH should consider in developing its RELs for TiO2?*
If NIOSH believes, as appears to be the case, that the effects of TiO2 are not chemical-specific, but rather result from non-specific particle responses, then consideration should be giving to recasting the evaluation of the RELs for TiO2 into an evaluation of poorly soluble, low toxicity (PSLT) particles in general. In particular, data from other PSLTs on biomarkers of inflammation, such as PMNs in BAL, could be used to perform a more robust quantitative analysis than is possible with data on TiO2 alone.

Response: While it seems like a practical solution to lump all PSLTs together into one REL analysis, there are several problems with that approach. First, there are conflicting opinions as to which particles would/should be included in PSLT. How "poorly soluble" and how "low toxicity" particles are to be considered as part of the group? This complicates the analysis substantially. NIOSH did look at including other PSLTs in its risk assessment for both inflammation and carcinogenicity. The data analyzed supported the potential utility of combining the datasets. However, we still have the problem of how to quantitatively link the inflammation data (an early step in secondary genotoxicity) with the cancer incidence so as not to set a REL that is overly protective.

Therefore, NIOSH has decided to proceed with publication of the document with a focus on TiO_2 and consider it a model of how the Institute would handle other such workplace exposures. However, there is nothing to prevent employers from using the TiO_2 RELs as a guideline for all worker exposures to PSLTs in the absence of specific RELs.

EX2: In preparing this review, I have evaluated the draft of the Current Intelligence Bulletin as well as the materials presented at the public meeting on February 27, 2006, which I was unable to attend. In this note, I provide general and specific comments as well as my specific responses to the charge given by NIOSH to the reviewers.

General Comments (EX2-continued):
In the *Current Intelligence Bulletin*, NIOSH presents a hazard evaluation and risk assessment for titanium dioxide (TiO_2). The draft is comprehensive in its coverage of TiO_2 and highlights the paucity of data available, and the very limited number of either epidemiological or toxicological studies on TiO_2. The epidemiological studies, while providing little indication of an association of TiO_2 with lung cancer risk, offer imprecise risk estimates that are likely to have been biased towards the null by misclassification. The animal studies are also quite limited and provide only a few data points for modeling dose-response relationships. Because the evidence is of limited scope and informativeness, NIOSH concludes that TiO_2 cannot be labeled as a "potential occupation carcinogen" at this time.

Response: In the revised CIB NIOSH has determined that sufficient data exist to classify ultrafine TiO_2 as a potential occupational carcinogen, but that the data for fine TiO_2 are insufficient.

EX2 comments continue:
Nonetheless, NIOSH proceeds to carry out a quantitative risk assessment and to recommend exposure limits. The argument for carcinogenicity largely hinges on the potential for lung inflammation caused by retained TiO_2 to cause lung cancer through a secondary, non-specific genotoxic mechanism. Such mechanisms have been proposed in a unifying fashion for linking diverse environmental agents and also host characteristics, e.g., obesity, to increased cancer risk. Given this proposed general mechanism, several questions immediately follow: 1) would not this same mechanism be expected to apply to other "particles not otherwise regulated"?; 2) given this postulated, generic mechanism, there is a broad range of relevant literature that is not reviewed; and 3) are inhalation bioassays for other particles postulated to act through this same mechanism also relevant?

Response: NIOSH would expect that this mechanism would operate for other poorly soluble low toxicity particles – not necessarily all in the class of "particles not otherwise regulated" however. NIOSH did review bioassay and inflammation from a variety of PSLTs and the dose response curves were similar for all analyzed. However, the decision was made to limit the scope of this document to TiO_2 in order to simplify the analysis, and not get into definitional arguments about how poorly soluble and how low toxicity does a particle need to be to fit in the class of PSLT. In addition, NIOSH has decided to use the TiO_2 document as a model for the analysis of similar particles rather than to consider the class of particles as a whole.

EX2 comments continue:
The proposal for exposure limits for fine and ultrafine TiO_2 particles follows from a concern that the tumor risks observed in the rats at the highest exposure concentrations warrants "…the use of prudent health-protective measures for workers until we have a more complete understanding of the possible health risks." This principle merits careful consideration as a basis for moving from high-level bioassay data in an animal model of uncertain relevance to a rationale based in reducing risk for human respiratory cancer, particularly given the absence of epidemiological evidence of increased risk in association with TiO_2. Why isn't NIOSH proposing exposure limits for other particles that may act through the same, nonspecific mechanism assumed in this instance for TiO_2.

Response: NIOSH limited the scope of this document to TiO_2 rather than consider all PSLT as a class for reasons described above. It was NIOSH's intention that the TiO_2 document be used as a model for future analyses of similar workplace hazards. That being said, however, there is nothing to prevent employers from implementing the RELs for TiO_2 to protect against other PSLT hazards in the absence of particle-specific RELs.

EX2 comments continue:
I see on major oversight that should be addressed: there is no discussion of the potential effect of TiO_2 in smokers compared with nonsmokers. Smoking is presumed to cause lung cancer through both the presence of specific carcinogens in tobacco smoke and the chronic inflammatory state of the airways and alveoli caused by smoking. How would the proposed mechanism for TiO_2 intersect with the consequences of smoking for the

lung? The differing dosimetry of particles in the lungs of smokers compared with nonsmokers?

Response: NIOSH has no information appropriate to this type of analysis.

EX2: Charge to Peer Reviewers

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

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

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

Response: As noted above, NIOSH reviewed bioassays and inflammation studies on other PSLT particles for comparison to TiO_2. There is reasonable evidence that they fit on the same dose-response curve. However, the Institute made the decision to limit the scope of this document to TiO_2. While there is an extensive literature on reactive oxygen species, some of which informed the mechanistic considerations in this document, extending the scope of the document to such an extent would greatly complicate the analysis, further delaying the publication and not necessarily improving the quality of the risk assessment. Instead, the Institute made the decision to use the TiO_2 document as a model for consideration of other PSLT hazards. Similarly, it could serve as a model for other inflammation hazards of a similar nature.

EX2: *Is the use of particle surface area as a dose metric appropriate for estimating worker risks from inhalation of TiO2?*

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

In proposing surface area as the dose metric, NIOSH emphasizes model fit in its analysis of the available rodent bioassay data. Considerations with regard to plausibility are limited in the draft; for example, would surface area be important because the smaller particles bring in a greater concentration of attached carcinogens; how does greater surface area produce more inflammation? At present, the evidence is empiric and limited. It overlooks issues of regional dosimetry by particle size in the human lung and

the sites of origin of human respiratory cancers. This topic needs mention, along with the trend of recent decades of increasing frequency of adenocarcinoma, presumed to be of peripheral rather than central origin.

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

Response: The Pocket Guide footnote has been removed. In the CIB, NIOSH has attempted to emphasize that particle surface area is one metric that may be appropriate to consider. Certainly particle surface area appears to fit the data better than inhaled particle mass. NIOSH recognizes that the true best metric may turn out to be particle number or some other metric correlated with surface area. However, NIOSH would point out that the resulting RELs are in fact mass-based based on two very broad categories of particle size. This takes into account that NIOSH is concerned about the smaller sized particles, but makes it as easy as possible to measure the exposures routinely in the workplace.

NIOSH has expanded its discussion of the selection of particle surface area as a metric for the risk assessment to address these concerns.

EX2 comments continue:

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

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

Response: NIOSH believes that the literature described by the reviewer goes well beyond the scope of this document. In addition, many references have been added since the public comment peer review draft was made public. The literature cited by the reviewer would be most appropriate if this document were addressing all PSLT. This is clearly not the case, here.

EX3: (A list of 22 references was included with EX3's comments. Use above link.) These comments review the NIOSH draft Current Intelligence Bulletin for titanium dioxide, a pigment widely used in paints.

The bulletin's conclusion that pigment grade, large particle titanium dioxide (TiO_2) should not be considered to pose a carcinogenic threat by inhalation is incorrect and should be withdrawn. The NIOSH statement that "low concentrations" pose a

"negligible risk of lung cancer" [line 48] is not supported by the evidence and should be withdrawn.

NIOSH classified TiO_2 as an OSHA Category I Human Carcinogen years ago, based on an inhalation study of pigment grade material.(Lee; Trochimowicz, and Reinhardt 1985) NIOSH notes that since then, a bioassay of ultrafine TiO_2 found it to be carcinogenic, but much more potent than the pigment grade material.(Heinrich U ; Fuhst R ; Rittinghausen S ; Creutzenberg O ; Bellmann B ; Koch W , and Levsen K. 1995)

Since the draft was released, an IARC working group has classified titanium dioxide as Group 2B, "possibly carcinogenic to humans" based on inadequate data in humans and sufficient data in laboratory animals.(Baan; Straif; Grosse; Secretan; El Ghissassi, and Cogliano 2006) Sufficient data in laboratory animals is equivalent to an OSHA Class I human carcinogen.

Response: NIOSH does not agree that the current data are sufficient to classify fine TiO_2 as a potential occupational carcinogen; however, NIOSH does regard ultrafine TiO_2 as a potential occupational carcinogen. As a point of clarification, NIOSH never classified TiO_2 as an "OSHA Category I Human Carcinogen". NIOSH has no such classification system and merely identifies appropriate chemicals as "potential occupational carcinogens" based on available human and/or animal data.

EX3 comments continue:
NIOSH has incorrectly interpreted the available epidemiology as implicitly providing evidence for safety.

Response: NIOSH did not interpret the available epidemiology data as providing evidence of safety. The Institute pointed out that the precision of the available epidemiology was limited, what conclusions might be drawn about the existing studies and conducted an analysis comparing the human and animal results to determine if there was an inconsistency in response across species.

EX3 comments continue:
This reviewer concurs with NIOSH that a common approach to setting occupational exposure limits to all poorly soluble low toxicity (PSLT) particles is appropriate. The new data suggests that inhalation of fine particles at prevailing exposure levels in many industries may be a major cause of occupational cancer and respiratory illness, and perhaps cardiac effects as well. This reviewer applauds NIOSH as the only public agency taking up this issue.

1. NIOSH correctly states that titanium dioxide and its appropriate exposure limit should be considered in the context of all PSLT data. NIOSH has failed to synthesize that data set, especially human evidence.

Response: Although NIOSH appreciates the desirability of developing RELs for a set of PSLT particles, that effort was beyond the scope of this document. This document focused on occupational exposure to TiO_2, although the Institute does recognize the implications of this work for occupational exposures to other PSLT particles.

EX3 comments continue:

2. The large body of epidemiological findings documenting increased community mortality and hospital admissions from pulmonary and cardiac causes with fluctuations of fine particulate matter in ambient air – community air pollution – must be taken into account. These community effects – which include frank mortality – occur with fluctuation in ambient exposure ***below*** established EPA ambient air standards for particulate matter.(Krewski; Burnett; Goldberg; Hoover; Siemiatycki; Jerrett; Abrahamowicz, and White 2003;Becker; Soukup; Sioutas, and Cassee 2003;Vedal; Brauer; White, and Petkau 2003;Pope; Burnett; Thun; Calle; Krewski; Ito, and Thurston 2002;Dockery; Schwartz, and Spengler 1992;Oberdorster; Gelein; Ferin, and Weiss 1995;Schwartz; Dockery, and Neas 1996) Lung cancer is also increased with particulate exposure.(Krewski; Burnett; Jerrett; Pope; Rainham; Calle; Thurston, and Thun 2005) These effects are seen both for PM10 [particulate matter 10 microns and less, essentially equivalent to thoracic particulate or total particulate collected with a closed face filter] or PM2.5 [particulate matter 2.5 microns and below, a somewhat smaller size fraction than respirable particulate which is essentially 4 microns and below.] These effects are directly relevant to a risk assessment for titanium dioxide.

Response: As stated above, the scope of this document was limited to occupational exposure to TiO_2.

EX3 comments continue:

3. The rat ***is*** the appropriate animal model for evaluating particulates for potential lung carcinogenicity in people. The mouse resists the effects of known human lung cancer agents such as silica and tobacco smoke. The hamster is very resistant to particulate agents; although the hamster provided the first clear evidence for carcinogenicity of tobacco smoke in an animal inhalation model, laryngeal tumors were generated, not lung tumors. The mouse and hamster produce false negatives for known human carcinogens, so null studies in the bioassay in these species should be given little weight.(Mauderly 1997) The rat is not "sensitive," it is "less resistant."

Response: NIOSH agrees with the commenter and has added similar statements to the final *C*IB.

EX3 comments continue:

5. Titanium dioxide of any particle size is an OSHA Category I carcinogen. The data available, and the "lung overload" hypothesis, do not support a threshold model. A threshold model predicts there is a dose level below which there is no dose response relationship.

The rat-specific "lung overload" mechanism is at best an unproven hypothesis to be applied to quantitative risk assessment. At worst, "lung overload" as an excuse to depart from more standard risk assessment methods is an unsubstantiated "Houdini Risk Assessment" scheme. Similarly, the argument that exposure-response relationships are "non-linear" – a code word for threshold, even though "non-linear" includes supra-linear

– is unsubstantiated, especially for exposure levels which prevail in the occupational environment.

The scientific issue is whether "lung overload," impaired clearance, macrophage hyperplasia and other non-malignant pathology are separate processes from carcinogenesis. If impaired clearance simply acts to increase residence time and exposure of lung tissue to PSLT particles, resulting in carcinogenic results, then the PSLT particles must have some carcinogenic potential in themselves. By contrast, if PSLT particles have no carcinogenic potential in themselves, then macrophage hyperplasia and impaired clearance from any cause have carcinogenic potential in the absence of PSLT particles. Since human PSLT exposure is ubiquitous, in the latter case, any condition that causes macrophage hyperplasia should be considered carcinogenic.

Imagine that impaired clearance and macrophage hyperplasia are, regardless of cause, carcinogenic. This might be biologically plausible if PSLT particles, which are ubiquitous, and also exist in the laboratory air breathed by bioassay animals, initiate lung tumors. Decreased clearance, and increased macrophage hyperplasia, will be linear with increased carcinogenesis, regardless of whether these effects are sub- or supra-linear with the exposure.

Imagine, in addition and contrast, that contact of PSLT with lung tissue by itself initiates carcinogenesis. Plausibly contact concentration and time will be first order with target cell initiation. Where PSLT exposure also impairs clearance and causes macrophage hyperplasia, the exposure response relationship will be steeper than first order, since concentration of exposure to PSLT is involved in two steps. This will be true even if both steps are first order. Therefore, an exposure response relationship that is linear in initiation [holding clearance constant], and linear in impaired clearance [holding PSLT contact with tissue constant], will be supra-linear for both in concert.

Perversely, if PSLT exposure causes both initiation, and impaired clearance, then the exposure response relationship in the high dose range will be greater than first order [steeper] than in the low dose range. Thus, the apparently steeper and higher order exposure response relationship in the high dose range will ***underestimate*** risk in the lower dose range.

Response: As noted above, NIOSH never classified TiO_2 as an "OSHA Category I Human Carcinogen." NIOSH has no such classification system and merely identifies appropriate chemicals as "potential occupational carcinogens" based on available human and/or animal data. OSHA similarly does not have a numerical classification system for carcinogens.

Regarding the non-linearity of the exposure-response relationship, NIOSH investigated the possibility that the data were consistent with a threshold response for inflammation. This was presented in the public-comment draft of the CIB, based on the data from Tran et al. (1999) and Cullen et al. (2002). Upon receipt of public and peer review comments, NIOSH further studied this issue with additional data obtained from the Hamner Institute

(from studies by Bermudez et al. (2002, 2004). These analyses did not support a threshold in the exposure-response relationship for inflammation.

However, NIOSH investigators did include non-linear models in the model space considered for its risk estimates. Using a model averaging technique, the cancer risk estimates were based on the data from Lee et al. (1985); Muhle et al. (1991) and Heinrich et al. (1995). The resulting exposure-response relationship is strongly sub-linear, which is consistent with the best-fitting models for TiO_2-induced tumorigenesis. NIOSH believes this data-driven analysis best characterizes all the available cancer data and is consistent with the proposed mechanism of action of titanium dioxide.

With regard to the lung overload and mechanism of action issues raised by this commenter, NIOSH has greatly expanded its discussion of these issues in Chapters 3 and 4 in order to specifically address this commenter's and others' concerns.

EX3 comments continue:
6. By contrast to the laboratory studies, people may experience impaired clearance and macrophage hyperplasia from causes other than TiO_2 exposure, along with TiO_2 exposure from occupational sources. Risk assessment models must take this into account. Thus, TiO_2 in humans doesn't have to be the complete carcinogen it needs to be in the laboratory studies.

Response: NIOSH agrees with the commenter that risks to sensitive subpopulations of workers (for example, those with impaired clearance and/or hyperplasia) should be considered in the full development of a risk assessment. However, since the quantitative relationship between impaired clearance, inflammation and carcinogenesis is not yet well understood for animals or humans, including these factors in a quantitative way in a risk assessment is not yet feasible.

EX5: Entire submission relates to issues with the overall document. Follow link above to Reviewer 5's comments.

Similar to the recent IARC report the NIOSH draft document on TiO_2 presents all available information on these particles. My concern is, that information on similar granular biopersistent particles (GBP) and the cumulating evidence of a similar underlying toxic mechanism have not been considered. Consequently although a non-genotoxic carcinogenicity is assumed and inflammation is seen as a basic mechanism a linear extrapolation is preferred to quantify the risk of human exposure.

Response: The dose-response modeling in the final does not include a linear component. Additional work was undertaken to characterize the dose-response for inflammation, particularly to determine whether there was support for a threshold response, but this was deemed unsuitable for the final risk assessment (see discussion in Chapter 4). In addition, this document was limited to consideration of the inflammation and carcinogenicity response after exposure to TiO_2 particles.

EX5 comments continue:
In 3.5.2 "Role of Chronic Inflammation in Lung Disease" inflammation is described as one effect of particle toxicity. Such effects have been shown in experimental studies and in humans during particle exposure. It is also described that according to Castranova (1998, 2000) chronic inflammation appears to be important in the etiology of dust-related disease in rats and humans. However, a conclusion, that inflammation is the relevant mechanism not only for chronic obstructive lung diseases but also for carcinogenicity is not taken

Response: In the public comment draft and in the final, NIOSH concludes that chronic inflammation leading to secondary genotoxicity is a plausible mechanism for the observed lung cancer in animal models.

EX5 comments continue:
The MAK-commission is presently evaluating GBPs including TiO_2. Especially on the basis of Paul Borm's recent review articles (Borm et al 2004, Knaapen et al 2004), previous workshops on particles and fibers (Greim et al 2001) and the ample literature about particle induced inflammation and carcinogenicity it is concluded, that inflammation is the relevant mechanism for tumor induction and that avoidance of inflammation protects from carcinogenicity. During the recent INIS Conference in Hannover (June 2006), to which David Dankovic contributed the NIOSH TiO_2 risk assessment, Schins of Borm's group presented recent mechanistic studies and myself have presented the regulatory consequences. There was unanimous agreement that GBP are non-genotoxic, the underlying mechanism in carcinogenesis is inflammation and thresholded, so that avoidance of inflammation protects from carcinogenicity.

Response: NIOSH agrees with the peer reviewer that the weight of evidence supports the conclusion that TiO_2 is non-genotoxic and that the carcinogenesis is related to persistent inflammation. NIOSH also concurs that avoidance of inflammation protects from carcinogenicity. Unfortunately, the animal data reviewed for the final version did not support a threshold for inflammation. It is unclear how to quantitatively relate a quantity of inflammation to the observed carcinogenesis in the animals in a way that would make sense for human risk assessment. Therefore, NIOSH relied on the cancer response for its risk assessment.

EX5 comments continue:
Although such exercises may provide some information on a hypothetical risk even for non-genotoxic carcinogens, the decision whether a mechanism is thresholded and whether a

NOEL can be assumed can only be made by understanding the underlying mechanism. In case of GBP there is the scientific consensus, that this is inflammation, which due to antioxidant mechanisms is not induced at low exposure.

Response: NIOSH concurs with the commenter that the weight of evidence supports inflammation and secondary genotoxicity as the underlying mechanism for TiO_2. However, additional analyses conducted on data provided by the Hamner Institute did not support a threshold for inflammation.

Comments about Chapter 1 (Introduction):

DECOS (Member 1): Table 1-1: MAK-value for TiO_2 currently under evaluation (footnote)

Response: At the time of the reviewer's comment, the MAK value for TiO_2 was under evaluation. In 2008, the published list of MAK values indicated that the value was withdrawn. Removed the value from Table 1.1 and changed the footnote.

EX2: Line 318: what are the implications of not being soluble for potential reactivity and generation of reactive oxygen species?

Response: Poorly soluble particles remain in the lungs and can elicit reactive oxygen/nitrogen species generation by macrophages and neutrophils that are recruited to try to clear the particles. This is how TiO_2 is thought to cause ROS generation in the lungs. (Other types of poorly soluble particles with reactive surfaces can also generate ROS on their surfaces).

EX2: Lines 343-344: information available on GSD?

Response: GSD not reported in Aitken et al. [2004]. For GSD of the mass median aerodynamic diameter of particles in experimental studies, see Table 4-1 in the CIB and Bermudez et al. [2002], Table 1.

EX2: Line 361: limitations of the NOES should be cited here.

Response: Deleted NOES sentences and revised text about number of workers.

Comments about Chapter 2 (Human studies):

DECOS (Member 1): Most (> 90 %) of the commercial (pigmentary) TiO_2 is available in a coated (silica) form and exposure of workers who handle or use TiO_2 would certainly be different qualitatively from production workers and a valubale asset to the set of epidemiologal data. This may be added to the summary (2.3) on page 20.

Response: This research need is already in Chapter 7 (Research Needs), Section 7.1 (Workplace exposures and human health) and the lack of such studies is stated in the beginning of Section 2.3 (Summary of Epidemiologic Studies). Added text to end of 2.3:

"…and to also study workers that manufacture or use products that contain TiO_2 (see Chapter 7 Research Needs)."

DECOS (Member 2): NIOSH does not seem to agree with the authors that the 3 epidemiological studies are negative. From their studies, Fryzek and Boffetta concluded that they did not observe a carcinogenic effect. Nevertheless, the NIOSH report refers toa "neglible effect" (line 49) and "no clear evidence" (line 716) suggesting some kind of a small, but negligible effect. However, based on the aforementioned study, the conclusion should be that there is no evidence.

Response: Not entirely negative; Boffetta et al. [2004] reported a statistically significant SMR for male lung cancer mortality. No change.

DECOS (Member 2): Further, the statistical power to detect mortality from non-malignant respiratory tract diseases is questioned (line 721-724). Although these investigations do not statistically exclude a small effect, it is more important to conclude that they do not support a possible long-term effect.

Response: Revised the summary of nonmalignant respiratory disease (NMRD) mortality.

EX2: Lines 471-475: why would alveolar proteinosis be linked to TiO_2?

Response: These lines in the case reports section describe one case of alveolar proteinosis in a long-term painter. The report's authors, Keller et al., stated "We propose that PAP may occur by impairment of the normal mechanisms of removal of normally produced alveolar phospholipid induced by the deposition of inorganic particles, in this case titanium, which induces accumulation of dust-laden macrophages, deposition of cellular and particulate debris, and eventual alveolar proteinosis" (Keller et al. 1995, p. 280). No change.

EX2: Lines 494-495: comment needed here on the location of the particles which are probably in the mediastinal lymph nodes and perhaps in peri-bronchiolar accumulations as for other particles. Information available?

Response: Regarding lines 494-495, the level of detail on the particle burdens within specific lung tissues and lung-associated lymph nodes is too much for a summary paragraph, and beyond the scope of the human studies/case reports section. The references are provided for readers interested in additional details on those studies. Revised this sentence and deleted the next sentence.

EX2: Line 624: this criticism seems off the mark as methods were not available for collecting ultrafines over the course of the study.

Response: Added "probably because collection methods were not available over the course of the study".

EX2: Lines 726-728: this sentence leaves the mistaken impression that an epidemiological study could be designed for this purpose.

Response: Added: "Further research is needed to determine whether such epidemiologic studies of TiO_2-exposed workers can be designed and conducted (see Chapter 7 Research Needs)."

EX3: 7. The cited mortality studies in occupational settings are inadequate to provide evidence of lack of risk from TiO_2 at prevailing exposure levels.(Fryzek; Chadda; Marano; White; Schweitzer; McLaughlin, and Blot 2003) At best it provides evidence that no greater than 5% of workers will perish from lung cancer attributable to titanium dioxide pigment exposure at 6.2 mg/M3. The following summary should be substituted for the section following line 581.

Fryzek and coworkers at the International Epidemiology Institute studied 4241 TiO_2 workers at four unidentified TiO_2 plants in the United States. The study sponsor was unidentified. The highest exposed job category, where about ¼ of the cohort was ever employed, endured a geometric mean exposure of 2.7 mg/M3. The arithmetic mean for this skewed distribution was 6.2 mg/M3 due to high exposures before 1985. Only 112 total and 11 respiratory cancer deaths were observed among this group. Other exposed categories endured geometric mean exposures below 1.0 mg/M3. Standardized mortality ratios (SMRs) were presented for both races (22% of the cohort was non-white) and genders (10% women) combined. The combination of SMR's for white and non-white workers will narrow the SMR because of the stronger healthy worker effect among non-whites. The analysis apparently included non-administrative salaried personnel, which would also lower the SMR. A separate analysis for white, male, hourly workers should have been presented.

The noted lower overall mortality observed [SMR = 0.8] is expected in an occupational cohort, and is of no health significance for evaluating effects of titanium dioxide. Given that overall mortality was only 13%, and the dilution of SMR by inclusion of non-whites and salaried personnel, this SMR is notable Despite these obstacles, deaths from lung cancer were as high as expected, therefore proportional mortality from lung cancer was increased.

The investigators opined that "Internal analyses revealed no significant trends or exposure-risk associations for total cancers, lung cancer, or other causes of death" and that "workers with likely higher levels of TiO_2 exposure had similar mortality patterns to those with less exposure." However, workers in each employment duration stratum and overall showed a distinct increase in SMR for lung cancer comparing those with less than 20 years latency to those with more than 20 years of latency. Increased mortality in the long latency, shorter duration strata is consistent health related termination of employment. This effect has been observed in other, much larger industrial cohorts.(Delzell; Brown, and Matthews 2003;Mirer 2003)

This study provides some evidence for an exposure related effect, given the latency effect, which is a measure of exposure response. It is inadequate to support a conclusion

of "not likely to be carcinogenic in humans." The upper confidence interval for respiratory cancer among those ever employed in the high exposure job category was 1.6, and among all exposed employees with greater than 20 years latency it was 1.5. Thus, at the prevailing exposure levels, we can possibly rule out a greater than 50% increase in lung cancer, or a unit risk of about 2.5 per 100. In some groups the upper confidence interval was two fold. This observation is entirely consistent with conventional extrapolation from the animal bioassay.

Response: Added to text: 1) that wage status (i.e., salaried or hourly) not reported; 2) proportion of workers in each race category (i.e., 58% white, 22% nonwhite, 20% unknown); 3) that results were not reported by race; 4) lung cancer SMR in subcategory of workers with 0 to 9 years worked and at least 20 years since hire.

EX3: 8. The Boffetta Montreal study (Boffetta; Gaborieau; Nadon; Parent; Weiderpass, and Siemiatycki 2001) is a population based case control study. The same power limitation applies. The upper confidence interval of the odds ratio is 1.5. No trend was apparent according to the estimated frequency, level, or duration of exposure. The upper confidence interval was 2.7 for medium or high exposure for at least 5 years.

Response: Comment repeats information in the draft and does not suggest changes. No change.

EX3: 9. The Boffetta European Study (Boffetta; Soutar; Cherrie; Granath; Andersen; Anttila; Blettner; Gaborieau; Klug; Langard; Luce; Merletti; Miller; Mirabelli; Pukkala; Adami, and Weiderpass 2004) provides evidence for an exposure related effect, contrary to the conclusions of the investigators and the NIOSH review. The investigators and the review note, correctly that lung cancer among males was increased to a significant level; the upper confidence limit was a 38% increase, corresponding to about 2% mortality attributable to exposure. The review fails to note that the SMR for lung cancer increased with latency [duration from first exposure] in all employment duration strata, becoming statistically significant only after 20 years latency. The absence of exposure response carries less force since the top quartile of exposure begins at 13 mg/M3-years, equivalent to 0.3 mg/M3 over 45 years. (Reviewer EX3 included Table 5 from p. 703 of Boffetta study with this comment).

Response: Added: "There was no consistent and monotonic increase in SMRs with duration of employment, although workers with more than 15 years of employment had slightly higher SMRs than workers with 5 to 15 years of employment and an effect of time since first employment was suggested for workers employed more than 10 years. (The authors indicated that the increase in lung cancer mortality with increasing time since first employment could be "explained by the large contribution of person-years to the categories with longest time since first employment from countries such as Germany, with increased overall lung cancer mortality [Boffetta et al. 2004])"."

Comments about Chapter 3 (Experimental studies in animals and comparison to humans):

NPCA: Additionally, NPCA concurs with the significant questions raised by the ACC comments concerning the relevance of the animal studies NIOSH relies upon as the basis for its recommendations. As was discussed extensively at the recent public hearing in Cincinnati, many of the animal studies summarized in Section 3 of the draft CIB either have been mischaracterized or misinterpreted by NIOSH, and the weight of the scientific evidence clearly refutes the appropriateness of the use of rats to characterize human lung responses to TiO_2. As the ACC comments observe, there are significant species differences in lung responses to overload concentrations of both pigment-grade and P25 ultrafine TiO_2 particles,[1] and that rats, as opposed to other species used in such studies, have a unique lung response not observed in other species, such as mice or hamsters, that is likely to be the responsible mechanism for idiosyncratic lung tumor development.

Response: In the draft CIB, NIOSH cited the studies showing the rat pulmonary responses to inhaled particles (such as TiO_2) to be greater in mice or hamsters, and also cited the studies that have associated chronic pulmonary inflammation and lung cancer. NIOSH also cited an analysis showing that mice and hamsters were false negatives in bioassays of some known human carcinogens. In the few cases where quantitative dose-response data of particles were available in both rats and humans, the rat did not overestimate the lung cancer risk in humans. Two expert advisory panels have recommended the rat as the best available animal model for predicting the hazard and risk of inhaled particles and fibers in humans. Some revisions were made to clarify and update the studies cited. NIOSH still considers the rat data to be relevant to human health risk assessment.

NPCA: Use of Particle Surface Area as a Dose Metric

We concur with comments submitted by the American Chemistry Council on this issue.

Response: See response to ACC comments.

DECOS (Member 1): Studies by intratracheal instillation of TiO_2 have not been included, although the NOEL when considering TiO_2 simply as one of the many poorly soluble low-toxicity particles is not that different from studies by inhalation (Borm et al, 2004). A recent follow-up of this so-called 19-dusts study (Morfeld et al, 2006) showed that PSP induced lung tumours in the rat is indeed best statistically described by a threshold, based on Cox-regression of all animals (n=750) in that study. Moreover, the study showed overall a factor 3 difference between ultrafine and fine particles as a whole. This again draws the attention for a better quantitative support of the difference between the RELs of ultrafine and fine TiO_2. Two published papers were attached to the submission: 1) 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 particles in a chronic rat experiment. Inhalation Toxicology 18:215-225. 2) Borm PJA et al. [2004]. Mini-review: Inhaled particles and lung cancer, Part B: paradigms and risk assessment. Int J Cancer 110:3-14.

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[1] P25 is a TiO_2 particulate mix comprised of 80 per cent anatase and 20 per cent rutile.

Response: Intratracheal instillation studies of TiO_2 were cited in the draft Chapter 3, and recent studies published since the draft CIB have been added, including Morfeld et al. [2006], as well as Dankovic et al. [2007], which showed that a threshold was statistically significant in some models but not in other models. In both the draft and final CIB, NIOSH investigated the quantitative relationship between the dose of ultrafine or fine TiO_2 and the pulmonary inflammation and lung tumor responses in rats. As in other studies, NIOSH found that ultrafine TiO_2 was more potent by mass but was similar to fine TiO_2 by particle surface area.

EX1: Responses to NIOSH Questions

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

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

Comparison of rat and human response

One important issue that needs attention, however, is the discussion of the relevance of the rat as a model for human lung tumors (in Sections 3.4 and 3.5). The document should more clearly describe (in Section 3.5.1) the results of the studies by Bermudez et al. (2002, 2004), which show that while the lung dosimetry and acute inflammatory responses to TiO2 in the mouse and the rat were similar, only the rat exhibited long-term, progressive sequelae involving metaplastic and fibroproliferative lesions. It is this progressive tissue response that appears to predispose the rat to the occurrence of lung tumors from TiO2.

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

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

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

Discussion of Lung Overload

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

As can be seen in Figures 3.3 and 3.4, the data are consistent with a threshold for tumor response on the order of 0.2 m2/g lung, which is in the range of surface area doses that has been associated with the onset of lung overload. Of coarse, the fact that increased tumor incidence is only observed above the lung burdens associated with overload does not necessarily imply that impaired clearance is an obligatory precursor for tumors. However, the sustained inflammatory and proliferative response in rats that is actually likely to be an obligatory precursor to tumors is, in fact, only seen at lung burdens well above overload (Bermudez et al. 2002, 2004).

Response: Chapter 3 revisions addressing these comments include: (1) clarified discussion of the role of persistent inflammation and cell proliferation on the rat lung tumor response; (2) cited and discussed the Nikula et al. (1997, 2001) studies; (3) cited additional studies of PSLT that are relevant to mechanisms of TiO_2 response (e.g., Elder et al. 2006; Muhle et al. 1991; Bellman et al. 1991; Morfeld et al. 2006); and (4) revised Section 3.4.2 to clarify discussion on rat lung overload and relevance to humans.

In response to the comment, "In fact, the weight of the evidence from studies on TiO2 and relevant materials such as coal dust clearly supports the existence of important differences between the non-specific cellular responses to high particle loads in the rat and human (progressive inflammation and alveolar proliferation vs. interstitialization) that would predispose the rat to lung tumors from TiO2" – the reviewer does not provide any references to support this interpretation. As cited in the draft CIB, qualitatively the

rat and human lung responses to inhaled particles are similar (Castranova 2000). Data are limited for quantitative comparison of rat and human dose-response relationships to inhaled particles. Where such data are available (e.g., diesel exhaust particulate, crystalline silica), the rat-based lung cancer risk estimates do not overestimate the human lung cancer risk. The lung inflammation response to those particles are qualitatively similar to those for TiO2, although crystalline silica is more potent in causing inflammation (as shown in Figure 3.2 of draft CIB) even after accounting for particle surface area. Appendix C of the final CIB provides a quantitative analysis showing that the rat-based risk estimates for TiO2 are statistically consistent with the human study results.

EX2: Lines 735-744: assays involving other particles might be cited here.

Response: The studies cited pertain to *in vitro* genotoxicity and mutagenicity of TiO_2. Citing assays of other particles would be beyond the scope of the document.

EX2: Lines 1027: "correlated better" is too vague.

Response: Clarified.

EX2: Lines 1050-1053: the assertion may be correct but it fails to acknowledge differing sites of deposition with the lung.

Response: These sentences describe the data on particle surface area dose and lung tumor response in the chronic inhalation studies of rats shown in Figure 3-3. Furthermore, this comment about different deposition sites is not correct because ultrafine and fine TiO_2 are respirable particles with similar aerodynamic diameters (Table 4-4 of draft CIB) and therefore would have similar deposition efficiency in the alveolar region of the lungs.

EX3: 4. The Lee study of pigment grade titanium dioxide has been incorrectly discounted because of the supposed high exposure levels, 250 mg/M3. The Lee study was analyzed without benefit of mortality adjusted statistics, as would be routine in National Toxicology Program bioassays. Animals were terminated at two years. Tobacco smoke doesn't produce a meaningful lung tumor yield in rates at exposures less than 100 mg/M3.(Finch GL 1995) A second study reports an effect level of 250 mg/M3, when animals were held 6 months after the two year exposure period. Similar exposure levels were needed to produce lung tumors in mice. Thus, pigment grade titanium dioxide has a similar potency to cigarette smoke in the animal models.

Silica and asbestos levels of 20 mg/M3 or greater are needed to generate a substantial tumor yield. Unit risks of silica at mg/M3 exposure levels in people are extremely high. If TiO_2 is 1/10 as potent as silica, it will still extrapolate to significant risks at mg/M3 exposure levels.

Various commenters have emphasized that the effect dose for pigment grade large particle TiO_2 is 250 mg/M3. Beyond frank carcinogenicity, 250 mg/M3 exposures to tobacco smoke are routinely used to evoke respiratory effects in rodents.(March; Barr;

Finch; Hahn; Hobbs; Menache, and Nikula 1999;Finch; Lundgren; Barr; Chen; Griffith; Hobbs; Hoover; Nikula, and Mauderly 1998)

Response: As noted in the revised CIB, NIOSH does not believe that the high dose data in the Lee study provides an adequate basis for classification of fine TiO_2 as a potential occupational carcinogen. However, in order to be health-protective in the event that fine TiO_2 is ultimately shown to be a human carcinogen, NIOSH included those data in the dose-response analyses and risk estimates. The mass-based "effect dose" for TiO_2 depends on particle size and surface area, as shown in the studies and analyses described in the TiO_2 CIB.

Comments about Chapter 4 (Dose-response modeling of rat data and extrapolation to humans):

DECOS (Member 2): The effects seen in experimental animals are due to overload. Considering this is the case, is it sound to perform a high dose-low dose extrapolation? And should it not be more appropriate to prevent overload and to chose a "non-overload" dose and calculate an exposure limit by applying assessment factors?

Response: NIOSH notes that the dose-response modeling was extrapolated to humans on the basis of the lung burden of particles, and adjusted for differences between rats and humans in particle deposition and clearance. NIOSH also notes that rats have a high rate of particle clearance, in comparison to humans, and that "overload" conditions may be required in order to generate lung burdens in rats comparable to those observed in workers with long-term exposure to insoluble particles.

DECOS (Member 3): (Only reviewed the sections on dose-response modelling)
The sections on dose-response modelling are not only very comprehensive but also very complex and not very transparent.
Therefore, this section is not further reviewed because it requires much more time than the reviewer could afford.

Response: We have re-written the dose-response modeling sections and attempted to improve their transparency.

EX1: *NIOSH Q2. Are the risk assessment and dosimetric modeling methods used in this document appropriate and relevant?*

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

- the use of highly sophisticated lung deposition and clearance modeling to perform particle dosimetry
- The use of Bayesian model averaging (BMA) to obtain central estimates of risk across alternative dose-response models

- the additional statistical modeling described in the Appendices, in particular the quantitative comparison of animal- and human-based risk estimates.

Documentation of Decision-Making

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

Response: We have revised the dose-response modeling section and attempted to improve the explanations for decisions which were made.

EX1 comments continue:

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

Response: We concur, and we have revised the rat-to-human extrapolation method accordingly.

EX1 comments continue:

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

Response: We have added additional explanation for choosing the MPPD/ICRP model.

EX1 comments continue:

Calculation of RELs Based on Critical Lung Dose for Inflammation

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

Response: We have revised the dose-response analysis. As discussed in the revised document, NIOSH believes that a REL based on pulmonary inflammation would be so low as to be infeasible to implement in numerous settings. The REL in the revised CIB is now based on a model average of the multistage, Weibull, and log-probit models, none of which are linear. NIOSH considers this modeling approach to be appropriate based on the secondary genotoxic mechanism of action of TiO_2, which is not expected to lead to a low-dose linear dose-response relationship.

EX1 comments continue:

To provide a quantitative risk assessment that is consistent with the conclusions of NIOSH regarding the mode of action for the effects of TiO_2, NIOSH should base the PELs for TiO_2 on the data for inflammation. The equivalent worker exposure concentrations calculated by OSHA for the two critical studies (Tran et al. 1999, Cullen et al. 2002), shown in Table 4-3, are in the range of 1 to 6 mg/m3 for fine TiO_2 and 0.1 to 0.7 mg/m3 for ultrafine. NIOSH should base the RELs on these results, providing a clear documentation of how the values were calculated. For example, using lung surface area scaling, the average of the two dosimetry model estimates, and the average of the results from the two experimental studies would result in a REL for fine TiO_2 of approximately 1 mg/m3, and a REL for ultrafines of approximately 0.1 mg/m3.

Response: As discussed in the revised document, NIOSH believes that a REL based on pulmonary inflammation would be so low as to be infeasible to implement in numerous settings.

EX1 comments continue:

Calculation of RELs Based on Rat Lung Tumor Data

Although the use of tumor data as the basis of the RELs for TiO_2 is inconsistent with the determination made by NIOSH that "insufficient evidence exists to designate TiO_2 as a 'potential occupational carcinogen' at this time," such an analysis could be justified for the purpose of providing corroborative evidence that the RELs based on inflammation would be adequately protective against cancer. However, the main cancer risk analysis conducted by NIOSH is based on the same linear dose-response approaches that would be used for genotoxic carcinogens, and the results of the quantitative analysis are not different from what one would obtain if a direct genotoxic mode of action was assumed, despite the fact that the mode of action for TiO_2 is described by NIOSH as "the accumulation of TiO_2 in the lungs, overloading of lung clearance mechanisms, followed by increased pulmonary inflammation and oxidative stress, cellular proliferation, and, at higher doses, tumorigenesis," which clearly is not a description of a genotoxic mode of action that would be expected to be linear to low doses.

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

Response: We concur that the lung tumor analysis should be based on model averaging, and the analysis has been revised accordingly. Linear extrapolation from the 10% excess risk BMD has also been dropped, as recommended. The REL in the revised CIB is now based on a model average of the multistage, Weibull, and log-probit models, none of which are linear. NIOSH considers this modeling approach to be appropriate based on the secondary genotoxic mechanism of action of TiO_2, which is not expected to lead to a low-dose linear dose-response relationship.

EX2: *Are the risk assessment and dosimetric modeling methods used in this document appropriate and relevant?*

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

Response: See response to DECOS (member 2), above, re the use of overloading doses in the rat.

EX2: comments continue:

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

Response: NIOSH believes that total lung dose is an appropriate dose metric for estimating excess risk for the lung as a whole.

EX2: Lines 1335-1337: would there have been differing patterns of deposition? Are models available for this consideration?

Response: The studies in question do not provide data on either regional deposition of TiO_2 or the regional deposition of lung tumors in the rat. We would need both types of data for the rat, and the ability to estimate regional deposition in humans, in order to potentially make use of regional deposition information for risk assessment purposes. Lacking such data, we believe that total lung dose is an adequate dose metric for estimating excess risk for the lung as a whole.

EX3: (Reviewer included "Table 4 Alveolar Cell Replication". Use above link to view). 11. A departure point for setting a REL should be the benchmark dose, or no effect level, for lung inflammation, probably in the rat. The benchmark dose is equivalent to about a 10% attack rate for the effect.(Gaylor; Ryan; Krewski, and Zhu 1998) The REL should be set below that by some extrapolation factor.

The lowest statistically significant effect level observed was 2 mg/M3 for 13 weeks for alveolar cell replication in rats exposed to ultrafine TiO_2.(Bermudez; Mangum; Wong; Asgharian; Hext; Warheit, and Everitt 2004) This elevation persists, although it is not statistically significant, for 13 weeks post exposure. This reviewer recommends that NIOSH calculate the benchmark dose for this and the other array of inflammation parameters, and then apply an appropriate extrapolation factor.

Response: NIOSH has conducted the benchmark dose analysis suggested by the reviewer, and has concluded that a TiO_2 REL based on inflammation would be very low, and most likely infeasible in many settings.

EX4: Entire submission relates to Chapter 4 (comments dated April 28, 2006—follow above link).

EX4 comments on Hazard Identification:

Generally speaking, the CIB is a reasonable and balanced document reflecting available scientific data. It is appropriate to conclude that lack of an exposure response relationship in epidemiologic studies of workers exposed to TiO_2 dust in workplace should not be interpreted as evidence of discordance between the mechanism presumed to operate in rats and the human potential for carcinogenicity. As to be explained, there are more

compelling reasons to support this conclusion. Reading through the document, it is apparent that NIOSH has made reasonable efforts to present a balanced picture about the available data and to use appropriate methods and procedures to estimate risk to workers. However, there are some important scientific issues that need to be more carefully addressed and/or discussed. In particular, the proposed MOA needs carefully articulated; otherwise the conceptual basis for this assessment and the data base used for risk calculation could be considered invalid if those issues are not properly addressed.

Response: We believe that the mode of action is now clearly stated.

Excerpt of EX4 comments on Mode of Action (MOA):

Available data does not support threshold effects for pulmonary inflammation, and cellular proliferation.

Response: We concur. A new analysis of pulmonary inflammation data has been added to the document, based on the Bermudez et al. studies cited by the reviewer, and we agree that the data do not support the existence of a threshold for pulmonary inflammation. Therefore, the analysis of pulmonary inflammation has been revised, and is now based on a benchmark dose approach rather than a threshold model approach.

EX4: comments on Particle Surface Area as Dosimetric:

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

Response: NIOSH agrees that accounting for covariates would be necessary if the quantitative risk estimates for TiO_2 were based on an analysis of multiple compounds, as in Figures 3-2 and 3-4. Since the quantitative risk estimates for TiO_2 are based entirely on TiO_2 data, covariates do not enter into the analysis.

EX4 comments on Differences in Background Conditions between Rats and Humans:

There is need to consider differences between animals and humans with respect to some relevant background variables when extrapolating risk from rats to humans. These variables include significantly higher lung cancer rates in humans than rats; higher background lung cancer rate implies that there is higher prevalence of precancerous cells in humans waiting to be affected by TiO_2 exposure. Higher background lung cancer rates also make it more difficult to detect a small increased risk in epidemiological studies. Another important issue is whether or not TiO_2 should be considered along with other particulate matter, giving the fact that humans are also exposed to a broad class of

chemically and physically diverse particles. Furthermore, since the thermal and mechanical history of particles and adsorption from environment determines characteristics of active surface sites, the induced toxicity may be different from that in animals where original TiO_2 was used, and thus, more uncertainties in human risk assessment due to the surface reactivity with environment and biological medium in human lungs. All these variables have the tendency to underestimate risks calculated from animal data.

Response: The NIOSH risk assessment for TiO_2 is predicated on the assumption that equal particle doses, in units of particle surface area per unit lung surface area, will produce equivalent responses in different species. Differences between rats and humans in particle deposition and clearance have been accounted for in the risk assessment, but toxicodynamic differences have not. NIOSH acknowledges that toxicodynamic differences such as those described by the reviewer may exist; however, NIOSH is not aware of quantitative toxicodynamic data adequate for use in the TiO_2 risk assessment.

Excerpt of EX4 comments on Threshold Assumption in Risk Calculations:

The statement on p.55 (Line #1323) "The probability that these threshold would be observed if the true relationship was linear is less than 0.01" could be misconstrued as evidence for a threshold. It should make clear that a real biological threshold effect can not be determined by statistical analysis alone.

Response: NIOSH concurs, and has revised the TiO_2 analysis to rely on benchmark dose estimates rather than threshold models.

Comments about Chapter 5 (Hazard classification and recommended exposure limits):

DECOS (Member 1): Later sub chronic studies by CIIT in 3 animal species (Bermudez et al, 2003) were not included although they would allow setting of a NOEL for non-carcinogenic endpoints also known to be associated to overload for both fine and ultrafine TiO_2 in rat (and hamster and mice). In this inhalation study (6 hrs/day, 5x per week, 3 months) the authors could show overload in rats with pigmentary TiO_2 at 50 mg/m^3 and for ultrafine TiO_2 at 10 mg/m^3. Indications for increased DNA synthesis in the centriacinar region were observed at 10 mg/m3 for fine TiO_2 and at 2 mg/m^3 for ultrafine TiO_2. Similar findings were reported for inflammatory response based on neutrophils. These data suggest a 5-fold stronger action of ultrafine TiO_2 compared to fine, and contradicts the current conservative approach of the NIOSH draft leading to a 15-fold difference in REL. The latter factor (15) merely „ reflects NIOSH greater concern „ (page 96, line 1996) but is not quantitatively supported by research data

Response: The Bermudez et al. subchronic studies are now included in the updated CIB, and the derivation of the RELs for fine and UF TiO_2 has been described in detail.

DECOS (Member 1): The potential effect of uF TiO_2 by uptake through the olfactory pathway should be included, as currently identied but not able to include in risk assessment.

Response: NIOSH is unaware of TiO_2-specific data on olfactory nerve uptake; therefore, any discussion of the potential effects of such uptake would be speculative at this time.

Comments about Chapter 6 (Measurement and control of TiO_2 aerosol in the workplace:

AC: Referring to lines 2043 & 2044, as an AIHA accredited laboratory director, I do not agree that NIOSH 7300 be the refenced method for TiO_2 since it has poor solubility in the acids used in the filter digestion. OSHA ID 125 is a better choice for the referenced analytical method.

Response: A statement has been added clarifying the need to insure the complete dissolution and recovery of TiO_2 from the sample when using NIOSH Method 7300. The following statement has been added: "When using NIOSH Method 7300, it is important that steps be taken (i.e., pre-treatment with sulfuric or hydrofluoric acid) to insure the complete dissolution and recovery of TiO_2 from the sample."

BD: Provide a table on specific respirator recommendations{including type of filter where acceptable}based on various employee exposure levels to Titanium Dioxide.

Response: The document "NIOSH Respirator Selection Logic" is cited as the appropriate reference source for determining the type of respirator required depending on types of aerosols present and the concentration of TiO_2. The document also states that a properly fit-tested half-facepiece particulate respirator with an N95 filter should provide protection up to 10 times the respective RELs for TiO_2.

NPCA: NIOSH recommends exposure limits of 1.5 mg/m3 for fine TiO_2 and 0.1 mg/m3 for ultrafine 70 TiO_2, as time-weighted average concentrations (TWA) for up to 10 hr/day during a 40-hour work week. In many industries, including and perhaps particularly, the coatings industry, the work environment is characterized by a variety of particulates of varying sizes and species. Most, if not all, current exposure data for TiO_2 is in the form of gravimetric total dust, and no specific information is available for TiO_2. Many coatings manufacturing facilities have put quite good dust control measures into place over the years. Thus, it is very difficult, if not impossible, to determine how stringent the proposed exposure limits are and whether it is even feasible to control workplace exposures to TiO_2 to the recommended level.

Response: NIOSH in 2007 initiated field research studies to determine the extent of workplace exposures to TiO_2 for the purpose of determining the types of industries where exposure occurs, the characteristics of exposure (e.g., size distribution), and whether exposure control measures being employed are effective in reducing exposures to below the RELs. The results will be published upon completion of the field studies.

NPCA: NIOSH has failed to address the critical issue of how industrial hygienists are expected to measure and appropriately speciate particulates in order to determine what fraction constitutes TiO_2. Unless there is a practicable way in which to make this crucial measurement, it will be virtually impossible to determine whether or not a REL for TiO_2 can be met. In this regard, NIOSH has failed to address or evaluate whether, given

current sampling methodologies, meeting the recommended exposure limit is technologically and/or economically feasible. In accordance with NIOSH's charter to develop and establish recommended occupational safety and health standards and devise appropriate exposure monitoring and control strategies, it does contend that its interim sampling recommendations are based on current methodology.[2] Having made that contention, it is critical that NIOSH address fully the sampling difficulties inherent in conforming to a REL for fine and ultrafine TiO_2 in a mixed-particulate workplace.

Response: NIOSH has proposed a tiered-approach sampling strategy that includes steps for the initial determination of the airborne size distribution of TiO_2 (e.g., initial particle characterization by electron microscopy). Once the TiO_2 size distribution has been determined for the particular work place, process, job task, etc. only respirable sampling using NIOSH Method 0600 would be required for routine measurement of exposures for comparison with the respective RELs. Method 0600 has been validated in the laboratory and field for various metals and therefore, should be adequate for measuring airborne TiO_2 at the same accuracy and reliability requirements. In 2007, NIOSH initiated field surveys to evaluate the extent and characteristics of TiO_2 in the workplace. The results will be published upon completion of the field studies.

NPCA: Any exposure assessment for TiO_2 done in order to assess risk must be conducted with a method that has been validated per NIOSH criteria, and complies with NIOSH-promulgated guidelines for development and evaluation of air sampling methods.[3] It is clear that any evaluation of occupational risk performed as part of the CIB must be done in conformance with a method that both meets NIOSH-established criteria and is listed in the NMAM. We view this failure to employ a validated sampling and analytical method as a serious flaw in the development of the CIB. We urge NIOSH to validate and employ an appropriate method for sampling and analyzing "fine and ultra fine particulates" before continuing this effort.

Response: See response to previous comments.

NPCA: Research protocols are being developed to measure levels of TiO_2 in the workplace and to investigate control technologies. This protocol should include investigations at workplaces with complex particulate exposures (e.g., a plant manufacturing architectural coatings).

Response: NIOSH has initiated research efforts to determine the extent and characteristics of occupational exposures to fine and ultrafine (including engineered) TiO_2. This research is being conducted through the NIOSH industry-wide research program and the Health Hazard Evaluation program. Results will be published upon completion of studies.

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[2] CIB, p. 5, line 90.

[3] A list of such validated methods is contained in the NIOSH Manual of Analytical Methods (NMAM).

EX1: *NIOSH Q3. Are the sampling and analysis methods adequate to characterize worker exposure to fine and ultrafine TiO_2?*

Probably. The sampling and analysis methods described by NIOSH appear to provide a reasonable interim approach for conducting an exposure assessment for TiO_2 in the workplace. There are a number of important issues that remain to be clarified, such as how to identify the number and surface area of primary TiO_2 particles in the ultrafine range, particularly in the case of workplace exposures involving particulate other than TiO_2. The recently published data on the primary particle size distribution of commercial TiO_2 pigments (Gibbs et al. 2006) suggests that many applications of TiO_2 will not involve workplace exposure to ultrafine particles. Similar studies with other TiO_2 materials may help to identify exposures of concern.

Response: NIOSH initiated studies in 2007 to characterize workplaces where exposure to TiO_2 occurs. In addition to the sampling scheme recommended by NIOSH in the draft TiO_2 CIB, other measurement instruments and methods are being used in field research studies to determine particle surface area, particle number, and other particle characteristics. These instruments are being used in work places where exposures to ultrafine or engineered TiO_2 occur. The field testing of these instruments is being conducted to determine their feasibility and usefulness in measuring airborne ultrafine TiO_2 and other nanoscale particles.

EX2: *Are the sampling and analysis methods adequate to characterize worker exposure to fine and ultrafine TiO_2?* Commenting on the details of the sampling and analysis methods is beyond my expertise. I am aware of the complexities of attempting to sample and characterize ultrafine particles in general and NIOSH acknowledges that there is presently no personal sampling device available for ultrafine aerosols.

Response: No response required.

EX3: 10. This reviewer concurs that smaller particle size is likely to increase toxicity per unit weight as well as increased penetration. Per unit weight, surface area increases as the square of the reduction in diameter, while particle count increases as the cube. We question whether available data can distinguish between surface area and particle number as the best measure. We note that particle counts were the basis for exposure limits prior to the 1970's, were phased out as mass became the easier technology for analysis. Now that direct reading real time particle counting and sizing is technologically feasible, it may be a better basis for a standard. This reviewer urges NIOSH to clarify terminology.

Response: As noted in the responses to previous comments, NIOSH has initiated research efforts to evaluate workplace exposures to TiO_2. Part of the research effort is to evaluate the proposed sampling strategy in the draft CIB. NIOSH is also investigating the feasibility of using other types of sampling devices that will provide information on particle surface area, particle size, and count. Data gathered from the measurement of aerosolized TiO_2 using these other instruments may provide information that can be used to better describe the health risk associated with exposure.

Comments about Chapter 7 (Research Needs): None.

Note from NIOSH: In 2005, NIOSH presented a Current Intelligence Bulletin (CIB) on TiO_2 for peer and public review. The CIB indicated that weight of evidence for tumorigenicity of TiO_2 (both fine and ultrafine) in animals warrants prudent health measures be taken to protect workers, and NIOSH provided those measures in the form of recommended exposure limits (RELs) and other guidance. However, in the hazard identification, NIOSH concluded in 2005 that there was insufficient evidence to classify TiO_2 as a potential occupational carcinogen, although explicitly stated greater concern for the carcinogenicity of ultrafine TiO_2. The basis for that concern was the finding in a single chronic inhalation study in rats showing significant increase in lung adenocarcinoma at 10 mg/m^3, in addition to evidence from subchronic studies in rats and mice supporting a secondary genotoxic mode of action for poorly-soluble particles via chronic inflammation and oxidative DNA damage related to particle surface area dose. When the CIB was peer reviewed, the peer reviewers, independently and not as a panel, supported, explicitly or implicitly, NIOSH's identification of TiO_2 mode of action as a secondary genotoxic carcinogen. Therefore, based on input from peer reviewers, NIOSH reconsidered its position and determined that there was sufficient evidence to identify ultrafine TiO_2 as a potential occupational carcinogen.

Previously, in the 2005 draft, the hazard assessment considered fine and ultrafine TiO_2 together as a single material. In the most recent prepublication draft, the hazard identification was reassessed for ultrafine and fine TiO_2. A reconsideration of the scientific information was consistent with the peer reviewers' support for considering TiO_2 a secondary genotoxic carcinogen. Additionally, based on a reviewer's comment on the 2005 draft, NIOSH obtained data from the Chemical Industry Institute of Toxicology (CIIT) on pulmonary inflammatory response in animals exposed to TiO_2 that further supported the determination of TiO_2 as a secondary genotoxic carcinogen and indicated that no threshold of risk was likely. However, while the animal data show that exposure to fine TiO_2 could result in lung tumors, and that the frequency of the tumors could be plotted by surface area on the same exposure-response curve for ultrafine TiO_2, NIOSH concluded that there is still insufficient evidence to classify fine TiO_2 as a potential occupational carcinogen. This is because the single animal study of fine TiO_2 observed a significant increase in tumors (adenomas) only at 250 mg/m^3, a dose that is generally considered by today's standards to be high for inhalation toxicology studies – and no increase in tumors at either 10 or 50 mg/m^3. Although the high dose of fine TiO_2 used in the animal study may have been considered questionable, the statistically significant increase in tumors observed in animals warranted precautionary measures to be taken to protect workers' health. Therefore, the particle surface area dose and tumor response model was used to derive the mass-equivalent RELs for ultrafine and fine TiO_2 (since workplace sampling is mass-based). This approach was supported by peer review comments to NIOSH. None of the peer reviewers rejected NIOSH's efforts to conduct cancer risk assessments for fine and ultrafine TiO_2 and develop RELs for them in the 2005 draft. NIOSH was also aware, that in the time since the peer reviews, that an expert review group from the International Agency for Research on Cancer (IARC) determined

that there is sufficient evidence to identify TiO_2 as "possibly carcinogenic to humans" (Group 2B).