1. Since one goal of the Roadmap is to support development of a strategy to address future research needs, I suggest that a more comprehensive and critical review of the literature (than is currently presented) would be helpful to better define the state of the science and to identify the most important of the unresolved issues. The review currently incorporated is incomplete (in that it entirely misses important contributions to the literature) and it tends to be phenomenological rather than critical in that it simply highlights issues and apparent conflicts, rather than critically evaluating whether various apparent conflicts can in fact be reconciled by considering such things as differences in the design and equipment used in various studies, differences in starting assumptions, or other factors. Examples of some of these potential deficiencies are presented in the page-specific comments listed below.

2. As the NAS review of the NIOSH Roadmap emphasizes in multiple places (e.g., bottom of Figure 3-1 on Page 48 and the top of page 49), human epidemiology data should be given precedence over other forms of data when evaluating asbestos risk. Yet, the current Roadmap seems to emphasize animal and in-vitro studies and seems to suggest only a limited role for epidemiology. It is correctly stated in the Roadmap that (with two exceptions) existing epidemiology studies are limited by the crude manner in which historical exposures were characterized and opportunities for conducting new epidemiology studies are limited by the small number of facilities actively mining or processing asbestos. What is not adequately considered, however, is the full potential for reconstructing the character of historical exposures relevant to the existing epidemiology studies.

Analyses of selected lung-tissue samples (from relevant cohort members), archived air filter samples (from relevant environments), and carefully chosen bulk samples (also from relevant environments) holds the potential for providing the detailed characterization data required to facilitate use of the existing epidemiology studies to test hypotheses concerning the effects of fiber size, type, and other fiber characteristics. While the availability of the first two types of samples may be somewhat limited, availability of bulk samples is not. Cross-comparison of all three types of samples can then serve to validate and quantify the uncertainty associated with use of each individual type of sample for defining the character of exposure in any particular environment. These can be formally linked to the intensities of exposures reported in the epidemiology studies to develop quantitative estimates of fully-characterized exposures that can then be incorporated into robust meta-analyses suitable for testing hypotheses of interest (see, for example, Berman and Crump 2003, 2008b; Berman 2010).

While the approach proposed above is subject to some uncertainty, it is unlikely to be less quantitative than development and use of models to quantitatively extrapolate results from animal and in-vitro studies to assess risk in humans. In fact, validation of such models will require that results from the animal and in-vitro studies be formally compared to results from human epidemiology studies. Thus, the best approach for filling current knowledge gaps
may be to pursue both kinds of research simultaneously and I suggest that the Roadmap might be modified to better reflect such an integrated approach.

3. In light of Comment No. 2 above, archived air-filter samples from sites where epidemiology studies have been conducted (to which NIOSH may have access) are especially valuable commodities and should be treated accordingly. This means, for example, that any analyses to be conducted on these filters in the future should be "gold plated" (i.e., they should be conducted in a manner facilitating the broadest most flexible use of the resulting data by multiple researchers both in and outside of NIOSH). In fact, prior to any future analysis, ideas for use of the data from these samples should be solicited from a broad range of researchers potentially interested in using the resulting data so that the protocol for analysis can address the broad needs that are identified. If this is not done, rare and special opportunities to advance knowledge may be lost. In fact, so that important questions concerning laboratory variation can also be addressed to maximize comparability with other studies, carefully selected subsets of the various filters should be analyzed by multiple laboratories using a common and robust protocol. This is consistent with the recommendation of the NAS that NIOSH should encourage broad support for and assistance with their research effort across multiple agencies and organizations.

4. Although the NAS may have failed to recognize the need to develop and standardize a sufficiently rich terminology to describe and distinguish research needs (when various parameters may not be well defined), the ultimate findings of such research, and the nature of particles that are ultimately regulated, I want to commend the authors of the Roadmap for working toward development of the needed terminology. To illustrate this point, consider that, if it is not possible to distinguish between asbestos and non-asbestos fibers by analysis using a particular method, to adequately discuss the utility and application of such a method will require terminology that distinguishes both the asbestos and non-asbestos fibers and the collective set of fibers that would be characterized using the method; a separate term is needed for the collective set of fibers that would be countable using this method.

5. Although there are statements throughout the Roadmap suggesting the difference or similarity of particles of biological importance in various environments, it is not clear how one can judge such "similarities" of particles of biological importance until there is: (1) better characterization of historical exposures and (2) identification of the characteristics of particles that most contribute to biological activity; this is a "chicken and egg" problem. For a hypothetical example, if it is biodurability and size (as opposed to surface chemistry and crystalline habit) that are important. Than two minerals of grossly disparate composition with nevertheless exhibit the same biodurability should be considered more similar than other minerals of closer chemical composition and habit but with differing biodurability. Given this consideration, I suggest softening or eliminating such statements from the Roadmap, unless they are directly linked to a particular line of published research.

PAGE-SPECIFIC COMMENTS

1. Page 1 of 163, First paragraph of introduction. I suggest that the terms, "elongate particles - EP" and "elongate mineral particles - EMP" be defined when they are introduced. Moreover, since this is new language that is being "retrofitted" to many decades of work (and necessarily so), the relationship between how people thought of and defined things historically needs to be linked concisely to the new terms. The next few paragraphs of the introduction are confusing due to this lack of concise definition because the authors are going back and forth between using the new language and other terms (such as asbestos, asbestosiform, cleavage fragments, other minerals) in relation to the new term, but there is no basis given for understanding how they are supposed to relate.

2. Page 1 of 163, First paragraph of introduction. I suggest that, when referring to past research efforts, as in this paragraph, references should be provided. If it is intended as an overview, I suggest at least referencing one or more review articles that provide an overview of the relevant literature.

3. Section 2.1 Background, Page 4 of 163. There is a rich history about the development of research and thinking concerning the understanding of the toxicity of asbestos that is entirely undocumented here (see, for example, Walton 1982; Nicholson 1986; OSHA 1990; HEI-AR 1991; ERG 2003; Berman and Crump 2003; which are more complete overviews that reflect the literally 100's of studies on the subject). I suggest that citing a single article (Stanton et al. 1981) may not be adequate to provide the reader with a reasonable understanding of the growth and evolution of concerns.

4. Second paragraph of Section 2.1, beginning on line 15 of Page 4 of 163. I suggest that any statements addressing general "interest" or "concern" need a citation to document the source of the author's understanding of such interest or concern and that, if the interest is considered "general" such a citation needs to include a good overview (at a minimum) or contain a reasonable subset of the very broad literature on the topic. Also, see previous comment.
5. Second paragraph of Section 2.1, beginning on line 15 of Page 4 of 163. With regard to "interest", it might be good to start with a discussion of those minerals for which there are indications or suggestions that disease has been associated with exposure to their associated particle dusts, otherwise it seems that one is simply defining a very broad universe of possibilities...every mineral creates particle dusts, but not all of them have been shown or are even suspected of being toxic.

6. Line 17 of Page 4 of 163. I suggest that the term "thoracic-sized" should be defined when introduced and the origin and history of the interest in this particular size fraction needs to be explained and documented. While some have referred to it, I am not sure that there is more than reasoned speculation to suggest it is the appropriate size range of interest. Distinctions between this size range and the traditional size range determined by PCM (which has also changed over time) also should be discussed at some point.

7. Paragraph beginning on Line 26 of Page 4 of 163. Although it may be beyond the scope of the Roadmap to attempt to facilitate general standardization of terminology, so as to promote broader understanding of the Roadmap itself, I suggest that the manner in which terms used in the Roadmap be standardized and concisely defined. Thus, I believe that the current glossary is inadequate both because several important terms are missing and because those that are presented are provided with multiple definitions, but no indication about which definition applies to their use within the Roadmap.

8. Paragraph beginning on Line 16 of Page 5 of 163. It would be good to indicate which mineralogical nomenclature is adopted for the Roadmap.

9. Entire Background Chapter 2. Comments 3 and 4 above regarding the need for adequate documentation of statements also apply to the rest of Chapter 2.

10. Paragraph beginning on Line 14 of Page 9 of 163. I believe that crocidolite is still being mined in Bolivia.

11. Paragraph beginning on Line 12 of Page 10 of 163. It is important to recognize that PCM cannot distinguish between fragments of non-asbestos minerals and those of asbestos-related minerals either. In fact, in some environments, PCM may not be capable of distinguishing asbestiform fibers of the asbestos minerals from organic fibers. For one example, it is unclear what fraction of PCM counts in an asbestos-cement plant may come from components of the cement itself, rather than anything having to do with an asbestos-related mineral. Thus, it seems that the problem identified in this paragraph is too narrowly focused so that it may misrepresent the full extent of materials that may contribute to a PCM count that may not otherwise contribute to asbestos-related disease. Given the ultimate importance of this issue, I suggest that it be restated more concisely and that it be adequately documented with references.

12. Paragraph beginning on Line 16 of Page 11 of 163. I suggest that the epidemiology studies indicating a link between asbestos exposure and disease (for the most common diseases) need to be documented and cited in the same manner that links to the less commonly-associated diseases are cited.

13. Paragraphs beginning on Lines 10 and 27 of Page 18 of 163. An important group of recent studies that explicitly addresses the issues considered in these paragraphs that were not cited are: Berman and Crump 2008a, b and Berman 2010. I would also like to suggest that the potential problems associated with several of the specific studies cited in these paragraphs, which have been identified by others, should also be discussed here alongside of the original studies cited. Otherwise, the discussion presented may not adequately communicate the needed understanding of the state of the science that seems to be intended here. For example, although Yano et al. (2001) is cited as an example of nearly pure chrysotile exposures, more recent statements by Dr. Yano himself contradict such assertions (REFERENCES). Moreover, the sensitivity analysis presented in Berman and Crump 2008b, still shows a two-orders of magnitude difference in the relative potency of chrysotile and amphibole asbestos toward induction of mesothelioma, even if one assumes (despite ample evidence to the contrary) that all of the predominantly chrysotile environments are in fact exposures to pure chrysotile. Similarly, several of the participants in the EPA peer-consultation workshop (ERG 2003) expressed concerns both with the methodology used by Suzuki and Yuen (2001) and, even ignoring the methodological problems, the fallacy of drawing conclusions concerning toxicity based solely on the presence of something in a target tissue absent any evidence showing some kind of dose-response.

14. Paragraph beginning on Line 27 of Page 18 of 163. I believe that the "amphibole hypothesis" generally refers more specifically to the potency of chrysotile toward mesothelioma, rather than to carcinogenicity in general (Berman and Crump 2008b, Berman 2010). Moreover, as described in Berman (2010), I suggest that one needs to be very careful about drawing conclusions concerning the presence (or absence) of amphibole asbestos in the exposures experienced by specific cohorts based on samples representing at best only a very small fraction of the time over which such exposures occurred (such as the samples considered in Stayner et al. 2007). In contrast to any conclusions that might be drawn from these samples, for example, both Case et al. (2000) and Green et al. (1997) indicate from lung analyses (which provide an integrated picture of cohort exposure) that South Carolina textile workers may have been exposed to substantial quantities of commercial amphibole asbestos, none of which was observed among the samples reported by Stayner et al.
15. Paragraph beginning on Line 2 of Page 19 of 163. As there is a rich literature of animal studies, I suggest that it may not provide the best picture of the state of the science, to pick out one such study (that may support a particular point) and then use phenomenological observations from that study to "prove" a point. This is especially true when studies exist that provide formal hypothesis testing of the explicit point being considered. In the case of the Davis et al. (1986) study that is cited, for example, Berman et al. (1995a,b) provide a formal test of the relative potency of chrysotile and amphibole asbestos to induce lung tumors and, separately, mesothelioma in rats (across a diverse set of mutually-consistent animal-inhalation studies). Moreover, as suggested in Berman and Crump (2008b) and Berman (2010), comparing potencies across exposures requires simultaneous consideration of both fiber size and type, if such comparisons are to be reasonably interpreted.

16. Paragraph beginning on Line 2 of Page 19 of 163. I suggest that it would be good to cite the other recent asbestos-related risk protocol (Berman and Crump 2008a,b) along with Hodgson and Darnton (2001). Moreover, an analysis of the time-dependence of disease in humans (presented in Berman and Crump 2008a) might be mentioned here because it indicates that, although there is much literature indicating that the biopersistence of amphiboles may explain their apparent greater potency (at least toward mesothelioma), the mechanism of the effect is not obvious because, although the potencies differ, the time development of both lung cancer and mesothelioma are similar in cohorts exposed either predominantly to chrysotile or amphibole asbestos.

17. Section 2.6.1.2 beginning on Page 19 of 163. This section covers an important issue as there is increasing evidence that the asbestiform varieties of a broader range of amphibole minerals (and potentially minerals from other families) can induce asbestos-related diseases. Research would be helpful here to better define the full range of minerals that occur in this habit and can induce asbestos-related disease and to better quantify the relative potency of the various amphiboles and the asbestiform varieties of other minerals as well. It should also be noted that it is not generally known whether the boundary for biological activity precisely conforms to the boundary between asbestiform and non-asbestiform habits and this should be a focus of the proposed research.

18. Paragraph beginning on line 36 of Page 20 of 163. I would like to suggest that the apparent penchant of regulatory agencies to redefine terms that otherwise have established definitions in various fields of science may have contributed to the current confusion regarding asbestos.
As an example, the discussion in this paragraph involves the "NIOSH definition of airborne asbestos fibers." Since the terms "asbestos," "asbestiform," and "fiber" have clear mineralogical definitions, if the NIOSH goal in 1990 was to regulate (or establish a policy for) particles composed of a defined set of minerals (with defined compositions) that satisfy the dimensional criteria defined in the analytical method used to determine their airborne concentrations, this could have been done simply by defining as hazardous the "dusts containing particles of the specified minerals satisfying the indicated dimensions," which are known or suspected to cause lung cancer, mesothelioma, asbestosis, and any of the other diseases associated with exposure to asbestos. Such operational definitions would clearly achieve the intentions of the regulations (or policies) while avoiding the confusion introduced by otherwise redefining terms that are already concisely defined by others. While it is clearly the responsibility (as well as the prerogative) of regulatory agencies to establish policies and regulate all materials that they consider hazardous, it is not necessary to redefine terms to effect such policies or regulations.

I would also like to point out for this paragraph that the 1990 NIOSH policy was developed 20 years ago so that it would be helpful to acknowledge that much relevant science has been published in the interim.

19. Paragraph beginning on Line 36 of Page 21 of 163. See comment No. 18 above. Also, I suggest that one should consider that questions concerning the relative health effects associated with particles exhibiting distinct crystalline habits is confounded by considerations involving the general dimensions of any particles that contribute to asbestos-related risk. For example, the size range of structures traditionally counted by PCM includes those that do not get into the lungs; given the density of the asbestos minerals, the thickest of elongate particles that can get into the lungs (even during mouth breathing) are about 1.5 μm in true diameter (Berman and Crump 2003, ERG 2003) and this can assuredly be considered one constraint on the boundary between biologically active fibers and those that are benign. Yet, while virtually all asbestiform fibers counted by PCM will be thinner than this cutoff, a substantial number of cleavage fragments will not (Siegrist and Wylie 1980, Wylie 1988, Wylie et al. 1993, Veblen and Wylie 1993). As a consequence, if the dimensional constraints for the analytical method employed to determine airborne concentrations of the regulated particles are not modified, applying this method to environments in which the majority of particles are cleavage fragments will result in counting large number of particles that cannot possibly contribute to the induction of disease (along with the few that might).

20. Section 2.6.1.3.2 beginning on Line 29 of Page 31 of 163. It seems it would be prudent to include discussion of a broader range of the available literature than what is cited in this section. For example, Berman et al. (1995a, b) presents a meta analysis of a set of mutually-consistent animal-inhalation studies that is informative of the effects of size and mineral type. A further refinement of this analysis is also provided in Berman and Crump (2003,
Section 6.4.3), which should perhaps be given greatest attention. Moreover, Berman and Crump (2003, Chapter 6) presents a detailed, critical review of the animal and in vitro literature (with some success in reconciling what otherwise seems to be disparate findings). This review includes critical comparison and analysis of the studies that are cited in this section of the Roadmap.

21. Section 2.6.1.3.3 beginning on Line 41 of Page 33 of 163. While the limitations to analytical methods cited in this section are important considerations that need to be further addressed, particularly with regard to the inability of current methods to easily distinguish among the crystalline habits of individual particles, considerations concerning the confounding effects of crystalline habit and the dimensional bounds defined for particles that are counted should be better addressed (see Comment No. 19 above). The bottom line is that, if the dimensional criteria for the analytical methods used to determine the concentration of regulated EMP’s are not modified, we run the risk of producing data that will severely mask and not reasonably reflect the relative hazards of exposures experienced in different environments (see also, Berman and Crump 2008b, Berman 2010). This, in turn, may severely impede the reliability of the decision making needed to formulate sound and health protective policies and regulations.

22. Section 2.7 beginning on Line 1 of Page 36 of 163. I would like to suggest that this review could be substantially beefed up and made less "phenomenological". For example, a newer and more complete and more critical review (in which several apparently contradictory findings were successfully reconciled) addressing the same issues can be found in Berman and Crump (2003, Chapter 6). Such an evaluation may ultimately help to better define the state of the science and more clearly define important but unresolved issues. This in turn may narrow and better focus the range of future research needs. Nevertheless this section does a good job of introducing the topics and many of the most important issues.

24. Section 2.7 beginning on Line 1 of Page 36 of 163. It is a bit surprising that little to no consideration has been given in this section to the human epidemiology database and what can be learned from it. Meta analyses such as Hodgson and Darnton (2000) and Berman and Crump (2003, 2008a,b) have gone a long way toward reconciling much of the epidemiology literature and, in doing so, have helped to identify the effects of fiber size and type. Although further work is clearly needed in this arena (Berman and Crump 2008b, Berman 2010), especially given the concerns raised in Section 2.7.4.1 regarding difficulties with extrapolation of results from animal and in-vitro studies to provide quantitative information suitable for human risk assessment (also reviewed in Berman and Crump 2003), it seems that the simplest and most direct route to the ultimate goal of developing a quantitative model of human risk still requires consideration of the human data. Moreover, any results from animal or in-vitro studies that are ultimately proposed for extrapolation to humans will also need to be validated against human data. Various studies have shown that a number of approaches for reconstructing historical exposures relevant to human cohorts show real promise (e.g., Dement et al. 2007, Stayner et al. 2007, Loomis et al. 2007, Berman and Crump 2003, 2008a,b, Berman 2010) and should certainly be considered going forward as part of any research strategy focused on resolving questions concerning health risks associated with asbestos and other EMP's.

25. Section 2.7.4.2 beginning on Line 29 of Page 45 of 163. I suggest that this section be updated to reflect a more complete set of findings from the literature, including especially the more recent literature. For example, the meta analysis of the animal inhalation database by Berman et al. (1995a,b) with its further revision in Berman and Crump (2003, Section 6.4.3) is informative in this arena. Moreover, the findings drawn from the meta analyses of the human data (Hodgson and Darnton 2000, Berman and Crump 2003, 2008a,b, Berman 2010) should also be addressed.

26. Paragraph beginning on Line 20 of Page 58 of 163. One of the advantages of the studies of Berman and Crump (2003, 2008a,b) over those of Dement et al. (2007), Stayner et al. (2007), and Hein et al. (2007) is that it they are meta analyses across a range of highly diverse environments that differ radically in the composition and characteristics of the relevant exposures. Under such conditions, it is highly unlikely that exposures to specific categories of structures would be correlated, as they do not relate to one another across environments. Therefore, despite the fact that findings from these various studies tend to support one another (at least with regard to the importance of fiber dimension), it is a bit surprising the former set of studies are not mentioned. As the two sets of studies are each subject to a unique set of limitations, taken together, the whole is much more powerful than the parts.

27. Sentence beginning on Line 24 of Page 60 f 163. While PCM may have an established, historic association with disease risk in single environments (as, apparently, do many measures of dust exposure in single asbestos environments), there is a poor of fit of exposures determined using PCM across environments (for example, Berman et al. 1995a,b, Berman and Crump 2008b). Therefore, because risk estimation requires extrapolation across environments (i.e., from an environment in which disease outcomes are known to one in which they are unknown and need to be predicted), the reliability of use of the PCM method for this purpose is not clear.

28. Paragraph beginning on Line 36 of Page 61 of 163. Differences between estimated and actual risks may also be attributable to differences in the fraction of particles that are detected by PCM but are too thick to get into the lung and differences in the actual potencies of various mineral types, which are not addressed when applying the current method.
Moreover, the large variation in exposure-response coefficients reported across the available epidemiology studies (based on PCM counts) vary for lung cancer by about a factor of 50 (excluding one negative study, which would make the ratio infinite if it were to be included) and by more than a factor of 1,000 for mesothelioma (Berman and Crump 2003, 2008a), which suggests that the reliability of PCM as an index of exposure suitable for predicting risk may need to be more carefully scrutinized.

29. Paragraph beginning on Line 26 of Page 66 of 163. I would like to suggest that it is perhaps the attempt in this paragraph to redefine asbestos that contributes to the confusion in this field. Might it not better to define the particles that are to be regulated operationally (and pick a new name for them), but not change a term with an established definition to fit the definition of what regulators wish to regulate?

30. Bullets under Objective 1 on Line 11 of Page 69 of 163. I am surprised that more work with epidemiological studies (including work to reconstruct historical exposures) is not highlighted as a major component of this objective both because much relevant information remains to be obtained from such work and because whatever findings are ultimately gleaned from animal and in-vitro studies will need to be validated against human studies, if they are to be quantitatively extrapolated to humans (see Comment No. 24 above). The limited role envisioned for epidemiology listed under the later objectives, do not do justice to the potential value of the work described here (involving exposure reconstruction, re-analysis of existing epidemiology studies supplemented with new ones, and conducting robust meta analyses). Moreover, this was a primary focus of the comments from the NAS concerning the last version of the Roadmap.

31. Section 3.3 beginning on Page 71. I agree that establishing a repository is critically important. I also suggest that some consideration be given in this section to the enormous effort that will be required to generate homogeneous samples from particular materials that can then be made available for distribution and testing. It makes little sense to characterize materials in the repository, if they are not prepared and maintained in such a manner so as to have confidence that the characteristics determined for the material will remain valid even after an aliquot of material is sent out for use in health-related or other studies. As an illustration of the substantial effort that will be involved, I suggest looking at the studies published documenting the development and distribution of the UICC samples (Rendall 1969, 1980; Timbrell and Rendall 1971; Timbrell 1980).

32. Text beginning on Line 27 of Page 74 and continuing to the end of the Section. I would like to suggest the range of mechanisms potentially contributing to asbestos-related diseases are much broader and more complex than the few mentioned in these paragraphs so that, if this is to be the source of focus on research needs, a more systematic listing and ranking would be helpful. As a start, I suggest considering the list and discussion found associated with Figure 6-4 and Table 6-5 of Berman and Crump (2003).

33. Step 1 beginning on Line 32 of Page 76. I suggest that careful thought be given to the need to standardize the nature of the characterization to be conducted on samples used during these studies. Not only must characterization address all of the characteristics of potential interest, but results will not be comparable across studies unless an effort is made up front to standardize the breadth of tests needed and the set of characteristics to determine and to track the inter-laboratory performance of the methods used for sample characterization. This point also applies to the analytical needs of the other steps of this list.

34. Section 3.4.1 beginning on Line 4 of Page 77. This section is very detailed but lean on references and could be beefed up.

35. Section 3.4.2 beginning on Line 27 of Page 80. It would be helpful to translate Aerodynamic Equivalent Diameters into true diameters for the kinds of structures common among asbestos dusts and dusts from other EMP's. For these kinds of particles, AED's are very different (and substantially larger) than true diameters. However, it is the true diameters that are defined during analysis, so these two types of diameters should not be confused. An example of a chart showing the relationship between these two can be found in Figure 6-2 of Berman and Crump (2003).

36. Sentence beginning on Line 33 of Page 82. Ultimately, any quantitative inference drawn either from in-vitro or whole animal studies will need to be validated against observations concerning disease incidence in humans, if they are going to be used to predict risk in humans.

37. Parenthetical remark beginning on Line 20 of Page 83. Actually, more of the epidemiology studies employed to develop existing risk protocols (particularly those involving mesothelioma risk) involve mixed and amphibole asbestos exposures than predominantly chrysotile exposures (e.g., Nicholson 1986; Hodgson and Darnton 2000; Berman and Crump 2003, 2008b; Berman 2010). Moreover, especially if it continues to be re-confirmed that chrysotile is of relatively limited potency toward the induction of mesothelioma, than use of chrysotile as the "gold standard" for validation may not be appropriate.
38. Section 3.5.1 beginning on Line 4 of Page 85. I suggest that a more flexible approach be considered for collecting and analyzing samples useful for characterizing the nature of historical as well as current exposures. Sources of data useful for this purpose may include not only archived filters (which are very limited in extent), but consideration of lung tissue samples (both new from various repositories and from re-analysis of archived samples already reported in the literature), and consideration of appropriately selected bulk samples, from which dusts can be generated under controlled conditions in the laboratory. Previous work suggests that all of these sources of data have a useful role to play (e.g., Berman 2010). See General Comment No. 2 above.

39. Sentence beginning on Line 23 of Page 87. I agree with the utility of well-designed meta analyses of the human epidemiology data and suggest that the published examples be cited (e.g., Nicholson 1986; Hodgson and Darnton 2000; Berman and Crump 2003, 2008b).

40. Section 3.5.4 beginning on Line 16 of Page 90. See Comment No. 34 above.

41. Paragraph beginning on Line 9 of Page 100. See Comment Nos. 36 and 38 and General Comment No. 2 above. Potentially, the proposed approach seems like a longer road to travel to get the same point than focusing on improving exposure characterization in existing epidemiology studies, developing new epidemiology studies in relevant environments, and conducting well designed meta analyses. At a minimum, a parallel track seems in order, as results from the human analyses and the animal analyses would complement one another.

42. Paragraph beginning on Line 28 of Page 100. See General Comment No. 2 above.

43. Paragraph beginning on Line 7 of Page 102. This paragraph clearly defines the intended, overall goal and focus of the research being described and perhaps should be given greater prominence by moving it to the front of the entire discussion so that it provides a framework that can be readily referenced to help focus the rest of the discussion in this Chapter.

44. Paragraph beginning on Line 24 of Page 104. See Comment No. 31 above.

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