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APPENDIX C – 1

OFFICE OF MANAGEMENT AND BUDGET

Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies; Republication

Editorial Note: Due to numerous errors, this document is being reprinted in its entirety. It was originally printed in the **Federal Register** on Thursday, January 3, 2002 at 67 FR 369–378 and was corrected on Tuesday, February 5, 2002 at 67 FR 5365.

AGENCY: Office of Management and Budget, Executive Office of the President.

ACTION: Final guidelines.

SUMMARY: These final guidelines implement section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001 (Public Law 106–554; H.R. 5658). Section 515 directs the Office of Management and Budget (OMB) to issue government-wide guidelines that "provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies." By October 1, 2002, agencies must issue their own implementing guidelines that include "administrative mechanisms allowing affected persons to seek and obtain correction of information maintained and disseminated by the agency" that does not comply with the OMB guidelines. These final guidelines also reflect the changes OMB made to the guidelines issued September 28, 2001, as a result of receiving additional comment on the "capable of being substantially reproduced" standard (paragraphs V.3.B, V.9, and V.10), which OMB previously issued on September 28, 2001, on an interim final basis.

DATES: *Effective Date:* January 3, 2002.

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SUPPLEMENTARY INFORMATION: In section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001 (Public Law 106–554; H.R. 5658), Congress directed the Office of Management and Budget (OMB) to issue, by September 30, 2001, government-wide guidelines that "provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies * * *" Section 515(b) goes on to state that the OMB guidelines shall:

"(1) apply to the sharing by Federal agencies of, and access to, information disseminated by Federal agencies; and

"(2) require that each Federal agency to which the guidelines apply—

"(A) issue guidelines ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by the agency, by not later than 1 year after the date of issuance of the guidelines under subsection (a);

"(B) establish administrative mechanisms allowing affected persons to seek and obtain correction of information maintained and disseminated by the agency that does not comply with the guidelines issued under subsection (a); and

"(C) report periodically to the Director—

"(i) the number and nature of complaints received by the agency regarding the accuracy of information disseminated by the agency and;

"(ii) how such complaints were handled by the agency."

Proposed guidelines were published in the **Federal Register** on June 28, 2001 (66 FR 34489). Final guidelines were published in the **Federal Register** on September 28, 2001 (66 FR 49718). The Supplementary Information to the final guidelines published in September 2001 provides background, the underlying principles OMB followed in issuing the final guidelines, and statements of intent concerning detailed provisions in the final guidelines.

In the final guidelilnes published in September 2001, OMB also requested additional comment on the "capable of being substantially reproduced" standard and the related definition of "influential scientific or statistical information" (paragraphs V.3.B, V.9, and V.10), which were issued on an interim final basis. The final guidelines published today discuss the public comments OMB received, the OMB response, and amendments to the final guidelines published in September 2001.

In developing agency-specific guidelines, agencies should refer both to the Supplementary Information to the final guidelines published in the **Federal Register** on September 28, 2001 (66 FR 49718), and also to the Supplementary Information published today. We stress that the three "Underlying Principles" that OMB followed in drafting the guidelines that we published on September 28, 2001 (66 FR 49719), are also applicable to the amended guidelines that we publish today.

In accordance with section 515, OMB has designed the guidelines to help agencies ensure and maximize the quality, utility, objectivity and integrity of the information that they disseminate (meaning to share with, or give access to, the public). It is crucial that information Federal agencies disseminate meets these guidelines. In this respect, the fact that the Internet enables agencies to communicate information quickly and easily to a wide audience not only offers great benefits to society, but also increases the potential harm that can result from the dissemination of information that does not meet basic information quality guidelines. Recognizing the wide variety of information Federal agencies disseminate and the wide variety of dissemination practices that agencies have, OMB developed the guidelines with several principles in mind.

First, OMB designed the guidelines to apply to a wide variety of government information dissemination activities that may range in importance and scope. OMB also designed the guidelines to be generic enough to fit all media, be they printed, electronic, or in other form. OMB sought to avoid the problems that would be inherent in developing detailed, prescriptive, "one-size-fits-all" government-wide guidelines that would artificially require different types of dissemination activities to be treated in the same manner. Through this flexibility, each agency will be able to incorporate the requirements of these OMB guidelines into the agency's own information resource management and administrative practices.

Second, OMB designed the guidelines so that agencies will meet basic information quality standards. Given the administrative mechanisms required by section 515 as well as the standards set forth in the Paperwork Reduction Act, it is clear that agencies should not disseminate substantive information that does not meet a basic level of quality. We recognize that some government information may need to meet higher or more specific information quality standards than those that would apply to other types of government information. The more important the information, the higher the quality standards to which it should be held, for example, in those situations involving "influential scientific, financial, or statistical information" (a phrase defined in these guidelines). The guidelines recognize, however, that

information quality comes at a cost. Accordingly, the agencies should weigh the costs (for example, including costs attributable to agency processing effort, respondent burden, maintenance of needed privacy, and assurances of suitable confidentiality) and the benefits of higher information quality in the development of information, and the level of quality to which the information disseminated will be held.

Third, OMB designed the guidelines so that agencies can apply them in a common-sense and workable manner. It is important that these guidelines do not impose unnecessary administrative burdens that would inhibit agencies from continuing to take advantage of the Internet and other technologies to disseminate information that can be of great benefit and value to the public. In this regard, OMB encourages agencies to incorporate the standards and procedures required by these guidelines into their existing information resources management and administrative practices rather than create new and potentially duplicative or contradictory processes. The primary example of this is that the guidelines recognize that, in accordance with OMB Circular A–130, agencies already have in place well-established information quality standards and administrative mechanisms that allow persons to seek and obtain correction of information that is maintained and disseminated by the agency. Under the OMB guidelines, agencies need only ensure that their own guidelines are consistent with these OMB guidelines, and then ensure that their administrative mechanisms satisfy the standards and procedural requirements in the new agency guidelines. Similarly, agencies may rely on their implementation of the Federal Government's computer security laws (formerly, the Computer Security Act, and now the computer security provisions of the Paperwork Reduction Act) to establish appropriate security safeguards for ensuring the "integrity" of the information that the agencies disseminate.

In addition, in response to concerns expressed by some of the agencies, we want to emphasize that OMB recognizes that Federal agencies provide a wide variety of data and information. Accordingly, OMB understands that the guidelines discussed below cannot be implemented in the same way by each agency. In some cases, for example, the data disseminated by an agency are not collected by that agency; rather, the information the agency must provide in a timely manner is compiled from a variety of sources that are constantly updated and revised and may be confidential. In such cases, while agencies' implementation of the guidelines may differ, the essence of the guidelines will apply. That is, these agencies must make their methods transparent by providing documentation, ensure quality by reviewing the underlying methods used in developing the data and consulting (as appropriate) with experts and users, and keep users informed about corrections and revisions.

Summary of OMB Guidelines

These guidelines apply to Federal agencies subject to the Paperwork Reduction Act (44 U.S.C. chapter 35). Agencies are directed to develop information resources management procedures for reviewing and substantiating (by documentation or other means selected by the agency) the quality (including the objectivity, utility, and integrity) of information before it is disseminated. In addition, agencies are to establish administrative mechanisms allowing affected persons to seek and obtain, where appropriate, correction of information disseminated by the agency that does not comply with the OMB or agency guidelines. Consistent with the underlying principles described above, these guidelines stress the importance of having agencies apply these standards and develop their administrative mechanisms so they can be implemented in a common sense and workable manner. Moreover, agencies must apply these standards flexibly, and in a manner appropriate to the nature and timeliness of the information to be disseminated, and incorporate them into existing agency information resources management and administrative practices.

Section 515 denotes four substantive terms regarding information disseminated by Federal agencies: quality, utility, objectivity, and integrity. It is not always clear how each substantive term relates—or how the four terms in aggregate relate—to the widely divergent types of information that agencies disseminate. The guidelines provide definitions that attempt to establish a clear meaning so that both the agency and the public can readily judge whether a particular type of information to be disseminated does or does not meet these attributes.

In the guidelines, OMB defines "quality" as the encompassing term, of which "utility," "objectivity," and "integrity" are the constituents. "Utility" refers to the usefulness of the information to the intended users. "Objectivity" focuses on whether the disseminated information is being presented in an accurate, clear, complete, and unbiased manner, and as a matter of substance, is accurate, reliable, and unbiased. "Integrity" refers to security—the protection of information from unauthorized access or revision, to ensure that the information is not compromised through corruption or falsification. OMB modeled the definitions of "information," "government information," "information dissemination product," and "dissemination" on the longstanding definitions of those terms in OMB Circular A–130, but tailored them to fit into the context of these guidelines.

In addition, Section 515 imposes two reporting requirements on the agencies. The first report, to be promulgated no later than October 1, 2002, must provide the agency's information quality guidelines that describe administrative mechanisms allowing affected persons to seek and obtain, where appropriate, correction of disseminated information that does not comply with the OMB and agency guidelines. The second report is an annual fiscal year report to OMB (to be first submitted on January 1, 2004) providing information (both quantitative and qualitative, where appropriate) on the number, nature, and resolution of complaints received by the agency regarding its perceived or confirmed failure to comply with these OMB and agency guidelines.

Public Comments and OMB Response

Applicability of Guidelines. Some comments raised concerns about the applicability of these guidelines, particularly in the context of scientific research conducted by Federally employed scientists or Federal grantees who publish and communicate their research findings in the same manner as their academic colleagues. OMB believes that information generated and disseminated in these contexts is not covered by these guidelines unless the agency represents the information as, or uses the information in support of, an official position of the agency.

As a general matter, these guidelines apply to "information" that is "disseminated" by agencies subject to the Paperwork Reduction Act (44 U.S.C. 3502(1)). See paragraphs II, V.5 and V.8. The definitions of "information" and "dissemination" establish the scope of the applicability of these guidelines. "Information" means "any communication or representation of knowledge such as facts or data * * *" This definition of information in paragraph V.5 does "not include opinions, where the agency's presentation makes it clear that what is

being offered is someone's opinion rather than fact or the agency's views."

"Dissemination" is defined to mean "agency initiated or sponsored distribution of information to the public." As used in paragraph V.8, "agency INITIATED * * * distribution of information to the public" refers to information that the agency disseminates, e.g., a risk assessment prepared by the agency to inform the agency's formulation of possible regulatory or other action. In addition, if an agency, as an institution, disseminates information prepared by an outside party in a manner that reasonably suggests that the agency agrees with the information, this appearance of having the information represent agency views makes agency dissemination of the information subject to these guidelines. By contrast, an agency does not "initiate" the dissemination of information when a Federally employed scientist or Federal grantee or contractor publishes and communicates his or her research findings in the same manner as his or her academic colleagues, even if the Federal agency retains ownership or other intellectual property rights because the Federal government paid for the research. To avoid confusion regarding whether the agency agrees with the information (and is therefore disseminating it through the employee or grantee), the researcher should include an appropriate disclaimer in the publication or speech to the effect that the "views are mine, and do not necessarily reflect the view" of the agency.

Similarly, as used in paragraph V.8., "agency * * * SPONSORED distribution of information to the public" refers to situations where an agency has directed a third-party to disseminate information, or where the agency has the authority to review and approve the information before release. Therefore, for example, if an agency through a procurement contract or a grant provides for a person to conduct research, and then the agency directs the person to disseminate the results (or the agency reviews and approves the results before they may be disseminated), then the agency has "sponsored" the dissemination of this information. By contrast, if the agency simply provides funding to support research, and it the researcher (not the agency) who decides whether to disseminate the results and—if the results are to be released—who determines the content and presentation of the dissemination, then the agency has not "sponsored" the dissemination even though it has funded the research and even if the Federal agency retains ownership or other intellectual property rights because the Federal government paid for the research. To avoid confusion regarding whether the agency is sponsoring the dissemination, the researcher should include an appropriate disclaimer in the publication or speech to the effect that the "views are mine, and do not necessarily reflect the view" of the agency. On the other hand, subsequent agency dissemination of such information requires that the information adhere to the agency's information quality guidelines. In sum, these guidelines govern an agency's dissemination of information, but generally do not govern a third-party's dissemination of information (the exception being where the agency is essentially using the third-party to disseminate information on the agency's behalf). Agencies, particularly those that fund scientific research, are encouraged to clarify the applicability of these guidelines to the various types of information they and their employees and grantees disseminate.

Paragraph V.8 also states that the definition of "dissemination" does not include "* * * distribution limited to correspondence with individuals or persons, press releases, archival records, public filings, subpoenas or adjudicative processes." The exemption from the definition of "dissemination" for "adjudicative processes" is intended to exclude, from the scope of these guidelines, the findings and determinations that an agency makes in the course of adjudications involving specific parties. There are well-established procedural safeguards and rights to address the quality of adjudicatory decisions and to provide persons with an opportunity to contest decisions. These guidelines do not impose any additional requirements on agencies during adjudicative proceedings and do not provide parties to such adjudicative proceedings any additional rights of challenge or appeal.

*The Presumption Favoring Peer-Reviewed Information.*As a general matter, in the scientific and research context, we regard technical information that has been subjected to formal, independent, external peer review as presumptively objective. As the guidelines state in paragraph V.3.b.i: "If data and analytic results have been subjected to formal, independent, external peer review, the information may generally be presumed to be of acceptable objectivity." An example of a formal, independent, external peer review is the review process used by scientific journals.

Most comments approved of the prominent role that peer review plays in the OMB guidelines. Some comments contended that peer review was not accepted as a universal standard that incorporates an established, practiced, and sufficient level of objectivity. Other comments stated that the guidelines would be better clarified by making peer review one of several factors that an agency should consider in assessing the objectivity (and quality in general) of original research. In addition, several comments noted that peer review does not establish whether analytic results are capable of being substantially reproduced. In light of the comments, the final guidelines in new paragraph V.3.b.i qualify the presumption in favor of peer-reviewed information as follows: "However, this presumption is rebuttable based on a persuasive showing by the petitioner in a particular instance."

We believe that transparency is important for peer review, and these guidelines set minimum standards for the transparency of agency-sponsored peer review. As we state in new paragraph V.3.b.i: "If data and analytic results have been subjected to formal, independent, external peer review, the information may generally be presumed to be of acceptable objectivity. However, this presumption is rebuttable based on a persuasive showing by the petitioner in a particular instance. If agency-sponsored peer review is employed to help satisfy the objectivity standard, the review process employed shall meet the general criteria for competent and credible peer review recommended by OMB–OIRA to the President's Management Council (9/20/01) (http://www.whitehouse.gov/omb/inforeg/oira_review-process.html), namely, 'that (a) peer reviewers be selected primarily on the basis of necessary technical expertise, (b) peer reviewers be expected to disclose to agencies prior technical/policy positions they may have taken on the issues at hand, (c) peer reviewers be expected to disclose to agencies their sources of personal and institutional funding (private or public sector), and (d) peer reviews be conducted in an open and rigorous manner.'"

The importance of these general criteria for competent and credible peer review has been supported by a number of expert bodies. For example, "the work of fully competent peer-review panels can be undermined by allegations of conflict of interest and bias. Therefore, the best interests of the Board are served by effective policies and procedures regarding potential conflicts of interest, impartiality, and panel balance." (*EPA's Science Advisory*

Board Panels: Improved Policies and Procedures Needed to Ensure Independence and Balance, GAO–01–536, General Accounting Office, Washington, DC, June 2001, page 19.) As another example, "risk analyses should be peer-reviewed and accessible—both physically and intellectually—so that decision-makers at all levels will be able to respond critically to risk characterizations. The intensity of the peer reviews should be commensurate with the significance of the risk or its management implications." (*Setting Priorities, Getting Results: A New Direction for EPA,* Summary Report, National Academy of Public Administration, Washington, DC, April 1995, page 23.)

These criteria for peer reviewers are generally consistent with the practices now followed by the National Research Council of the National Academy of Sciences. In considering these criteria for peer reviewers, we note that there are many types of peer reviews and that agency guidelines concerning the use of peer review should tailor the rigor of peer review to the importance of the information involved. More generally, agencies should define their peer-review standards in appropriate ways, given the nature and importance of the information they disseminate.

Is Journal Peer Review Always Sufficient? Some comments argued that journal peer review should be adequate to demonstrate quality, even for influential information that can be expected to have major effects on public policy. OMB believes that this position overstates the effectiveness of journal peer review as a quality-control mechanism.

Although journal peer review is clearly valuable, there are cases where flawed science has been published in respected journals. For example, the NIH Office of Research Integrity recently reported the following case regarding environmental health research:

> "Based on the report of an investigation conducted by [XX] University, dated July 16, 1999, and additional analysis conducted by ORI in its oversight review, the US Public Health Service found that Dr. [X] engaged in scientific misconduct. Dr. [X] committed scientific misconduct by intentionally falsifying the research results published in the journal SCIENCE and by providing falsified and fabricated materials to investigating officials at [XX] University in response to a request for original data to support the research results and conclusions report in the SCIENCE paper. In addition, PHS finds that there is no original data or other corroborating evidence to support the research results and conclusions reported in the SCIENCE paper as a whole." (66 FR 52137, October 12, 2001).

Although such cases of falsification are presumably rare, there is a significant scholarly literature documenting quality problems with articles published in peer-reviewed research. "In a [peer-reviewed] meta-analysis that surprised many—and some doubt—researchers found little evidence that peer review actually improves the quality of research papers." (*See, e.g., Science,* Vol. 293, page 2187 (September 21, 2001.)) In part for this reason, many agencies have already adopted peer review and science advisory practices that go beyond journal peer review. *See, e.g.,* Sheila Jasanoff, *The Fifth Branch: Science Advisers as Policy Makers,* Cambridge, MA, Harvard University Press, 1990; Mark R. Powell, *Science at EPA: Information in the Regulatory Process.* Resources for the Future, Washington, DC., 1999, pages 138–139; 151–153; *Implementation of the Environmental Protection Agency's Peer Review Program: An SAB Evaluation of Three Reviews,* EPA–SAB–RSAC–01–009, A Review of the Research Strategies Advisory Committee (RSAC) of the EPA Science Advisory Board (SAB), Washington, DC., September 26, 2001. For information likely to have an important public policy or private sector impact, OMB believes that additional quality checks beyond peer review are appropriate.

Definition of "Influential". OMB guidelines apply stricter quality standards to the dissemination of information that is considered "influential." Comments noted that the breadth of the definition of "influential" in interim final paragraph V.9 requires much speculation on the part of agencies.

We believe that this criticism has merit and have therefore narrowed the definition. In this narrower definition, "influential", when used in the phrase "influential scientific, financial, or statistical information", is amended to mean that "the agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public policies or important private sector decisions." The intent of the new phrase "clear and substantial" is to reduce the need for speculation on the part of agencies. We added the present tense—"or does have"—to this narrower definition because on occasion, an information dissemination may occur simultaneously with a particular policy change. In response to a public comment, we added an explicit reference to "financial" information as consistent with our original intent.

Given the differences in the many Federal agencies covered by these guidelines, and the differences in the nature of the information they disseminate, we also believe it will be helpful if agencies elaborate on this definition of "influential" in the context of their missions and duties, with due consideration of the nature of the information they disseminate. As we state in amended paragraph V.9, "Each agency is authorized to define 'influential' in ways appropriate for it given the nature and multiplicity of issues for which the agency is responsible."

Reproducibility. As we state in new paragraph V.3.b.ii: "If an agency is responsible for disseminating influential scientific, financial, or statistical information, agency guidelines shall include a high degree of transparency about data and methods to facilitate the reproducibility of such information by qualified third parties." OMB believes that a reproducibility standard is practical and appropriate for information that is considered "influential", as defined in paragraph V.9—that "will have or does have a clear and substantial impact on important public policies or important private sector decisions." The reproducibility standard applicable to influential scientific, financial, or statistical information is intended to ensure that information disseminated by agencies is sufficiently transparent in terms of data and methods of analysis that it would be feasible for a replication to be conducted. The fact that the use of original and supporting data and analytic results have been deemed "defensible" by peer-review procedures does not necessarily imply that the results are transparent and replicable.

Reproducibility of Original and Supporting Data. Several of the comments objected to the exclusion of original and supporting data from the reproducibility requirements. Comments instead suggested that OMB should apply the reproducibility standard to original data, and that OMB should provide flexibility to the agencies in determining what constitutes "original and supporting" data. OMB agrees and asks that agencies consider, in developing their own guidelines, which categories of original and supporting data should be subject to the reproducibility standard and which should not. To help in resolving this issue, we also ask agencies to consult directly with relevant scientific and technical communities on the feasibility of having the selected categories of original and supporting data subject to the reproducibility standard. Agencies are encouraged to address ethical, feasibility, and confidentiality issues

with care. As we state in new paragraph V.3.b.ii.A, "Agencies may identify, in consultation with the relevant scientific and technical communities, those particular types of data that can practicably be subjected to a reproducibility requirement, given ethical, feasibility, or confidentiality constraints." Further, as we state in our expanded definition of "reproducibility" in paragraph V.10, "If agencies apply the reproducibility test to specific types of original or supporting data, the associated guidelines shall provide relevant definitions of reproducibility (*e.g.*, standards for replication of laboratory data)." OMB urges caution in the treatment of original and supporting data because it may often be impractical or even impermissible or unethical to apply the reproducibility standard to such data. For example, it may not be ethical to repeat a "negative" (ineffective) clinical (therapeutic) experiment and it may not be feasible to replicate the radiation exposures studied after the Chernobyl accident. When agencies submit their draft agency guidelines for OMB review, agencies should include a description of the extent to which the reproducibility standard is applicable and reflect consultations with relevant scientific and technical communities that were used in developing guidelines related to applicability of the reproducibility standard to original and supporting data.

It is also important to emphasize that the reproducibility standard does not apply to all original and supporting data disseminated by agencies. As we state in new paragraph V.3.b.ii.A, "With regard to original and supporting data related [to influential scientific, financial, or statistical information], agency guidelines shall not require that all disseminated data be subjected to a reproducibility requirement." In addition, we encourage agencies to address how greater transparency can be achieved regarding original and supporting data. As we also state in new paragraph V.3.b.ii.A, "It is understood that reproducibility of data is an indication of transparency about research design and methods and thus a replication exercise (*i.e.*, a new experiment, test, or sample) shall not be required prior to each dissemination." Agency guidelines need to achieve a high degree of transparency about data even when reproducibility is not required.

Reproducibility of Analytic Results. Many public comments were critical of the reproducibility standard and expressed concern that agencies would be required to reproduce each analytical result before it is disseminated. While several comments commended OMB for establishing an appropriate balance in the "capable of being substantially reproduced" standard, others considered this standard to be inherently subjective. There were also comments that suggested the standard would cause more burden for agencies.

It is not OMB's intent that each agency must reproduce each analytic result before it is disseminated. The purpose of the reproducibility standard is to cultivate a consistent agency commitment to transparency about how analytic results are generated: the specific data used, the various assumptions employed, the specific analytic methods applied, and the statistical procedures employed. If sufficient transparency is achieved on each of these matters, then an analytic result should meet the "capable of being substantially reproduced" standard.

While there is much variation in types of analytic results, OMB believes that reproducibility is a practical standard to apply to most types of analytic results. As we state in new paragraph V.3.b.ii.B, "With regard to analytic results related [to influential scientific, financial, or statistical information], agency guidelines shall generally require sufficient transparency about data and methods that an independent reanalysis could be undertaken by a qualified member of the public. These transparency standards apply to agency analysis of data from a single study as well as to analyses that combine information from multiple studies." We elaborate upon this principle in our expanded definition of "reproducibility" in paragraph V.10: "With respect to analytic results, 'capable of being substantially reproduced' means that independent analysis of the original or supporting data using identical methods would generate similar analytic results, subject to an acceptable degree of imprecision or error."

Even in a situation where the original and supporting data are protected by confidentiality concerns, or the analytic computer models or other research methods may be kept confidential to protect intellectual property, it may still be feasible to have the analytic results subject to the reproducibility standard. For example, a qualified party, operating under the same confidentiality protections as the original analysts, may be asked to use the same data, computer model or statistical methods to replicate the analytic results reported in the original study. *See, e.g.*, "Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality," A Special Report of the Health Effects Institute's Particle Epidemiology Reanalysis Project, Cambridge, MA, 2000.

The primary benefit of public transparency is not necessarily that errors in analytic results will be detected, although error correction is clearly valuable. The more important benefit of transparency is that the public will be able to assess how much an agency's analytic result hinges on the specific analytic choices made by the agency. Concreteness about analytic choices allows, for example, the implications of alternative technical choices to be readily assessed. This type of sensitivity analysis is widely regarded as an essential feature of high-quality analysis, yet sensitivity analysis cannot be undertaken by outside parties unless a high degree of transparency is achieved. The OMB guidelines do not compel such sensitivity analysis as a necessary dimension of quality, but the transparency achieved by reproducibility will allow the public to undertake sensitivity studies of interest.

We acknowledge that confidentiality concerns will sometimes preclude public access as an approach to reproducibility. In response to public comment, we have clarified that such concerns do include interests in "intellectual property." To ensure that the OMB guidelines have sufficient flexibility with regard to analytic transparency, OMB has, in new paragraph V.3.b.ii.B.i, provided agencies an alternative approach for classes or types of analytic results that cannot practically be subject to the reproducibility standard. "[In those situations involving influential scientific, financial, or statistical information * * *] making the data and methods publicly available will assist in determining whether analytic results are reproducible. However, the objectivity standard does not override other compelling interests such as privacy, trade secrets, intellectual property, and other confidentiality protections." Specifically, in cases where reproducibility will not occur due to other compelling interests, we expect agencies (1) to perform robustness checks appropriate to the importance of the information involved, e.g., determining whether a specific statistic is sensitive to the choice of analytic method, and, accompanying the information disseminated, to document their efforts to assure the needed robustness in information quality, and (2) address in their guidelines the

degree to which they anticipate the opportunity for reproducibility to be limited by the confidentiality of underlying data. As we state in new paragraph V.3.b.ii.B.*ii*, "In situations where public access to data and methods will not occur due to other compelling interests, agencies shall apply especially rigorous robustness checks to analytic results and document what checks were undertaken. Agency guidelines shall, however, in all cases, require a disclosure of the specific data sources that have been used and the specific quantitative methods and assumptions that have been employed."

Given the differences in the many Federal agencies covered by these guidelines, and the differences in robustness checks and the level of detail for documentation thereof that might be appropriate for different agencies, we also believe it will be helpful if agencies elaborate on these matters in the context of their missions and duties, with due consideration of the nature of the information they disseminate. As we state in new paragraph V.3.b.ii.B.ii, "Each agency is authorized to define the type of robustness checks, and the level of detail for documentation thereof, in ways appropriate for it given the nature and multiplicity of issues for which the agency is responsible."

We leave the determination of the appropriate degree of rigor to the discretion of agencies and the relevant scientific and technical communities that work with the agencies. We do, however, establish a general standard for the appropriate degree of rigor in our expanded definition of "reproducibility" in paragraph V.10: " 'Reproducibility' means that the information is capable of being substantially reproduced, subject to an acceptable degree of imprecision. For information judged to have more (less) important impacts, the degree of imprecision that is tolerated is reduced (increased)." OMB will review each agency's treatment of this issue when reviewing the agency guidelines as a whole.

Comments also expressed concerns regarding interim final paragraph V.3.B.iii, "making the data and models publicly available will assist in determining whether analytic results are capable of being substantially reproduced," and whether it could be interpreted to constitute public dissemination of these materials, rendering moot the reproducibility test. (For the equivalent provision, see new paragraph V.3.b.ii.B.*i*.) The OMB guidelines do not require agencies to reproduce each disseminated analytic result by independent reanalysis. Thus, public dissemination of data and models *per se* does not mean that the analytic result has been reproduced. It means only that the result should be CAPABLE of being reproduced. The transparency associated with this capability of reproduction is what the OMB guidelines are designed to achieve.

We also want to build on a general observation that we made in our final guidelines published in September 2001. In those guidelines we stated: "... in those situations involving influential scientific[, financial,] or statistical information, the substantial reproducibility standard is added as a quality standard above and beyond some peer review quality standards" (66 FR 49722 (September 28, 2001)). A hypothetical example may serve to illustrate this point. Assume that two Federal agencies initiated or sponsored the dissemination of five scientific studies after October 1, 2002 (see paragraph III.4) that were, before dissemination, subjected to formal, independent, external peer review, i.e., that met the presumptive standard for "objectivity" under paragraph V.3.b.i. Further assume, at the time of dissemination, that neither agency reasonably expected that the dissemination of any of these studies would have "a clear and substantial impact" on important public policies, *i.e.*, that these studies were not considered "influential" under paragraph V.9, and thus not subject to the reproducibility standards in paragraphs V.3.b.ii.A or B. Then assume, two years later, in 2005, that one of the agencies decides to issue an important and far-reaching regulation based clearly and substantially on the agency's evaluation of the analytic results set forth in these five studies and that such agency reliance on these five studies as published in the agency's notice of proposed rulemaking would constitute dissemination of these five studies. These guidelines would require the rulemaking agency, prior to publishing the notice of proposed rulemaking, to evaluate these five studies to determine if the analytic results stated therein would meet the "capable of being substantially reproduced" standards in paragraph V.3.b.ii.B and, if necessary, related standards governing original and supporting data in paragraph V.3.b.ii.A. If the agency were to decide that any of the five studies would not meet the reproducibility standard, the agency may still rely on them but only if they satisfy the transparency standard and—as applicable—the disclosure of robustness checks required by these guidelines. Otherwise, the agency should not disseminate any of the studies that did not meet the applicable standards in the guidelines at the time it publishes the notice of proposed rulemaking.

Some comments suggested that OMB consider replacing the reproducibility standard with a standard concerning "confirmation" of results for influential scientific and statistical information. Although we encourage agencies to consider "confirmation" as a relevant standard—at least in some cases—for assessing the objectivity of original and supporting data, we believe that "confirmation" is too stringent a standard to apply to analytic results. Often the regulatory impact analysis prepared by an agency for a major rule, for example, will be the only formal analysis of an important subject. It would be unlikely that the results of the regulatory impact analysis had already been confirmed by other analyses. The "capable of being substantially reproduced" standard is less stringent than a "confirmation" standard because it simply requires that an agency's analysis be sufficiently transparent that another qualified party could replicate it through reanalysis.

Health, Safety, and Environmental Information. We note, in the scientific context, that in 1996 the Congress, for health decisions under the Safe Drinking Water Act, adopted a basic standard of quality for the use of science in agency decisionmaking. Under 42 U.S.C. 300g–1(b)(3)(A), an agency is directed, "to the degree that an Agency action is based on science," to use "(i) the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices; and (ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data)."

We further note that in the 1996 amendments to the Safe Drinking Water Act, Congress adopted a basic quality standard for the dissemination of public information about risks of adverse health effects. Under 42 U.S.C. 300g–1(b)(3)(B), the agency is directed, "to ensure that the presentation of information [risk] effects is comprehensive, informative, and understandable." The agency is further directed, "in a document made available to the public in support of a regulation [to] specify, to the extent practicable—(i) each population addressed by any estimate [of applicable risk effects]; (ii) the expected risk or central estimate of

risk for the specific populations [affected]; (iii) each appropriate upper-bound or lower-bound estimate of risk; (iv) each significant uncertainty identified in the process of the assessment of [risk] effects and the studies that would assist in resolving the uncertainty; and (v) peer-reviewed studies known to the [agency] that support, are directly relevant to, or fail to support any estimate of [risk] effects and the methodology used to reconcile inconsistencies in the scientific data."

As suggested in several comments, we have included these congressional standards directly in new paragraph V.3.b.ii.C, and made them applicable to the information disseminated by all the agencies subject to these guidelines: "With regard to analysis of risks to human health, safety and the environment maintained or disseminated by the agencies, agencies shall either adopt or adapt the quality principles applied by Congress to risk information used and disseminated pursuant to the Safe Drinking Water Act Amendments of 1996 (42 U.S.C. 300g–1(b)(3)(A) & (B))." The word "adapt" is intended to provide agencies flexibility in applying these principles to various types of risk assessment.

Comments also argued that the continued flow of vital information from agencies responsible for disseminating health and medical information to medical providers, patients, and the public may be disrupted due to these peer review and reproducibility standards. OMB responded by adding to new paragraph V.3.b.ii.C: "Agencies responsible for dissemination of vital health and medical information shall interpret the reproducibility and peer-review standards in a manner appropriate to assuring the timely flow of vital information from agencies to medical providers, patients, health agencies, and the public. Information quality standards may be waived temporarily by agencies under urgent situations (*e.g.*, imminent threats to public health or homeland security) in accordance with the latitude specified in agency-specific guidelines."

Administrative Correction Mechanisms. In addition to commenting on the substantive standards in these guidelines, many of the comments noted that the OMB guidelines on the administrative correction of information do not specify a time period in which the agency investigation and response must be made. OMB has added the following new paragraph III.3.i to direct agencies to specify appropriate time periods in which the investigation and response need to be made. "Agencies shall specify appropriate time periods for agency decisions on whether and how to correct the information, and agencies shall notify the affected persons of the corrections made."

Several comments stated that the OMB guidelines needed to direct agencies to consider incorporating an administrative appeal process into their administrative mechanisms for the correction of information. OMB agreed, and added the following new paragraph III.3.ii: "If the person who requested the correction does not agree with the agency's decision (including the corrective action, if any), the person may file for reconsideration within the agency. The agency shall establish an administrative appeal process to review the agency's initial decision, and specify appropriate time limits in which to resolve such requests for reconsideration." Recognizing that many agencies already have a process in place to respond to public concerns, it is not necessarily OMB's intent to require these agencies to establish a new or different process. Rather, our intent is to ensure that agency guidelines specify an objective administrative appeal process that, upon furthercomplaint by the affected person, reviews an agency's decision to disagree with the correction request. An objective process will ensure that the office that originally disseminates the information does not have responsibility for both the initial response and resolution of a disagreement. In addition, the agency guidelines should specify that if the agency believes other agencies may have an interest in the resolution of any administrative appeal, the agency should consult with those other agencies about their possible interest.

Overall, OMB does not envision administrative mechanisms that would burden agencies with frivolous claims. Instead, the correction process should serve to address the genuine and valid needs of the agency and its constituents without disrupting agency processes. Agencies, in making their determination of whether or not to correct information, may reject claims made in bad faith or without justification, and are required to undertake only the degree of correction that they conclude is appropriate for the nature and timeliness of the information involved, and explain such practices in their annual fiscal year reports to OMB.

OMB's issuance of these final guidelines is the beginning of an evolutionary process that will include draft agency guidelines, public comment, final agency guidelines, development of experience with OMB and agency guidelines, and continued refinement of both OMB and agency guidelines. Just as OMB requested public comment before issuing these final guidelines, OMB will refine these guidelines as experience develops and further public comment is obtained.

Dated: December 21, 2001.

John D. Graham,

Administrator, Office of Information and Regulatory Affairs.

Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies

I. OMB Responsibilities

Section 515 of the Treasury and General Government Appropriations Act for FY2001 (Public Law 106–554) directs the Office of Management and Budget to issue government-wide guidelines that provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information, including statistical information, disseminated by Federal agencies.

II. Agency Responsibilities

Section 515 directs agencies subject to the Paperwork Reduction Act (44 U.S.C. 3502(1)) to—

1. Issue their own information quality guidelines ensuring and maximizing the quality, objectivity, utility, and integrity of information, including statistical information, disseminated by the agency no later than one year after the date of issuance of the OMB guidelines;

2. Establish administrative mechanisms allowing affected persons to seek and obtain correction of information maintained and disseminated by the agency that does not comply with these OMB guidelines; and

3. Report to the Director of OMB the number and nature of complaints received by the agency regarding agency compliance with these OMB guidelines concerning the quality, objectivity, utility, and integrity of information and how such complaints were resolved.

III. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies

1. Overall, agencies shall adopt a basic standard of quality (including objectivity, utility, and integrity) as a performance goal and should take appropriate steps to incorporate information quality criteria into agency information dissemination practices. Quality is to be ensured and established at levels appropriate to the nature and timeliness of the information to be disseminated. Agencies shall adopt

specific standards of quality that are appropriate for the various categories of information they disseminate.

2. As a matter of good and effective agency information resources management, agencies shall develop a process for reviewing the quality (including the objectivity, utility, and integrity) of information before it is disseminated. Agencies shall treat information quality as integral to every step of an agency's development of information, including creation, collection, maintenance, and dissemination. This process shall enable the agency to substantiate the quality of the information it has disseminated through documentation or other means appropriate to the information.

3. To facilitate public review, agencies shall establish administrative mechanisms allowing affected persons to seek and obtain, where appropriate, timely correction of information maintained and disseminated by the agency that does not comply with OMB or agency guidelines. These administrative mechanisms shall be flexible, appropriate to the nature and timeliness of the disseminated information, and incorporated into agency information resources management and administrative practices.

i. Agencies shall specify appropriate time periods for agency decisions on whether and how to correct the information, and agencies shall notify the affected persons of the corrections made.

ii. If the person who requested the correction does not agree with the agency's decision (including the corrective action, if any), the person may file for reconsideration within the agency. The agency shall establish an administrative appeal process to review the agency's initial decision, and specify appropriate time limits in which to resolve such requests for reconsideration.

4. The agency's pre-dissemination review, under paragraph III.2, shall apply to information that the agency first disseminates on or after October 1, 2002. The agency's administrative mechanisms, under paragraph III.3., shall apply to information that the agency disseminates on or after October 1, 2002, regardless of when the agency first disseminated the information.

IV. Agency Reporting Requirements

1. Agencies must designate the Chief Information Officer or another official to be responsible for agency compliance with these guidelines.

2. The agency shall respond to complaints in a manner appropriate to the nature and extent of the complaint. Examples of appropriate responses include personal contacts via letter or telephone, form letters, press releases or mass mailings that correct a widely disseminated error or address a frequently raised complaint.

3. Each agency must prepare a draft report, no later than April 1, 2002, providing the agency's information quality guidelines and explaining how such guidelines will ensure and maximize the quality, objectivity, utility, and integrity of information, including statistical information, disseminated by the agency. This report must also detail the administrative mechanisms developed by that agency to allow affected persons to seek and obtain appropriate correction of information maintained and disseminated by the agency that does not comply with the OMB or the agency guidelines.

4. The agency must publish a notice of availability of this draft report in the **Federal Register**, and post this report on the agency's website, to provide an opportunity for public comment.

5. Upon consideration of public comment and after appropriate revision, the agency must submit this draft report to OMB for review regarding consistency with these OMB guidelines no later than July 1, 2002. Upon completion of that OMB review and completion of this report, agencies must publish notice of the availability of this report in its final form in the **Federal Register**, and post this report on the agency's web site no later than October 1, 2002.

6. On an annual fiscal-year basis, each agency must submit a report to the Director of OMB providing information (both quantitative and qualitative, where appropriate) on the number and nature of complaints received by the agency regarding agency compliance with these OMB guidelines and how such complaints were resolved. Agencies must submit these reports no later than January 1 of each following year, with the first report due January 1, 2004.

V. Definitions

1. "Quality" is an encompassing term comprising utility, objectivity, and integrity. Therefore, the guidelines sometimes refer to these four statutory terms, collectively, as "quality."

2. "Utility" refers to the usefulness of the information to its intended users, including the public. In assessing the usefulness of information that the agency disseminates to the public, the agency needs to consider the uses of the information not only from the perspective of the agency but also from the perspective of the public. As a result, when transparency of information is relevant for assessing the information's usefulness from the public's perspective, the agency must take care to ensure that transparency has been addressed in its review of the information.

3. "Objectivity" involves two distinct elements, presentation and substance.

a. "Objectivity" includes whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner. This involves whether the information is presented within a proper context. Sometimes, in disseminating certain types of information to the public, other information must also be disseminated in order to ensure an accurate, clear, complete, and unbiased presentation. Also, the agency needs to identify the sources of the disseminated information (to the extent possible, consistent with confidentiality protections) and, in a scientific, financial, or statistical context, the supporting data and models, so that the public can assess for itself whether there may be some reason to question the objectivity of the sources. Where appropriate, data should have full, accurate, transparent documentation, and error sources affecting data quality should be identified and disclosed to users.

b. In addition, "objectivity" involves a focus on ensuring accurate, reliable, and unbiased information. In a scientific, financial, or statistical context, the original and supporting data shall be generated, and the analytic results shall be developed, using sound statistical and research methods.

i. If data and analytic results have been subjected to formal, independent, external peer review, the information may generally be presumed to be of acceptable objectivity. However, this presumption is rebuttable based on a persuasive showing by the petitioner in a particular instance. If agency-sponsored peer review is employed to help satisfy the objectivity standard, the review process employed shall meet the general criteria for competent and credible peer review recommended by OMB–OIRA to the President's Management Council (9/20/01) (http://www.whitehouse.gov/omb/inforeg/oira_review-process.html), namely, "that (a) peer reviewers be selected primarily on the basis of necessary technical expertise, (b) peer reviewers be expected to disclose to agencies prior technical/policy positions they may have taken on the issues at hand, (c) peer reviewers be expected to disclose to agencies their sources of personal and

institutional funding (private or public sector), and (d) peer reviews be conducted in an open and rigorous manner."

ii. If an agency is responsible for disseminating influential scientific, financial, or statistical information, agency guidelines shall include a high degree of transparency about data and methods to facilitate the reproducibility of such information by qualified third parties.

A. With regard to original and supporting data related thereto, agency guidelines shall not require that all disseminated data be subjected to a reproducibility requirement. Agencies may identify, in consultation with the relevant scientific and technical communities, those particular types of data that can practicable be subjected to a reproducibility requirement, given ethical, feasibility, or confidentiality constraints. It is understood that reproducibility of data is an indication of transparency about research design and methods and thus a replication exercise (i.e., a new experiment, test, or sample) shall not be required prior to each dissemination.

B. With regard to analytic results related thereto, agency guidelines shall generally require sufficient transparency about data and methods that an independent reanalysis could be undertaken by a qualified member of the public. These transparency standards apply to agency analysis of data from a single study as well as to analyses that combine information from multiple studies.

i. Making the data and methods publicly available will assist in determining whether analytic results are reproducible. However, the objectivity standard does not override other compelling interests such as privacy, trade secrets, intellectual property, and other confidentiality protections.

ii. In situations where public access to data and methods will not occur due to other compelling interests, agencies shall apply especially rigorous robustness checks to analytic results and document what checks were undertaken. Agency guidelines shall, however, in all cases, require a disclosure of the specific data sources that have been used and the specific quantitative methods and assumptions that have been employed. Each agency is authorized to define the type of robustness checks, and the level of detail for documentation thereof, in ways appropriate for it given the nature and multiplicity of issues for which the agency is responsible.

C. With regard to analysis of risks to human health, safety and the environment maintained or disseminated by the agencies, agencies shall either adopt or adapt the quality principles applied by Congress to risk information used and disseminated pursuant to the Safe Drinking Water Act Amendments of 1996 (42 U.S.C. 300g–1(b)(3)(A) & (B)). Agencies responsible for dissemination of vital health and medical information shall interpret the reproducibility and peer-review standards in a manner appropriate to assuring the timely flow of vital information from agencies to medical providers, patients, health agencies, and the public. Information quality standards may be waived temporarily by agencies under urgent situations (*e.g.*, imminent threats to public health or homeland security) in accordance with the latitude specified in agency-specific guidelines.

4. "Integrity" refers to the security of information—protection of the information from unauthorized access or revision, to ensure that the information is not compromised through corruption or falsification.

5. "Information" means any communication or representation of knowledge such as facts or data, in any medium or form, including textual, numerical, graphic, cartographic, narrative, or audiovisual forms. This definition includes information that an agency disseminates from a web page, but does not include the provision of hyperlinks to information that others disseminate. This definition does not include opinions, where the agency's presentation makes it clear that what is being offered is someone's opinion rather than fact or the agency's views.

6. "Government information" means information created, collected, processed, disseminated, or disposed of by or for the Federal Government.

7. "Information dissemination product" means any books, paper, map, machine-readable material, audiovisual production, or other documentary material, regardless of physical form or characteristic, an agency disseminates to the public. This definition includes any electronic document, CD–ROM, or web page.

8. "Dissemination" means agency initiated or sponsored distribution of information to the public (see 5 CFR 1320.3(d) (definition of "Conduct or Sponsor")). Dissemination does not include distribution limited to government employees or agency contractors or grantees; intra- or inter-agency use or sharing of government information; and responses to requests for agency records under the Freedom of Information Act, the Privacy Act, the Federal Advisory Committee Act or other similar law. This definition also does not include distribution limited to correspondence with individuals or persons, press releases, archival records, public filings, subpoenas or adjudicative processes.

9. "Influential", when used in the phrase "influential scientific, financial, or statistical information", means that the agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public policies or important private sector decisions. Each agency is authorized to define "influential" in ways appropriate for it given the nature and multiplicity of issues for which the agency is responsible.

10. "Reproducibility" means that the information is capable of being substantially reproduced, subject to an acceptable degree of imprecision. For information judged to have more (less) important impacts, the degree of imprecision that is tolerated is reduced (increased). If agencies apply the reproducibility test to specific types of original or supporting data, the associated guidelines shall provide relevant definitions of reproducibility (*e.g.*, standards for replication of laboratory data). With respect to analytic results, "capable of being substantially reproduced" means that independent analysis of the original or supporting data using identical methods would generate similar analytic results, subject to an acceptable degree of imprecision or error.

[FR Doc. 02–59 Filed 1–2–02; 1:36 pm]
BILLING CODE 3110–01–M

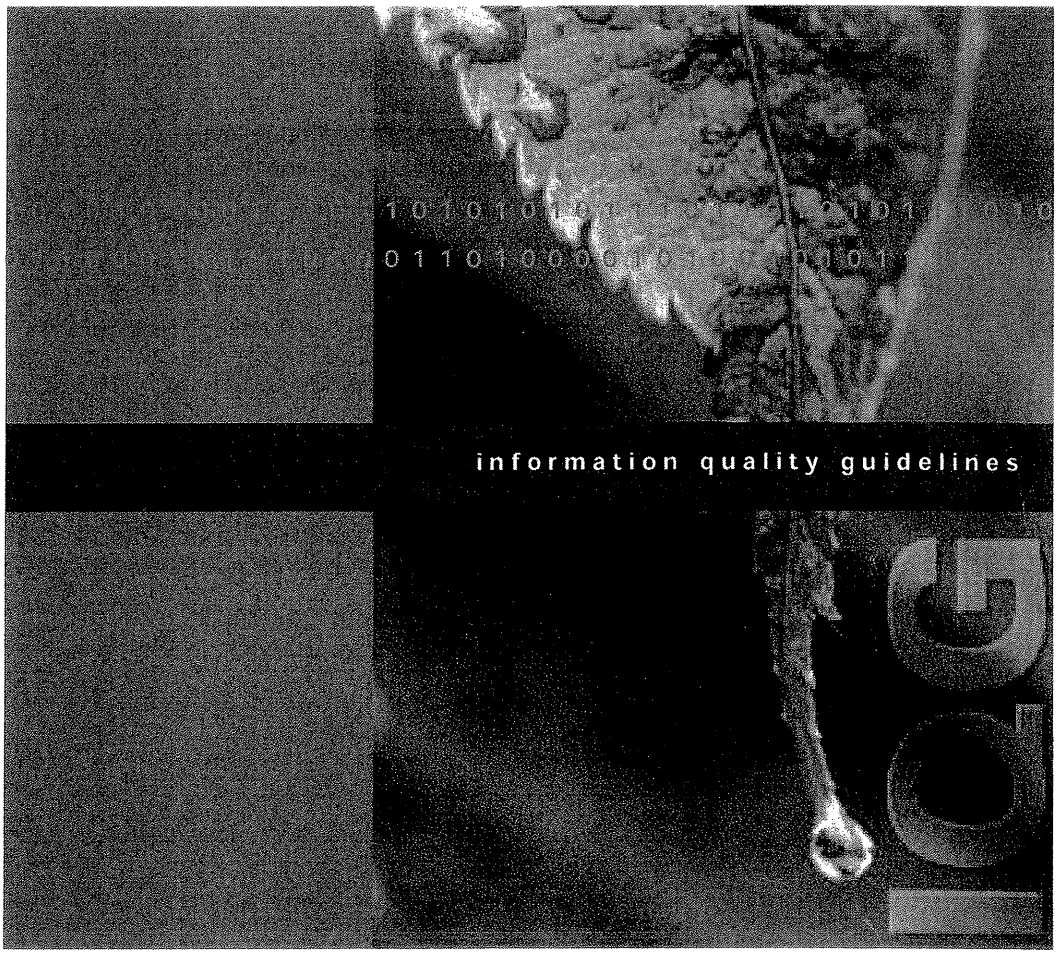
Editorial Note: Due to numerous errors, this document is being reprinted in its entirety. It was originally printed in the **Federal Register** on Thursday, January 3, 2002 at 67 FR 369–378 and was corrected on Tuesday, February 5, 2002 at 67 FR 5365.

[FR Doc. R2–59 Filed 2–21–02; 8:45 am]
BILLING CODE 1505–01–D

APPENDIX C – 2

EXCERPTS

Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency



EPA/260R-02-008
October 2002

Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity, of Information Disseminated by the Environmental Protection Agency

Prepared by:

U.S. Environmental Protection Agency
Office of Environmental Information (2810)
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Addendum
06/24/2004

This addendum updates the contact information for submittal of Requests for Correction under the Information Quality Guidelines (Section 8.2 of the *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by EPA*, October, 2002)

An affected person may submit an RFC via any one of the methods listed here:

- **E-mail** at quality@epa.gov
- **Fax** at (202) 565-2441
- **Mail** to Information Quality Guidelines Staff, Mail Code 2811R, U.S. EPA, 1200 Pennsylvania Ave., N.W., Washington, DC, 20460
- **By courier or in person** to Information Quality Guidelines Staff, Ronald Reagan Building, Room M1200, 1300 Pennsylvania Ave., N.W., Washington, DC

Addendum
05/13/2005

This addendum updates the link for the EPA Integrated Error Correction Process found in Section 4.4, footnote 8, page 12 of the *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by EPA*, October, 2002.

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[8] Integrated Error Correction Process for Environmental Data.
http://oaspub.epa.gov/enviro/ets_grab_error.smart_form

Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency

Table of Contents

1 Introduction

The Environmental Protection Agency (EPA) is committed to providing public access to environmental information. This commitment is integral to our mission to protect human health and the environment. One of our goals is that all parts of society - including communities, individuals, businesses, State and local governments, Tribal governments - have access to accurate information sufficient to effectively participate in managing human health and environmental risks. To fulfill this and other important goals, EPA must rely upon information of appropriate quality for each decision we make.

Developed in response to guidelines issued by the Office of Management and Budget (OMB)[1] under Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001 (Public Law 106-554; H.R. 5658), the *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency* (the Guidelines) contain EPA's policy and procedural guidance for ensuring and maximizing the quality of information we disseminate. The Guidelines also outline administrative mechanisms for EPA pre-dissemination review of information products and describe some new mechanisms to enable affected persons to seek and obtain corrections from EPA regarding disseminated information that they believe does not comply with EPA or OMB guidelines. Beyond policies and procedures these Guidelines also incorporate the following performance goals:

- Disseminated information should adhere to a basic standard of quality, including objectivity, utility, and integrity.
- The principles of information quality should be integrated into each step of EPA's development of information, including creation, collection, maintenance, and dissemination.
- Administrative mechanisms for correction should be flexible, appropriate to the nature and timeliness of the disseminated information, and incorporated into EPA's information resources management and administrative practices.

OMB encourages agencies to incorporate standards and procedures into existing information resources management practices rather than create new, potentially duplicative processes. EPA has taken this advice and relies on numerous existing quality-related policies in these Guidelines. EPA will work to ensure seamless implementation into existing practices. It is expected that EPA managers and staff will familiarize themselves with these Guidelines, and will carefully review existing program policies and procedures in order to accommodate the principles outlined in this document.

[1]Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies, OMB, 2002. (67 FR 8452) Herein after "OMB guidelines". http://www.whitehouse.gov/omb/fedreg/reproducible2.pdf

EPA's Guidelines are intended to carry out OMB's government-wide policy regarding information we disseminate to the public. Our Guidelines reflect EPA's best effort to present our goals and commitments for ensuring and maximizing the quality of information we disseminate. As such, they are not a regulation and do not change or substitute for any legal requirements. They provide non-binding policy and procedural guidance, and are therefore not intended to create legal rights, impose legally binding requirements or obligations on EPA or the public when applied in particular situations, or change or impact the status of information we disseminate, nor to contravene any other legal requirements that may apply to particular agency determinations or other actions. EPA's intention is to fully implement these Guidelines in order to achieve the purposes of Section 515.

These Guidelines are the product of an open, collaborative process between EPA and numerous EPA stakeholders. The Guidelines development process is described in the Appendix to this document. EPA received many public comments and has addressed most comments in these Guidelines. A discussion of public comments is also provided in the Appendix and is grouped by overarching themes and comments by Guidelines topic areas. EPA views these Guidelines as a living document, and anticipates their revision as we work to further ensure and maximize information quality.

2 EPA Mission and Commitment to Quality

2.1 EPA's Mission and Commitment to Public Access

The mission of the EPA is to protect human health and safeguard the natural environment upon which life depends. EPA is committed to making America's air cleaner, water purer, and land better protected and to work closely with its Federal, State, Tribal, and local government partners; with citizens; and with the regulated community to accomplish its mission. In addition, the United States plays a leadership role in working with other nations to protect the global environment.

EPA's commitment to expanding and enhancing access to environmental information is articulated in our Strategic Plan. EPA works every day to expand the public's right to know about and understand their environment by providing and facilitating access to a wealth of information about public health and local environmental issues and conditions. This enhances citizen understanding and involvement and provides people with tools to protect their families and their communities.

EPA statutory responsibilities to protect human health and safeguard the natural environment are described in the statutes that mandate and govern our programs. EPA manages those programs in concert with numerous other government and private sector partners. As Congress intended, each statute provides regulatory expectations including information quality considerations and principles. Some statutes are more specific than others, but overall, each directs EPA and other agencies in how we regulate to protect human health and the environment. For example, the Safe Drinking Water Act (SDWA) Amendments of 1996 set forth certain quality principles for how EPA should conduct human health risk assessments and characterize the potential risks to humans from drinking water contaminants. Information quality is a key component of every statute that governs our mission.

2.2 Information Management in EPA

The collection, use, and dissemination of information of known and appropriate quality are integral to ensuring that EPA achieves its mission. Information about human health and the environment -- environmental characteristics; physical, chemical, and biological processes; and chemical and other pollutants -- underlies all environmental management and health protection decisions. The availability of, and access to, information and the analytical tools to understand it are essential for assessing environmental and human health risks, designing appropriate and cost-effective policies and response strategies, and measuring environmental improvements.

EPA works every day to ensure information quality, but we do not wait until the point of dissemination to consider important quality principles. While the final review of a document before it is published is very important to ensuring a product of high quality, we know that in order to maximize quality, we must start much earlier. When you read an EPA report at your local library or view EPA information on our web site, that information is the result of processes

undertaken by EPA and our partners that assured quality along each step of the way. To better describe this interrelated information quality process, the following presents some of the major roles that EPA plays in its effort to ensure and maximize the quality of the information:

- **EPA is a collector and generator of information:** While most of our programs rely on States, Tribes, or the private sector to collect and report information to EPA, there are some programs in which EPA collects its own information. One example is the Agency's enforcement and compliance program, under which EPA collects samples in the field or conducts onsite inspections. We also conduct original, scientific research at headquarters, in Regional Offices, and at our research laboratories to investigate and better understand how our environment works, how humans react to chemical pollutants and other environmental contaminants, and how to model our natural environment to assess the potential impact of environmental management activities. Ensuring the quality of collected information is central to our mission.

- **EPA is a recipient of information:** EPA receives a large amount of information that external parties volunteer or provide under statutory and other mandates. Much of the environmental information submitted to EPA is processed and stored in Agency information management systems. While, we work to ensure and maximize the integrity of that information through a variety of mechanisms and policies, we have varying levels of quality controls over information developed or collected by outside parties. This information generally falls into one of four categories:

  - **Information collected through contracts with EPA**. Examples of this information include studies and collection and analysis of data by parties that are under a contractual obligation with EPA. Since EPA is responsible for managing the work assigned to contractors, EPA has a relatively high degree of control over the quality of this information.

  - **Information collected through grants and cooperative agreements with EPA**. Examples of this information include scientific studies that are performed under research grants and data collected by State agencies or other grantees to assess regulatory compliance or environmental trends. Although EPA has less control over grantees than contractors, EPA can and does include conditions in grants and cooperative agreements requiring recipients to meet certain criteria.

  - **Information submitted to EPA as part of a requirement under a statute, regulation, permit, order or other mandate**. Examples of this information include required test data for pesticides or chemicals, Toxics Release Inventory (TRI) submissions and compliance information submitted to EPA by States and the regulated community. EPA ensures

quality control of such information through regulatory requirements, such as requiring samples to be analyzed by specific analytical procedures and by certified laboratories. However, each EPA program has specific statutory authorities which may affect its ability to impose certain quality practices.

- The final category of information that is not included in any of the above three categories includes **information that is either voluntarily submitted to EPA in hopes of influencing a decision or that EPA obtains for use in developing a policy, regulatory, or other decision.** Examples of this information include scientific studies published in journal articles and test data obtained from other Federal agencies, industry, and others. EPA may not have any financial ties or regulatory requirements to control the quality of this type of information.

While the quality of information submitted to EPA is the responsibility of the original collector of the information, we nevertheless maintain a robust quality system, that addresses information related to the first three bullets above by including regulatory requirements for quality assurance for EPA contracts, grants, and assistance agreements. For the fourth category, we intend to develop and publish factors that EPA would use in the future to assess the quality of voluntary submissions or information that the Agency gathers for its own use.

- **EPA is a user of information:** Upon placement in our information management systems, information becomes available for use by many people and systems. EPA users may include Program managers, information product developers, or automated financial tracking systems. Depending on the extent of public release, users may also include city planners, homeowners, teachers, engineers, or community activists, to name a few. To satisfy this broad spectrum of users, it is critical that we present information in an unbiased context with thorough documentation.

  EPA is moving beyond routine administration of regulatory information and working in concert with States and other stakeholders to provide new information products that are responsive to identified users. Increasingly, information products are derived from information originally collected to support State or Federal regulatory programs or management activities. Assuring the suitability of this information for new applications is of paramount importance.

- **EPA is a conduit for information:** Another major role that EPA plays in the management of information is as a provider of public access. Such access enables public involvement in how EPA achieves it mission. We provide access to a variety of information holdings. Some information distributed by EPA includes information collected through contracts; information collected through grants and

cooperative agreements; information submitted to EPA as part of a requirement under a statute, regulation, permit, order, or other mandate; and information that is either voluntarily submitted to EPA in hopes of influencing a decision or that EPA obtains for use in developing a policy, regulatory, or other decision. In some cases, EPA serves as an important conduit for information generated by external parties; however, the quality of that information is the responsibility of the external information developer, unless EPA endorses or adopts it.

2.3 EPA's Relationship with State, Tribal, and Local Governments

As mentioned in the previous section, EPA works with a variety of partners to achieve its mission. Our key government partners not only provide information, they also work with EPA to manage and implement programs and communicate with the public about issues of concern. In addition to implementing national programs through EPA Headquarters Program Offices, a vast network of EPA Regions and other Federal, State, Tribal and local governments implement both mandated and voluntary programs. This same network collects, uses, and distributes a wide range of information. EPA plans to coordinate with these partners to ensure the Guidelines are appropriate and effective.

One major mechanism to ensure and maximize information integrity is the National Environmental Information Exchange Network (NEIEN, or Network). The result of an important partnership between EPA, States and Tribal governments, the Network seeks to enhance the Agency's information architecture to ensure timely and one-stop reporting from many of EPA's information partners. Key components include the establishment of the Central Data Exchange (CDX) portal and a System of Access for internal and external users. When fully implemented, the Network and its many components will enhance EPA and the public's ability to access, use, and integrate information and the ability of external providers to report to EPA.

3 OMB Guidelines

In Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001 (Public Law 106-554; H.R. 5658), Congress directed OMB to issue government-wide guidelines that "provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies...." The OMB guidelines direct agencies subject to the Paperwork Reduction Act (44 U.S.C. 3502(1)) to:

- Issue their own information quality guidelines to ensure and maximize the quality, objectivity, utility, and integrity of information, including statistical information, by no later than one year after the date of issuance of the OMB guidelines;

- Establish administrative mechanisms allowing affected persons to seek and obtain correction of information maintained and disseminated by the agency that does not comply with the OMB or agency guidelines; and

- Report to the Director of OMB the number and nature of complaints received by the agency regarding agency compliance with OMB guidelines concerning the quality, objectivity, utility, and integrity of information and how such complaints were resolved.

The OMB guidelines provide some basic principles for agencies to consider when developing their own guidelines including:

- Guidelines should be flexible enough to address all communication media and variety of scope and importance of information products.

- Some agency information may need to meet higher or more specific expectations for objectivity, utility, and integrity. Information of greater importance should be held to a higher quality standard.

- Ensuring and maximizing quality, objectivity, utility, and integrity comes at a cost, so agencies should use an approach that weighs the costs and benefits of higher information quality.

- Agencies should adopt a common sense approach that builds on existing processes and procedures. It is important that agency guidelines do not impose unnecessary administrative burdens or inhibit agencies from disseminating quality information to the public.

4 Existing Policies and Procedures that Ensure and Maximize Information Quality

EPA is dedicated to the collection, generation, and dissemination of high quality information. We disseminate a wide variety of information products, ranging from comprehensive scientific assessments of potential health risks,[2] to web-based applications that provide compliance information and map the location of regulated entities,[3] to simple fact sheets for school children.[4] As a result of this diversity of information-related products and practices, different EPA programs have evolved specialized approaches to information quality assurance. The OMB guidelines encourage agencies to avoid the creation of "new and potentially duplicative or contradictory processes." Further, OMB stresses that its guidelines are not intended to "impose unnecessary administrative burdens that would inhibit agencies from continuing to take advantage of the Internet and other technologies to disseminate information that can be of great benefit and value to the public." In this spirit, EPA seeks to foster the continuous improvement of existing information quality activities and programs. In implementing these guidelines, we note that ensuring the quality of information is a key objective alongside other EPA objectives, such as ensuring the success of Agency missions, observing budget and resource priorities and restraints, and providing useful information to the public. EPA intends to implement these Guidelines in a way that will achieve all these objectives in a harmonious way in conjunction with our existing guidelines and policies, some of which are outlined below. These examples illustrate some of the numerous systems and practices in place that address the quality, objectivity, utility, and integrity of information.

4.1 Quality System

The EPA Agency-wide Quality System helps ensure that EPA organizations maximize the quality of environmental information, including information disseminated by the Agency. A graded approach is used to establish quality criteria that are appropriate for the intended use of the information and the resources available. The Quality System is documented in EPA Order 5360.1 A2, "Policy and Program Requirements for the Mandatory Agency-wide Quality System" and the "EPA Quality Manual."[5] To implement the Quality System, EPA organizations (1) assign a quality assurance manager, or person assigned to an equivalent position, who has sufficient technical and management expertise and authority to conduct independent oversight of the implementation of the organization's quality system; (2) develop a Quality Management Plan, which documents the organization's quality system; (3) conduct an annual assessment of the organization's quality system; (4) use a systematic planning process to develop acceptance or performance criteria prior to the initiation of all projects that involve environmental information

[2] http://cfpub.epa.gov/ncea/cfm/partmatt.cfm

[3] http://www.epa.gov/enviro/wme/

[4] http://www.epa.gov/kids

[5] EPA Quality Manual for Environmental Programs 5360 A1. May 2000. http://www.epa.gov/quality/qs-docs/5360.pdf

collection and/or use; (5) develop Quality Assurance Project Plan(s), or equivalent document(s) for all applicable projects and tasks involving environmental data; (6) conduct an assessment of existing data, when used to support Agency decisions or other secondary purposes, to verify that they are of sufficient quantity and adequate quality for their intended use; (7) implement all Agency-wide Quality System components in all applicable EPA-funded extramural agreements; and (8) provide appropriate training, for all levels of management and staff.

The EPA Quality System may also apply to non-EPA organizations, with key principles incorporated in the applicable regulations governing contracts, grants, and cooperative agreements. EPA Quality System provisions may also be invoked as part of negotiated agreements such as memoranda of understanding. Non-EPA organizations that may be subject to EPA Quality System requirements include (a) any organization or individual under direct contract to EPA to furnish services or items or perform work (i.e., a contractor) under the authority of 48 CFR part 46, (including applicable work assignments, delivery orders, and task orders); and (b) other government agencies receiving assistance from EPA through interagency agreements. Separate quality assurance requirements for assistance recipients are set forth in 40 CFR part 30 (governing assistance agreements with institutions of higher education, hospitals, and other non-profit recipients of financial assistance) and 40 CFR parts 31 and 35 (government assistance agreements with State, Tribal, and local governments).

4.2 Peer Review Policy

In addition to the Quality System, EPA's Peer Review Policy provides that major scientifically and technically based work products (including scientific, engineering, economic, or statistical documents) related to Agency decisions should be peer-reviewed. Agency managers within Headquarters, Regions, laboratories, and field offices determine and are accountable for the decision whether to employ peer review in particular instances and, if so, its character, scope, and timing. These decisions are made consistent with program goals and priorities, resource constraints, and statutory or court-ordered deadlines. For those work products that are intended to support the most important decisions or that have special importance in their own right, external peer review is the procedure of choice. For other work products, internal peer review is an acceptable alternative to external peer review. Peer review is not restricted to the penultimate version of work products; in fact, peer review at the planning stage can often be extremely beneficial. The basis for EPA peer review policy is articulated in *Peer Review and Peer Involvement at the U.S. Environmental Protection Agency*.[6] The Peer Review Policy was first issued in January, 1993, and was updated in June, 1994. In addition to the policy, EPA has published a Peer Review Handbook,[7] which provides detailed guidance for implementing the policy. The handbook was last revised December, 2000.

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[6]Peer Review and Peer Involvement at the U.S. EPA. June 7, 1994. http://www.epa.gov/osp/spc/perevmem.htm

[7]Peer Review Handbook, 2nd Edition, U.S. EPA, Science Policy Council, December 2000, EPA 100-B-00-001. http://www.epa.gov/osp/spc/prhandbk.pdf

4.3 Action Development Process

The Agency's Action Development Process also serves to ensure and maximize the quality of EPA disseminated information. Top Agency actions and Economically Significant actions as designated under Executive Order 12866 are developed as part of the Agency's Action Development Process. The Action Development Process ensures the early and timely involvement of senior management at key decision milestones to facilitate the consideration of a broad range of regulatory and non-regulatory options and analytic approaches. Of particular importance to the Action Development Process is ensuring that our scientists, economists, and others with technical expertise are appropriately involved in determining needed analyses and research, identifying alternatives, and selecting options. Program Offices and Regional Offices are invited to participate to provide their unique perspectives and expertise. Effective consultation with policy advisors (e.g., Senior Policy Council, Science Policy Council), co-regulators (e.g., States, Tribes, and local governments), and stakeholders is also part of the process. Final Agency Review (FAR) generally takes place before the release of substantive information associated with these actions. The FAR process ensures the consistency of any policy determinations, as well as the quality of the information underlying each policy determination and its presentation.

4.4 Integrated Error Correction Process

The Agency's Integrated Error Correction Process[8] (IECP) is a process by which members of the public can notify EPA of a potential data error in information EPA distributes or disseminates. This process builds on existing data processes through which discrete, numerical errors in our data systems are reported to EPA. The IECP has made these tools more prominent and easier to use. Individuals who identify potential data errors on the EPA web site can contact us through the IECP by using the "Report Error" button or error correction hypertext found on major data bases throughout EPA's web site. EPA reviews the error notification and assists in bringing the notification to resolution with those who are responsible for the data within or outside the Agency, as appropriate. The IECP tracks this entire process from notification through final resolution.

[8]Integrated Error Correction Process for Environmental Data. http://www.epa.gov/cdx/iecp.html

4.5 Information Resources Management Manual

The EPA Information Resources Management (IRM) Manual[9] articulates and describes many of our information development and management procedures and policies, including information security, data standards, records management, information collection, and library services. Especially important in the context of the Guidelines provided in this document, the IRM Manual describes how we maintain and ensure information integrity. We believe that maintaining information integrity refers to keeping information "unaltered," i.e., free from unauthorized or accidental modification or destruction. These integrity principles apply to all information. Inappropriately changed or modified data or software impacts information integrity and compromises the value of the information system. Because of the importance of EPA's information to the decisions made by the Agency, its partners, and the public, it is our responsibility to ensure that the information is, and remains, accurate and credible.

Beyond addressing integrity concerns, the IRM Manual also includes Agency policy on public access and records management. These are key chapters that enable EPA to ensure transparency and the reproducibility of information.

4.6 Risk Characterization Policy and Handbook

The EPA Risk Characterization Policy and Handbook[10] provide guidance for risk characterization that is designed to ensure that critical information from each stage of a risk assessment is used in forming conclusions about risk. The Policy calls for a transparent process and products that are clear, consistent and reasonable. The Handbook is designed to provide risk assessors, risk managers, and other decision-makers an understanding of the goals and principles of risk characterization.

4.7 Program-Specific Policies

We mentioned just a few of the Agency's major policies that ensure and maximize the quality of information we disseminate. In addition to these Agency-wide systems and procedures, Program Offices and Regions implement many Office-level and program-specific procedures to ensure and maximize information quality. The purpose of these Guidelines is to serve as a common thread that ties all these policies together under the topics provided by OMB: objectivity, integrity and utility. EPA's approach to ensuring and maximizing quality is necessarily distributed across all levels of EPA's organizational hierarchy, including Offices, Regions, divisions, projects, and even products. Oftentimes, there are different quality considerations for different types of products. For example, the quality principles associated with a risk assessment

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[9] EPA Directive 2100 Information Resources Management Policy Manual. http://www.epa.gov/irmpoli8/polman/

[10] Risk Characterization Handbook, U.S. EPA, Science Policy Council, December 2000. http://www.epa.gov/osp/spc/2riskchr.htm

differ from those associated with developing a new model. The Agency currently has a comprehensive but distributed system of policies to address such unique quality considerations. These Guidelines provide us with a mechanism to help coordinate and synthesize our quality policies and procedures.

4.8 EPA Commitment to Continuous Improvement

As suggested above, we will continue to work to ensure that our many policies and procedures are appropriately implemented, synthesized, and revised as needed. One way to build on achievements and learn from mistakes is to document lessons learned about specific activities or products. For example, the documents that present guidance and tools for implementing the Quality System are routinely subjected to external peer review during their development; comments from the reviewers are addressed and responses reviewed by management before the document is issued. Each document is formally reviewed every five years and is either reissued, revised as needed, or rescinded. If important new information or approaches evolve between reviews, the document may be reviewed and revised more frequently.

4.9 Summary of New Activities and Initiatives

In response to OMB's guidelines, EPA recognizes that it will be incorporating new policies and administrative mechanisms. As we reaffirm our commitment to our existing policies and procedures that ensure and maximize quality, we also plan to address the following new areas of focus and commitment:

- Working with the public to develop assessment factors that we will use to assess the quality of information developed by external parties, prior to EPA's use of that information.

- Affirming a new commitment to information quality, especially the transparency of information products.

- Establishing Agency-wide correction process and request for reconsideration panel to provide a centralized point of access for all affected parties to seek and obtain the correction of disseminated information that they believe does not conform to these Guidelines or the OMB guidelines.

5 Guidelines Scope and Applicability

5.1 What is "Quality" According to the Guidelines?

Consistent with the OMB guidelines, EPA is issuing these Guidelines to ensure and maximize the quality, including objectivity, utility and integrity, of disseminated information. Objectivity, integrity, and utility are defined here, consistent with the OMB guidelines. "Objectivity" focuses on whether the disseminated information is being presented in an accurate, clear, complete, and unbiased manner, and as a matter of substance, is accurate, reliable, and unbiased. "Integrity" refers to security, such as the protection of information from unauthorized access or revision, to ensure that the information is not compromised through corruption or falsification. "Utility" refers to the usefulness of the information to the intended users.

5.2 What is the Purpose of these Guidelines?

The collection, use, and dissemination of information of known and appropriate quality is integral to ensuring that EPA achieves its mission. Information about the environment and human health underlies all environmental management decisions. Information and the analytical tools to understand it are essential for assessing environmental and human health risks, designing appropriate and cost-effective policies and response strategies, and measuring environmental improvements.

These Guidelines describe EPA's policy and procedures for reviewing and substantiating the quality of information before EPA disseminates it. They describe our administrative mechanisms for enabling affected persons to seek and obtain, where appropriate, correction of information disseminated by EPA that they believe does not comply with EPA or OMB guidelines.

5.3 When Do these Guidelines Apply?

These Guidelines apply to "information" EPA disseminates to the public. "Information," for purposes of these Guidelines, generally includes any communication or representation of knowledge such as facts or data, in any medium or form. Preliminary information EPA disseminates to the public is also considered "information" for the purposes of the Guidelines. Information generally includes material that EPA disseminates from a web page. However not all web content is considered "information" under these Guidelines (e.g., certain information from outside sources that is not adopted, endorsed, or used by EPA to support an Agency decision or position).

For purposes of these Guidelines, EPA disseminates information to the public when EPA initiates or sponsors the distribution of information to the public.

- EPA initiates a distribution of information if EPA prepares the information and distributes it to support or represent EPA's viewpoint, or to formulate or support a regulation, guidance, or other Agency decision or position.

- EPA initiates a distribution of information if EPA distributes information prepared or submitted by an outside party in a manner that reasonably suggests that EPA endorses or agrees with it; if EPA indicates in its distribution that the information supports or represents EPA's viewpoint; or if EPA in its distribution proposes to use or uses the information to formulate or support a regulation, guidance, policy, or other Agency decision or position.

- Agency-sponsored distribution includes instances where EPA reviews and comments on information distributed by an outside party in a manner that indicates EPA is endorsing it, directs the outside party to disseminate it on EPA's behalf, or otherwise adopts or endorses it.

EPA intends to use notices to explain the status of information, so that users will be aware of whether the information is being distributed to support or represent EPA's viewpoint.

5.4 What is Not Covered by these Guidelines?

If an item is not considered "information," these Guidelines do not apply. Examples of items that are not considered information include Internet hyperlinks and other references to information distributed by others, and opinions, where EPA's presentation makes it clear that what is being offered is someone's opinion rather than fact or EPA's views.

"Dissemination" for the purposes of these Guidelines does not include distributions of information that EPA does not initiate or sponsor. Below is a sample of various types of information that would not generally be considered disseminated by EPA to the public:

- Distribution of information intended only for government employees (including intra- or interagency use or sharing) or recipients of government contracts, grants, or cooperative agreements. Intra-agency use of information includes use of information pertaining to basic agency operations, such as management, personnel, and organizational information.

- EPA's response to requests for agency records under the Freedom of Information Act (FOIA), the Privacy Act, the Federal Advisory Committee Act (FACA), or other similar laws.

- Distribution of information in correspondence directed to individuals or persons (i.e., any individual, group, or entity, including any government or political subdivision thereof, or Federal governmental component/unit).

- Information of an ephemeral nature, such as press releases, fact sheets, press conferences, and similar communications, in any medium that advises the public of an event or activity or announces information EPA has disseminated

elsewhere; interviews, speeches, and similar communications that EPA does not disseminate to the public beyond their original context, such as by placing them on the Internet. If a speech, press release, or other "ephemeral" communication is about an information product disseminated elsewhere by EPA, the product itself will be covered by these Guidelines.

- Information presented to Congress as part of the legislative or oversight processes, such as testimony of officials, information, or drafting assistance provided to Congress in connection with pending or proposed legislation, unless EPA simultaneously disseminates this information to the public.

- Background information such as published articles distributed by libraries or by other distribution methods that do not imply that EPA has adopted or endorsed the materials. This includes outdated or superseded EPA information that is provided as background information but no longer reflects EPA policy or influences EPA decisions, where the outdated or superseded nature of such material is reasonably apparent from its form of presentation or date of issuance, or where EPA indicates that the materials are provided as background materials and do not represent EPA's current view.

- These Guidelines do not apply to information distributed by recipients of EPA contracts, grants, or cooperative agreements, unless the information is disseminated on EPA's behalf, as when EPA specifically directs or approves the dissemination. These Guidelines do not apply to the distribution of any type of research by Federal employees and recipients of EPA funds, where the researcher (not EPA) decides whether and how to communicate and publish the research, does so in the same manner as his or her academic colleagues, and distributes the research in a manner that indicates it does not necessarily represent EPA's official position (for example, by including an appropriate disclaimer). The Guidelines do not apply even if EPA retains ownership or other intellectual property rights because the Federal government paid for the research.

- Distribution of information in public filings to EPA, including information submitted to EPA by any individual or person (as discussed above), either voluntarily or under mandates or requirements (such as filings required by statutes, regulations, orders, permits, or licenses). The Guidelines do not apply where EPA distributes this information simply to provide the public with quicker and easier access to materials submitted to EPA that are publicly available. This will generally be the case so long as EPA is not the author, and is not endorsing, adopting, using, or proposing to use the information to support an Agency decision or position.

- Distribution of information in documents filed in or prepared specifically for a judicial case or an administrative adjudication and intended to be limited to such

actions, including information developed during the conduct of any criminal or civil action or administrative enforcement action, investigation, or audit involving an agency against specific parties.

5.5 What Happens if Information is Initially Not Covered by these Guidelines, but EPA Subsequently Disseminates it to the Public?

If a particular distribution of information is not covered by these Guidelines, the Guidelines may still apply to a subsequent dissemination of the information in which EPA adopts, endorses, or uses the information to formulate or support a regulation, guidance, or other Agency decision or position. For example, if EPA simply makes a public filing (such as facility data required by regulation) available to the public, these Guidelines would not apply to that distribution of information. However, if EPA later includes the information in a background document in support of a rulemaking, these Guidelines would apply to that later dissemination of the information in that document.

5.6 How does EPA Ensure the Objectivity, Utility, and Integrity of information that is not covered by these Guidelines?

These Guidelines apply only to information EPA disseminates to the public, outlined in section 5.3, above. Other information distributed by EPA that is not covered by these Guidelines is still subject to all applicable EPA policies, quality review processes, and correction procedures. These include quality management plans for programs that collect, manage, and use environmental information, peer review, and other procedures that are specific to individual programs and, therefore, not described in these Guidelines. It is EPA's policy that all of the information it distributes meets a basic standard of information quality, and that its utility, objectivity, and integrity be scaled and appropriate to the nature and timeliness of the planned and anticipated uses. Ensuring the quality of EPA information is not necessarily dependent on any plans to disseminate the information. EPA continues to produce, collect, and use information that is of the appropriate quality, irrespective of these Guidelines or the prospects for dissemination of the information.

6 Guidelines for Ensuring and Maximizing Information Quality

6.1 How does EPA Ensure and Maximize the Quality of Disseminated Information?

EPA ensures and maximizes the quality of the information we disseminate by implementing well established policies and procedures within the Agency as appropriate to the information product. There are many tools that the Agency uses such as the Quality System,[11] review by senior management, peer review process,[12] communications product review process,[13] the web guide,[14] and the error correction process.[15] Beyond our internal quality management system, EPA also ensures the quality of information we disseminate by seeking input from experts and the general public. EPA consults with groups such as the Science Advisory Board and the Science Advisory Panel, in addition to seeking public input through public comment periods and by hosting public meetings.

For the purposes of the Guidelines, EPA recognizes that if data and analytic results are subjected to formal, independent, external peer review, the information may generally be presumed to be of acceptable objectivity. However, this presumption of objectivity is rebuttable. The Agency uses a graded approach and uses these tools to establish the appropriate quality, objectivity, utility, and integrity of information products based on the intended use of the information and the resources available. As part of this graded approach, EPA recognizes that some of the information it disseminates includes influential scientific, financial, or statistical information, and that this category should meet a higher standard of quality.

6.2 How Does EPA Define Influential Information for these Guidelines?

"Influential," when used in the phrase "influential scientific, financial, or statistical information," means that the Agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact (i.e., potential change or effect) on important public policies or private sector decisions.[16] For the purposes of the EPA's

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[11]EPA Quality Manual for Environmental Programs 5360 A1. May 2000. http://www.epa.gov/quality/qs-docs/5360.pdf

[12]Peer Review Handbook, 2nd Edition, U.S. EPA, Science Policy Council, December 2000, EPA 100-B-00-001. http://www.epa.gov/osp/spc/prhandbk.pdf

[13]EPA's Print and Web Communications Product Review Guide. http://www.epa.gov/dced/pdf/review.pdf

[14]Web Guide. U.S. EPA. http://www.epa.gov/webguide/resources/webserv.html

[15]Integrated Error Correction Process. http://www.epa.gov/cdx/iecp.html

[16]The term "clear and substantial impact" is used as part of a definition to distinguish different categories of information for purposes of these Guidelines. EPA does not intend the classification of information under this definition to change or impact the status of the information in any other setting, such as for purposes of determining whether the dissemination of the information is a final Agency action.

Information Quality Guidelines, EPA will generally consider the following classes of information to be influential, and, to the extent that they contain scientific, financial, or statistical information, that information should adhere to a rigorous standard of quality:

- Information disseminated in support of top Agency actions (i.e., rules, substantive notices, policy documents, studies, guidance) that demand the ongoing involvement of the Administrator's Office and extensive cross-Agency involvement; issues that have the potential to result in major cross-Agency or cross-media policies, are highly controversial, or provide a significant opportunity to advance the Administrator's priorities. Top Agency actions usually have potentially great or widespread impacts on the private sector, the public or state, local or tribal governments. This category may also include precedent-setting or controversial scientific or economic issues.

- Information disseminated in support of Economically Significant actions as defined in Executive Order 12866, entitled *Regulatory Planning and Review* (58 FR 51735, October 4, 1993), Agency actions that are likely to have an annual effect on the economy of $100 million or more or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, Tribal, or local governments or communities.

- Major work products undergoing peer review as called for under the Agency's Peer Review Policy. Described in the *Science Policy Council Peer Review Handbook,* the EPA Peer Review Policy regards major scientific and technical work products as those that have a major impact, involve precedential, novel, and/or controversial issues, or the Agency has a legal and/or statutory obligation to conduct a peer review. These Major work products are typically subjected to external peer review. Some products that may not be considered "major" under the EPA Peer Review Policy may be subjected to external peer review but EPA does not consider such products influential for purposes of these Guidelines.

- Case-by-case: The Agency may make determinations of what constitutes "influential information" beyond those classes of information already identified on a case-by-case basis for other types of disseminated information that may have a clear and substantial impact on important public policies or private sector decisions.

6.3 How Does EPA Ensure and Maximize the Quality of "Influential" Information?

EPA recognizes that influential scientific, financial, or statistical information should be subject to a higher degree of quality (for example, transparency about data and methods) than information that may not have a clear and substantial impact on important public policies or private sector decisions. A higher degree of transparency about data and methods will facilitate

the reproducibility of such information by qualified third parties, to an acceptable degree of imprecision. For disseminated influential original and supporting data, EPA intends to ensure reproducibility according to commonly accepted scientific, financial, or statistical standards. It is important that analytic results for influential information have a higher degree of transparency regarding (1) the source of the data used, (2) the various assumptions employed, (3) the analytic methods applied, and (4) the statistical procedures employed. It is also important that the degree of rigor with which each of these factors is presented and discussed be scaled as appropriate, and that all factors be presented and discussed. In addition, if access to data and methods cannot occur due to compelling interests such as privacy, trade secrets, intellectual property, and other confidentiality protections, EPA should, to the extent practicable, apply especially rigorous robustness checks to analytic results and carefully document all checks that were undertaken. Original and supporting data may not be subject to the high and specific degree of transparency provided for analytic results; however, EPA should apply, to the extent practicable, relevant Agency policies and procedures to achieve reproducibility, given ethical, feasibility, and confidentiality constraints.

Several Agency-wide and Program- and Region-specific policies and processes that EPA uses to ensure and maximize the quality of environmental data, including disseminated information products, would also apply to information considered "influential" under these Guidelines. Agency-wide processes of particular importance to ensure the quality, objectivity, and transparency of "influential" information include the Agency's Quality System, Action Development Process, Peer Review Policy, and related procedures. Many "influential" information products may be subject to more than one of these processes.

6.4 How Does EPA Ensure and Maximize the Quality of "Influential" Scientific Risk Assessment Information?

EPA conducts and disseminates a variety of risk assessments. When evaluating environmental problems or establishing standards, EPA must comply with statutory requirements and mandates set by Congress based on media (air, water, solid, and hazardous waste) or other environmental interests (pesticides and chemicals). Consistent with EPA's current practices, application of these principles involves a "weight-of-evidence" approach that considers all relevant information and its quality, consistent with the level of effort and complexity of detail appropriate to a particular risk assessment. In our dissemination of influential scientific information regarding human health, safety[17] or environmental[18] risk assessments, EPA will ensure, to the extent practicable

[17]"Safety risk assessment" describes a variety of analyses, investigations, or case studies conducted by EPA to respond to environmental emergencies. For example, we work to ensure that the chemical industry and state and local entities take action to prevent, plan and prepare for, and respond to chemical emergencies through the development and sharing of information, tools, and guidance for hazards analyses and risk assessment.

[18]Because the assessment of "environmental risk" is being distinguished from "human health risk," the term "environmental risk" as used in these Guidelines does not directly involve human health concerns. In other words, an "environmental risk assessment" is in this case the equivalent to what EPA commonly calls an "ecological risk

and consistent with Agency statutes and existing legislative regulations, the objectivity[19] of such information disseminated by the Agency by applying the following adaptation of the quality principles found in the Safe Drinking Water Act[20] (SDWA) Amendments of 1996[21]:

(A) The substance of the information is accurate, reliable and unbiased. This involves the use of:

(i) the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies; and

(ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies the use of the data).

(B) The presentation of information on human health, safety, or environmental risks, consistent with the purpose of the information, is comprehensive, informative, and understandable. In a document made available to the public, EPA specifies:

(i) each population addressed by any estimate of applicable human health risk or each risk assessment endpoint, including populations if applicable, addressed by any estimate of applicable ecological risk[22];

(ii) the expected risk or central estimate of human health risk for the specific

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assessment".

[19]OMB stated in its guidelines that in disseminating information agencies shall develop a process for reviewing the quality of the information. "Quality" includes objectivity, utility, and integrity. "Objectivity" involves two distinct elements, presentation and substance. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies, OMB, 2002. (67 FR 8452) http://www.whitehouse.gov/omb/fedreg/reproducible2.pdf

[20]Safe Drinking Water Act Amendments of 1996, 42 U.S.C. 300g-1(b)(3)(A) & (B)

[21]The exception is risk assessments conducted under SDWA which will adhere to the SDWA principles as amended in 1996.

[22]Agency assessments of human health risks necessarily focus on populations. Agency assessments of ecological risks address a variety of entities, some of which can be described as populations and others (such as ecosystems) which cannot. The phrase "assessment endpoint" is intended to reflect the broader range of interests inherent in ecological risk assessments. As discussed in the *EPA Guidelines for Ecological Risk Assessment* (found at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12460), assessment endpoints are explicit expressions of the actual environmental value that is to be protected, operationally defined by an ecological entity and its attributes. Furthermore, those Guidelines explain that an ecological entity can be a species (e.g., eelgrass, piping plover), a community (e.g., benthic invertebrates), an ecosystem (e.g., wetland), or other entity of concern. An attribute of an assessment endpoint is the characteristic about the entity of concern that is important to protect and potentially at risk. Examples of attributes include abundance (of a population), species richness (of a community), or function (of an ecosystem). Assessment endpoints and ecological risk assessments are discussed more fully in those Guidelines as well as other EPA sources such as *Ecological Risk Assessment Guidance for Superfund: Process for Designing and Conducting Ecological Risk Assessments - Interim Final* found at http://www.epa.gov/oerrpage/superfund/programs/risk/ecorisk/ecorisk.htm

populations affected or the ecological assessment endpoints[23], including populations if applicable;

(iii) each appropriate upper-bound or lower-bound estimate of risk;

(iv) each significant uncertainty identified in the process of the assessment of risk and studies that would assist in resolving the uncertainty; and

(v) peer-reviewed studies known to the Administrator that support, are directly relevant to, or fail to support any estimate of risk and the methodology used to reconcile inconsistencies in the scientific data.

In applying these principles, "best available" usually refers to the availability at the time an assessment is made. However, EPA also recognizes that scientific knowledge about risk is rapidly changing and that risk information may need to be updated over time. When deciding which influential risk assessment should be updated and when to update it, the Agency will take into account its statutes and the extent to which the updated risk assessment will have a clear and substantial impact on important public policies or private sector decisions. In some situations, the Agency may need to weigh the resources needed and the potential delay associated with incorporating additional information in comparison to the value of the new information in terms of its potential to improve the substance and presentation of the assessment.

Adaptation clarifications

In order to provide more clarity on how EPA adapted the SDWA principles in this guidance in light of our numerous statutes, regulations, guidance and policies that address how to conduct a risk assessment and characterize risk we discuss four adaptations EPA has made to the SDWA quality principles language.

EPA adapted the SDWA principles by adding the phrase "consistent with Agency statutes and existing legislative regulations, the objectivity of such information disseminated by the Agency" in the introductory paragraph, therefore applying to both paragraphs (A) and (B). This was done to explain EPA's intent regarding these quality principles and their implementation consistent with our statutes and existing legislative regulations. Also, as noted earlier, EPA intends to implement these quality principles in conjunction with our guidelines and policies. The procedures set forth in other EPA guidelines set out in more detail EPA's policies for conducting risk assessments, including Agency-wide guidance on various types of risk assessments and program-specific guidance. EPA recognizes that the wide array of programs within EPA have resulted not only in Agency-wide guidance, but in specific protocols that reflect the requirements, including limitations, that are mandated by the various statutes administered by the Agency. For example, the Agency developed several pesticide science policy papers that explained to the public in detail how EPA would implement specific statutory requirements in the Food Quality Protection Act (FQPA) that addressed how we perform risk assessments. We also recognize that emerging issues such endocrine disruption, bioengineered organisms, and genomics may involve some modifications to the existing paradigm for assessing human health

[23]Ibid.

and ecological risks. This does not mean a radical departure from existing guidance or the SDWA principles, but rather indicates that flexibility may be warranted as new information and approaches develop.

EPA introduced the following two adaptations in order to accommodate the range of real-world situations that we confront in the implementation of our diverse programs. EPA adapted the SDWA quality principles by moving the phrase "to the extent practicable" from paragraph (B) to the introductory paragraph in this Guidelines section to cover both parts (A) and (B) of the SDWA adaptation.[24] The phrase refers to situations under (A) where EPA may be called upon to conduct "influential" scientific risk assessments based on limited information or in novel situations, and under (B) in recognition that all such "presentation" information may not be available in every instance. The level of effort and complexity of a risk assessment should also balance the information needs for decision making with the effort needed to develop such information. For example, under the Federal Insecticide, Fungicide and Rodenticide Act[25] (FIFRA) and the Toxic Substances and Control Act[26] (TSCA), regulated entities are obligated to provide information to EPA concerning incidents/test data that may reveal a problem with a pesticide or chemical. We also receive such information voluntarily from other sources. EPA carefully reviews incident reports and factors them as appropriate into risk assessments and decision-making, even though these may not be considered information collected by acceptable methods or best available method as stated in A(ii). Incident information played an important role in the Agency's conclusion that use of chlordane/heptachlor termiticides could result in exposures to persons living in treated homes, and that the registrations needed to be modified accordingly. Similarly, incident reports concerning birdkills and fishkills were important components of the risk assessments for the reregistration of the pesticides phorate and terbufos, respectively. In addition, this adaptation recognizes that while many of the studies incorporated into risk assessments have been peer reviewed, data from other sources may not be peer reviewed. EPA takes many actions based on studies and supporting data provided by outside sources, including confidential or proprietary information that has not been peer reviewed. For example, industry can be required by regulation to submit data for pesticides under FIFRA or for chemicals under TSCA. The data are developed using test guidelines and Good Laboratory Practices (GLPs) in accordance with EPA regulations. While there is not a requirement to have studies peer reviewed, such studies are reviewed by Agency scientists to ensure that they were conducted according to the appropriate test guidelines and GLPs and that the data are valid.

The flexibility provided by applying "to the extent practicable" to paragraph (A) is appropriate in many circumstances to conserve Agency resources and those of the regulated community who otherwise might have to generate significant additional data. This flexibility is already provided

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[24]The discussion in this and following paragraphs gives some examples of the types of assessments that may under some circumstances be considered influential. These examples are representative of assessments performed under other EPA programs, such as CERCLA

[25]7 U.S.C. 136 et seq.

[26]15 U.S.C. 2601 et seq.

for paragraph (B) in the SDWA quality principles. Pesticide and chemical risk assessments are frequently performed iteratively, with the first iteration employing protective (conservative) assumptions to identify possible risks. Only if potential risks are identified in a screening level assessment, is it necessary to pursue a more refined, data-intensive risk assessment. This is exhibited, for example, in guidance developed for use in CERCLA and RCRA on tiered approaches. In other cases, reliance on "structure activity relationship" or "bridging data" allows the Agency to rely on data from similar chemicals rather than require the generation of new, chemical-specific data. While such assessments may or may not be considered influential under the Guidelines, this adaptation of the SDWA principles reflects EPA's reliance on less-refined risk assessments where further refinement could significantly increase the cost of the risk assessment without significantly enhancing the assessment or changing the regulatory outcome.

In emergency and other time critical circumstances, risk assessments may have to rely on information at hand or that can be made readily available rather than data such as described in (A). One such scenario is risk assessments addressing Emergency Exemption requests submitted under Section 18 of FIFRA[27] which, because of the emergency nature of the request, must be completed within a short time frame. As an example, EPA granted an emergency exemption under Section 18 to allow use of an unregistered pesticide to decontaminate anthrax in a Senate office building. The scientific review and risk assessment to support this action were necessarily constrained by the urgency of the action. Other time-sensitive actions include the reviews of new chemicals under TSCA. Under Section 5 of TSCA[28], EPA must review a large number of pre-manufacture notifications (more than 1,000) every year, not all of which necessarily include "influential" risk assessments, and each review must be completed within a short time frame (generally 90 days). The nature of the reviews and risk assessment associated with these pre-manufacture notifications are affected by the limited time available and the large volume of notifications submitted.

The flexibility provided by applying "to the extent practicable" to paragraph (A) is appropriate to account for safety risk assessment practices. This flexibility is already provided for paragraph (B) in the SDWA quality principles. We applied the same SDWA adaptation for use with human health risk assessments to safety risk assessments with the needed flexibility to apply the principles to the extent practicable. "Safety risk assessments" include a variety of analyses, investigations, or case studies conducted by EPA concerning safety issues. EPA works to ensure that the chemical industry and state and local entities take action to prevent, plan and prepare for, and respond to environmental emergencies and site specific response actions through the development and sharing of information, tools and guidance for hazard analyses and risk assessment. For example, although the chemical industry shoulders most of the responsibility for safety risk assessment and management, EPA may also conduct chemical hazard analyses, investigate the root causes and mechanisms associated with accidental chemical releases, and assess the probability and consequences of accidental releases in support of agency risk

[27] Section 18 of FIFRA, 7 U.S.C. 136p

[28] Section 5 of TSCA, 15 U.S.C. 2604

assessments. Although safety risk assessments can be different from traditional human health risk assessments because they may combine a variety of available information and may use expert judgement based on that information, these assessments provide useful information that is sufficient for the intended purpose.

Next, EPA adapted the SDWA quality principles by adding the clause "including, when available, peer reviewed science and supporting studies" to paragraph (A)(i). It now reads: "the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies." In the Agency's development of "influential" scientific risk assessments, we intend to use all relevant information, including peer reviewed studies, studies that have not been peer reviewed, and incident information; evaluate that information based on sound scientific practices as described in our risk assessment guidelines and policies; and reach a position based on careful consideration of all such information (*i.e.*, a process typically referred to as the "weight-of-evidence" approach[29]). In this approach, a well-developed, peer-reviewed study would generally be accorded greater weight than information from a less well-developed study that had not been peer-reviewed, but both studies would be considered. Thus the Agency uses a "weight-of-evidence" process when evaluating peer-reviewed studies along with all other information.

Oftentimes under various EPA-managed programs, EPA receives information that has not been peer-reviewed and we have to make decisions based on the information available. While many of the studies incorporated in risk assessments have been peer reviewed, data from other sources, such as studies submitted to the Agency for pesticides under FIFRA[30] and for chemicals under TSCA, may not always be peer reviewed. Rather, such data, developed under approved guidelines and the application of Good Laboratory Practices (GLPs), are routinely used in the development of risk assessments. Risk assessments may also include more limited data sets such as monitoring data used to support the exposure element of a risk assessment. In cases where these data may not themselves have been peer reviewed their quality and appropriate use would be addressed as part of the peer review of the overall risk assessment as called for under the Agency's peer review guidelines.

Lastly, EPA adapted the SDWA principles for influential environmental ("ecological") risk assessments that are disseminated in order to use terms that are most suited for such risk assessments. Specifically, EPA assessments of ecological risks address a variety of entities,

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[29] The weight-of-evidence approach generally considers all relevant information in an integrative assessment that takes into account the kinds of evidence available, the quality and quantity of the evidence, the strengths and limitations associated of each type of evidence, and explains how the various types of evidence fit together. See, e.g., EPA's *Proposed Guidelines for Carcinogen Risk Assessment* (Federal Register 61(79): 17960-18011; April 23, 1996) and EPA's *Guidelines for Carcinogen Risk Assessment* (Federal Register 51(185): 33992-34003; September 24, 1986), available from: www.epa.gov/ncea/raf/, and EPA's Risk Characterization Handbook (*Science Policy Council Handbook: Risk Characterization*, EPA 100-B-00-002, Washington, DC: U.S. EPA, December 2000).

[30] 40 CFR part 158

some of which can be described as populations and others (such as ecosystems) which cannot. Therefore, a specific modification was made to include "assessment endpoints, including populations if applicable" in place of the term "population" for ecological risk assessments and EPA added a footnote directing the reader to various EPA risk policies for further discussion of these concepts in greater detail.

6.5 Does EPA Ensure and Maximize the Quality of Information from External Sources?

Ensuring and maximizing the quality of information from States, other governments, and third parties is a complex undertaking, involving thoughtful collaboration with States, Tribes, the scientific and technical community, and other external information providers. EPA will continue to take steps to ensure that the quality and transparency of information provided by external sources are sufficient for the intended use. For instance, since 1998, the use of environmental data collected by others or for other purposes, including literature, industry surveys, compilations from computerized data bases and information systems, and results from computerized or mathematical models of environmental processes and conditions has been within the scope of the Agency's Quality System[31].

For information that is either voluntarily submitted to EPA in hopes of influencing a decision or that EPA obtains for use in developing a policy, regulatory, or other decision, EPA will continue to work with States and other governments, the scientific and technical community, and other interested information providers to develop and publish factors that EPA would use to assess the quality of this type of information.

For all proposed collections of information that will be disseminated to the public, EPA intends to demonstrate in our Paperwork Reduction Act[32] clearance submissions that the proposed collection of information will result in information that will be collected, maintained and used in ways consistent with the OMB guidelines and these EPA Guidelines. These Guidelines apply to all information EPA disseminates to the public; accordingly, if EPA later identifies a new use for the information that was collected, such use would not be precluded and the Guidelines would apply to the dissemination of the information to the public.

[31] EPA Quality Manual for Environmental Programs 5360 A1. May 2000, Section 1.3.1. http://www.epa.gov/quality/qs-docs/5360.pdf

[32] 44 U.S.C. 3501 et seq.

7 Administrative Mechanism for Pre-dissemination Review

7.1 What are the Administrative Mechanisms for Pre-dissemination Reviews?

Each EPA Program Office and Region will incorporate the information quality principles outlined in section 6 of these Guidelines into their existing pre-dissemination review procedures as appropriate. Offices and Regions may develop unique and new procedures, as needed, to provide additional assurance that the information disseminated by or on behalf of their organizations is consistent with these Guidelines. EPA intends to facilitate implementation of consistent cross-Agency pre-dissemination reviews by establishing a model of minimum review standards based on existing policies. Such a model for pre-dissemination review would still provide that responsibility for the reviews remains in the appropriate EPA Office or Region.

For the purposes of the Guidelines, EPA recognizes that pre-dissemination review procedures may include peer reviews and quality reviews that may occur at many steps in development of information, not only at the point immediately prior to the dissemination of the information.

8 Administrative Mechanisms for Correction of Information

8.1 What are EPA's Administrative Mechanisms for Affected Persons to Seek and Obtain Correction of Information?

EPA's Office of Environmental Information (OEI) manages the administrative mechanisms that enable affected persons to seek and obtain, where appropriate, correction of information disseminated by the Agency that does not comply with EPA or OMB Information Quality Guidelines. Working with the Program Offices, Regions, laboratories, and field offices, OEI will receive complaints (or copies) and distribute them to the appropriate EPA information owners. "Information owners" are the responsible persons designated by management in the applicable EPA Program Office, or those who have responsibility for the quality, objectivity, utility, and integrity of the information product or data disseminated by EPA. If a person believes that information disseminated by EPA may not comply with the Guidelines, we encourage the person to consult informally with the contact person listed in the information product before submitting a request for correction of information. An informal contact can result in a quick and efficient resolution of questions about information quality.

8.2 What Should be Included in a Request for Correction of Information?

Persons requesting a correction of information should include the following information in their Request for Correction (RFC):

- Name and contact information for the individual or organization submitting a complaint; identification of an individual to serve as a contact.
- A description of the information the person believes does not comply with EPA or OMB guidelines, including specific citations to the information and to the EPA or OMB guidelines, if applicable.
- An explanation of how the information does not comply with EPA or OMB guidelines and a recommendation of corrective action. EPA considers that the complainant has the burden of demonstrating that the information does not comply with EPA or OMB guidelines and that a particular corrective action would be appropriate.
- An explanation of how the alleged error affects or how a correction would benefit the requestor.
- An affected person may submit an RFC via any one of methods listed here:
  - **Internet** at http://www.epa.gov/oei/qualityguidelines
  - **E-mail** at quality.guidelines@epa.gov
  - **Fax** at (202) 566-0255

- **Mail** to *Information Quality Guidelines Staff*, Mail Code 28221T, U.S. EPA, 1200 Pennsylvania Ave., N.W., Washington, DC, 20460
- **By courier or in person** to *Information Quality Guidelines Staff*, OEI Docket Center, Room B128, EPA West Building, 1301 Constitution Ave., N.W., Washington, DC

8.3 When Does EPA Intend to Consider a Request for Correction of Information?

EPA seeks public and stakeholder input on a wide variety of issues, including the identification and resolution of discrepancies in EPA data and information. EPA may decline to review an RFC under these Guidelines and consider it for correction if:

- The request does not address information disseminated to the public covered by these Guidelines (see section 5.3 or OMB's guidelines). In many cases, EPA provides other correction processes for information not covered by these Guidelines.

- The request omits one or more of the elements recommended in section 8.2 and there is insufficient information for EPA to provide a satisfactory response.

- The request itself is "frivolous," including those made in bad faith, made without justification or trivial, and for which a response would be duplicative. More information on this subject may be found in the OMB guidelines.

8.4 How Does EPA Intend to Respond to a Request for Correction of Information?

EPA intends to use the following process:

- Each RFC will be tracked in an OEI system.

- If an RFC is deemed appropriate for consideration, the information owner office or region makes a decision on the request on the basis of the information in question, including a request submitted under section 8.2. Rejections of a request for correction should be decided at the highest level of the information owner office or region. EPA's goal is to respond to requests within 90 days of receipt, by 1) providing either a decision on the request, or 2) if the request requires more than 90 calendar days to resolve, informing the complainant that more time is required and indicate the reason why and an estimated decision date.

- If a request is approved, EPA determines what corrective action is appropriate. Considerations relevant to the determination of appropriate corrective action include the nature and timeliness of the information involved and such factors as the significance of the error on the use of the information and the magnitude of

the error. For requests involving information from outside sources, considerations may include coordinating with the source and other practical limitations on EPA's ability to take corrective action.

- Whether or not EPA determines that corrective action is appropriate, EPA provides notice of its decision to the requester.

- For approved requests, EPA assigns a steward for the correction who marks the information as designated for corrections as appropriate, establishes a schedule for correction, and reports correction resolution to both the tracking system and to the requestor.

OEI will provide reports on behalf of EPA to OMB on an annual basis beginning January 1, 2004 regarding the number, nature, and resolution of complaints received by EPA.

8.5 How Does EPA Expect to Process Requests for Correction of Information on Which EPA has Sought Public Comment?

When EPA provides opportunities for public participation by seeking comments on information, the public comment process should address concerns about EPA's information. For example, when EPA issues a notice of proposed rulemaking supported by studies and other information described in the proposal or included in the rulemaking docket, it disseminates this information within the meaning of the Guidelines. The public may then raise issues in comments regarding the information. If a group or an individual raises a question regarding information supporting a proposed rule, EPA generally expects to treat it procedurally like a comment to the rulemaking, addressing it in the response to comments rather than through a separate response mechanism. This approach would also generally apply to other processes involving a structured opportunity for public comment on a draft or proposed document before a final document is issued, such as a draft report, risk assessment, or guidance document. EPA believes that the thorough consideration provided by the public comment process serves the purposes of the Guidelines, provides an opportunity for correction of any information that does not comply with the Guidelines, and does not duplicate or interfere with the orderly conduct of the action. In cases where the Agency disseminates a study, analysis, or other information prior to the final Agency action or information product, it is EPA policy to consider requests for correction prior to the final Agency action or information product in those cases where the Agency has determined that an earlier response would not unduly delay issuance of the Agency action or information product and the complainant has shown a reasonable likelihood of suffering actual harm from the Agency's dissemination if the Agency does not resolve the complaint prior to the final Agency action or information product. EPA does not expect this to be the norm in rulemakings that it conducts, and thus will usually address information quality issues in connection with the final Agency action or information product.

EPA generally would not consider a complaint that could have been submitted as a timely comment in the rulemaking or other action but was submitted after the comment period. If EPA cannot respond to a complaint in the response to comments for the action (for example, because the complaint is submitted too late to be considered and could not have been timely submitted, or because the complaint is not germane to the action), EPA will consider whether a separate response to the complaint is appropriate.

generate and data or information generated by external parties, including States. State information, when submitted to EPA, may not be covered by these Guidelines, but our subsequent use of the information may in fact be covered. We note, however, that there may be practical limitations on the type of corrective action that may be taken, since EPA does not intend to alter information submitted by States. However, EPA does intend to work closely with our State counterparts to ensure and maximize the quality of information that EPA disseminates. Furthermore, one commenter stated that if regulatory information is submitted to an authorized or delegated State program, then the State is the primary custodian of the information and the Guidelines would not cover that information. We agree with that statement.

We also received comments regarding the use of labels, or disclaimers, to notify the public whether information is generated by EPA or an external party. We agree that disclaimers and other notifications should be used to explain the status of information wherever possible, and we are developing appropriate language and format.

A statement regarding Paperwork Reduction Act clearance submissions has been added in response to comment by OMB.

A.3.4 Influential Information

EPA received a range of comments on its definition of "influential." Below we provide a summary of the comments raised and EPA's response.

Several commenters generally assert that the definition is too narrow. Other commenters indicated that under EPA's draft definition, only Economically Significant actions, as defined in Executive Order 12866, or only Economically Significant actions and information disseminated in support of top Agency actions, are considered "influential." We disagree. To demonstrate the broad range of activities covered by our adoption of OMB's definition, we reiterate the definition below and include an example of each type of action, to illustrate the breadth of our definition. "Influential," when used in the phrase "influential scientific, financial, or statistical information," means that the Agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public policies or important private sector decisions. We will generally consider the following classes of information to be influential: information disseminated in support of top Agency actions; information disseminated in support of "economically significant" actions; major work products undergoing peer review; and other disseminated information that will have or does have a clear and substantial impact (i.e., potential change or impact) on important public policies or important private sector decisions as determined by EPA on a case-by-case basis. In general, influential information would be the scientific, financial or statistical information that provides a substantial basis for EPA's position on key issues in top Agency actions and Economically Significant actions. If the information provides a substantial basis for EPA's position, EPA believes it would generally have a clear and substantial impact.

Top Agency actions: An example of a top Agency action is the review of the National Ambient Air Quality Standards (NAAQS) for Particulate Matter. Under the Clean Air Act, EPA is to periodically review (1) the latest scientific knowledge about the effects on public health and public welfare (e.g., the environment) associated with the presence of such pollutants in the ambient air and (2) the standards, which are based on this science. The Act further directs that the Administrator shall make any revisions to the standards as may be appropriate, based on the latest science, that in her judgment are requisite to protect the public health with an adequate margin of safety and to protect the public welfare from any known or anticipated adverse effects. The standards establish allowable levels of the pollutant in the ambient air across the United States, and States must development implementation plans to attain the standards. The PM NAAQS were last revised in 1997, and the next periodic review is now being conducted.

"Economically significant" rules: An example of a rule found to be economically significant is the Disposal of Polychlorinated Biphenyls (PCBs) Final Rule. In 1998, EPA amended its rules under the Toxic Substances Control Act (TSCA), which addresses the manufacture, processing, distribution in commerce, use, cleanup, storage and disposal of PCBs. This rule provides flexibility in selecting disposal technologies for PCB wastes and expands the list of available decontamination procedures; provides less burdensome mechanisms for obtaining EPA approval for a variety of activities; clarifies and/or modifies certain provisions where implementation questions have arisen; modifies the requirements regarding the use and disposal of PCB equipment; and addresses outstanding issues associated with the notification and manifesting of PCB wastes and changes in the operation of commercial storage facilities. EPA would consider the information that provides the principal basis for this rule to be influential information.

Peer reviewed work products: An example of a major work product undergoing peer review is the IRIS Documentation: Reference Dose for Methylmercury. Methylmercury contamination is the basis for fish advisories. It is necessary to determine an intake to humans that is without appreciable risk in order to devise strategies for decreasing mercury emissions into the environment. After EPA derived a reference dose (RfD) of 0.0001 mg/kg-day in 1995, industry argued that it was not based on sound science. Congress ordered EPA to fund an National Research Council/National Academy of the Sciences panel to determine whether our RfD was scientifically justifiable. The panel concluded that the 0.0001 mg/kg-day was an appropriate RfD, based on newer studies than the 1995 RfD. The information in this document was evaluated, incorporated, and subjected to comment by the Office of Water, where it contributed in large part to Chapter 4 of *Drinking Water Criteria for the Protection of Human Health: Methylmercury* (EPA/823/R-01/001) January 2001. The peer review mechanism was an external peer review workshop and public comment session held on November 15, 2000, accompanied by a public comment period from October 30 to November 29, 2000.

Case-by-base determination – PBT Chemicals Rule: An example of a case-by-case determination is the Guidance Document for Reporting Releases and Other Waste

Regarding robustness checks, commenters were concerned that the EPA did not use the term "especially rigorous robustness checks." We have modified our Guidelines to include this term. Some commenters speculated on the ability of the Agency's Peer Review program to meet the intent of the Guidelines and were concerned about the process to rebut a peer review used to support the objectivity demonstration for disseminated information. Our Peer Review program has been subject to external review and we routinely verify implementation of the program. Affected persons wishing to rebut a formal peer review may do so using the complaint resolution process in these Guidelines, provided that the information being questioned is considered to be "disseminated" according to the Guidelines.

Regarding analytic results, some commenters indicated that the transparency factors identified by EPA (section 6.3 of the Guidelines) are not a complete list of the items that would be needed to demonstrate a higher degree of quality for influential information. EPA agreed with the list of four items that was initially provided by the OMB and recognizes that, in some cases, additional information regarding disseminated information would facilitate increased quality. However, given the variety of information disseminated by the Agency, we cannot reasonably provide additional details for such a demonstration at this time. Also, in regards to laboratory results, which were mentioned by several commenters, these Guidelines are not the appropriate place to set out for the science community EPA's view of what constitutes adequate demonstration of test method validation or minimum quality assurance and quality control. Those technical considerations should be addressed in the appropriate quality planning documentation or in regulatory requirements.

EPA has developed general language addressing the concept of reproducibility and may provide more detail after appropriate consultation with scientific and technical communities, as called for by OMB in its guidelines. We have already begun to consult relevant scientific and technical experts within the Agency, and also have planned an expedited consultation with EPA's Science Advisory Board (SAB) on October 1, 2002. Based on these initial consultations, EPA may seek additional input from the SAB in 2003. These consultations will allow EPA to constructively and appropriately refine the application of existing policies and procedures, to further improve reproducibility. In the interim, EPA intends to base the reproducibility of disseminated original and supporting data on commonly accepted scientific, financial, or statistical standards.

A.3.6 Influential Risk Assessment

General Risk Assessment

Risk assessment is a process where information is analyzed to determine if an environmental hazard might cause harm to exposed persons and ecosystems (paraphrased from Risk Assessment in the Federal Government, National Research Council, 1983). That is:

$$\text{Risk} = \text{hazard} \times \text{exposure}$$

For a chemical or other stressor to be "risky," it must have both an inherent adverse effect on an

organism, population, or other endpoint and it must be present in the environment at concentrations and locations that an organism, population, or other endpoint is exposed to the stressor. Risk assessment is a tool to determine the likelihood of harm or loss of an organism, population, or other endpoint because of exposure to a chemical or other stressor. To assist those who must make risk management decisions, risk assessments include discussions on uncertainty, variability and the continuum between exposure and adverse effects.

Risk assessments may be performed iteratively, with the first iteration employing protective (conservative) assumptions to identify possible risks. Only if potential risks are identified in a screening level assessment is it necessary to pursue a more refined, data-intensive risk assessment. The screening level assessments may not result in "central estimates" of risk or upper and lower-bounds of risks. Nevertheless, such assessments may be useful in making regulatory decisions, as when the absence of concern from a screening level assessment is used (along with other information) to approve the new use of a pesticide or chemical or to decide whether to remediate very low levels of waste contamination.

APPENDIX C – 3

Integrated Risk Information System (IRIS)

IRIS Public Meetings

- **Hexavalent Chromium: Sep 19 & 25**
- **IRIS Bimonthly Meeting: Oct 23-24**
- **Mouse Lung Tumor Workshop: Oct 24-25**

1 2 3 4

IRIS Most Viewed Chemicals

Full List of IRIS Chemicals

Acrylamide	Cadmium	Mercury, elemental
Arsenic, inorganic	Chromium (VI)	Methylmercury (MeHg)
Benzene	1,4-Dioxane	Polychlorinated biphenyls (PCBs)
Bisphenol A	Formaldehyde	Silver

EPA's Integrated Risk Information System (IRIS) is a human health assessment program that evaluates information on health effects that may result from exposure to environmental contaminants. Through the IRIS Program, EPA provides the highest quality science-based human health assessments to support the Agency's regulatory activities. The IRIS database is web accessible and contains information on more than 550 chemical substances. Learn more.

What's New in IRIS

- 09/30/13: EPA announces the availability of the final IRIS Toxicological Review and IRIS Summary for Methanol (Noncancer). The Interagency Science Discussion Draft of the Methanol (Noncancer) IRIS assessment was also released. New!
- 09/30/13: EPA announces an extension of the public comment period for the draft document, *Toxicological Review of Benzo[a]pyrene (Public Comment Draft)*. (Deadline for comment is November 21st) New!
- 09/20/13: EPA announces the availability of the final IRIS Toxicological Review and IRIS Summary for 1,4-Dioxane. The Interagency Science Discussion Draft of the 1,4-Dioxane IRIS assessment (with Inhalation Update) was also released. New!
- 08/28/13: EPA's Science Advisory Board (SAB) announces a request for nominations of experts to augment the SAB Chemical Assessment Advisory Committee for the review of the draft IRIS Toxicological Reviews of Ammonia and Trimethylbenzenes (Revised External Review Drafts), and the draft Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft) (Deadline for nominations is September 18th)
- 08/28/13: EPA announces an extension of the public comment period for the draft document, Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft). (Deadline for comment is October 11th)
- 08/27/13: EPA announces the availability of the final IRIS Toxicological Review and IRIS Summary for Biphenyl. The Interagency Science Discussion Draft of the Biphenyl IRIS assessment was also released.

See more recent additions

Recent Final Assessments

- Methanol New! (09/30/13)
- 1,4-Dioxane New! (09/20/13)

Draft Assessments under External Peer Review

- Ammonia – Revised (08/28/13)
- Trimethylbenzenes – Revised (08/28/13)
- Benzo[a]pyrene (08/21/13)

- Biphenyl (08/27/13)
- Tetrahydrofuran (02/21/12)
- 2,3,7,8-Tetrachlorodibenzo-p-dioxin (02/17/12)

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- Ethylene Oxide (inhalation cancer) - Revised (07/02/13)

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Last updated on Monday, September 30, 2013

APPENDIX C – 4

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 21 2012

OFFICE OF
ENVIRONMENTAL INFORMATION

Mr. Gregory Dolan
Executive Director – Americas/Europe
Methanol Institute
124 West Street South
Suite 203
Alexandria, VA 22314

Dear Mr. Dolan:

I am providing you with another status update on the EPA response to your July 2010, Information Quality Guidelines Request for Correction (RFC 10005). As noted in our June 2011 interim response, EPA placed the IRIS Methanol Toxicological Review (Cancer) on hold. The external peer review draft assessment noted in your Request for Correction containing the methanol cancer analysis has now been archived on the IRIS website[1]. Further development of an IRIS methanol assessment for cancer will follow the established IRIS process, which includes opportunities for public comment.

We will provide a final response or a status update in 90 business days.

Sincerely,

for

Monica D. Jones,
Acting Director, Quality Staff

[1] http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=56521

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 24 2012

OFFICE OF
ENVIRONMENTAL INFORMATION

Gregory Dolan, Executive Director – Americas/Europe
Methanol Institute
124 West Street South
Suite 203
Alexandria, VA 22314

Dear Mr. Dolan:

The December 2009 Integrated Risk Information System (IRIS) Toxicological Review of Methanol (External Review Draft)[1] which is the subject of the Methanol Institute's information quality guidelines Request for Correction (RFC 10005)[2] has been archived.[3]

In March 2012, EPA announced that it would no longer rely on certain data[4] that were used in the December 2009 draft Toxicological Review of methanol to characterize the carcinogenic potential of methanol. Since the document upon which the Methanol Institute's Request for Correction is based is no longer being considered, As a result, EPA plans to close the associated RFC.

The IRIS assessment development process[5] offers multiple opportunities for the public, including the Methanol Institute, to provide input on draft assessments. The current status of the cancer and non-cancer methanol assessments is available on the IRISTrack website[6] and will be updated as new information becomes available.

If you have questions about the decision to close your RFC, please contact me at (202) 564-1641. If you have questions about the IRIS assessment for methanol, please contact Jeffrey Gift at (919) 541-4828.

Sincerely,

Monica D. Jones

Monica D. Jones, Director
Quality Staff

---

[1] IRIS Toxicological Review of Methanol (External Review Draft), U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-09/013, December 2009.
[2] RFC 10005, July 2010 (http://epa.gov/quality/informationguidelines/documents/RFC10005.pdf)
[3] http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=506440
[4] See the Ramazzini update - http://www.epa.gov/IRIS/ramazzini.htm
[5] http://www.epa.gov/iris/process.htm
[6] http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=225977

cc: Lek Kadeli, Acting Assistant Administrator,
Office of Research and Development
Malcolm D. Jackson, Assistant Administrator and Chief Information Officer,
Office of Environmental Information (2810A)
Jeff Gift, RTP Division, Office of Research and Development (B243-01)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 24 2012

OFFICE OF
ENVIRONMENTAL INFORMATION

Lynn L. Bergeson, Managing Director
Bergeson & Campbell, P.C.
1203 Nineteenth Street, N.W.
Suite 300
Washington, D.C. 20036-2401

Dear Ms. Bergeson:

The February 2010, Integrated Risk Information System (IRIS) Toxicological Review of Inorganic Arsenic (External Review Draft)[1] which is the subject of the Organic Arsenical Products Task Force (OAPTF) and Wood Preservative Science Council (WPSC) Request for Correction (RFC 10004)[2] has been archived. As a result, EPA plans to close this RFC.

EPA plans to initiate the development of a new Toxicological Review of inorganic arsenic in the near future[3]. Information on the new schedule will be available on the IRIS Substance Assessment Tracking System (IRISTrack[4]) as it becomes available.

The IRIS assessment development process[5] offers multiple opportunities for the public, including OAPTF and WPSC, to provide input on draft assessments. In addition, the OAPTF and WPSC will be able to provide comments on scientific issues related to the evaluation of inorganic arsenic toxicity during a public workshop, which will be hosted by the National Academy of Sciences (NAS). When the draft IRIS assessment is completed, it will be provided to the NAS for external peer review.

If you have questions about the decision to close your RFC, please contact me at (202) 564-1641. If you have questions about the IRIS assessment for inorganic arsenic, please contact Reeder Sams at (919) 541-0661.

Sincerely,

Monica D Jones

Monica D. Jones, Director
Quality Staff

---

[1] IRIS Toxicological Review of Inorganic Arsenic (External Review Draft), U.S. Environmental Protection Agency, EPA/635/R-10/001, Washington, DC, February 2010. (http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=494787)
[2] RFC 10004, June 2010 (http://epa.gov/quality/informationguidelines/documents/10004.pdf)
[3] http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=225977
[4] http://cfpub.epa.gov/ncea/iristrac/
[5] http://www.epa.gov/iris/process.htm

cc: Lek Kadeli, Acting Assistant Administrator,
Office of Research and Development
Malcolm D. Jackson, Assistant Administrator and Chief Information Officer,
Office of Environmental Information (2810A)
Reeder Sams, Acting Deputy Division Director
RTP Division, Office of Research and Development (B-243-01)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 8 2011

OFFICE OF
ENVIRONMENTAL INFORMATION

Lynn L. Bergeson, Managing Director
Bergeson & Campbell, P.C.,
1203 Nineteenth Street, N.W.
Suite 300
Washington, D.C. 20036-2401

Dear Ms. Bergeson:

I am providing you with a status update on the June 14, 2010, Information Quality Guidelines (IQG) Request for Correction (RFC 10004), which was submitted to the U.S. Environmental Protection Agency (EPA), on behalf of the Organic Arsenical Products Task Force (OAPTF) and the Wood Preservative Science Council (WPSC). This RFC is related to the Integrated Risk Information System (IRIS) Toxicological Review of Inorganic Arsenic.

EPA expects to address the information quality concerns raised in your RFC through the IRIS peer review and public comment-response process. The SAB peer review for the Toxicological Review of Inorganic Arsenic was completed earlier this year[1] and the Agency is considering the recommendations and making revisions to the document. A summary of the Agency's planned responses to the SAB is available on the web[2]. OAPTF and WPSC RFC comments that were not specifically addressed by the SAB will be addressed by EPA in the final Toxicological Review and documented in the appendices.

We will update you on the status of the RFC response within 90 business days.

Sincerely,

Monica D. Jones, Acting Director
Quality Staff

[1] http://yosemite.epa.gov/sab/sabproduct.nsf/WebReportsbyYearBOARD!OpenView&Start=1&Count=800&Collapse=1#1
[2] http://yosemite.epa.gov/sab/sabproduct.nsf/9FCEE4E20ABD6EB48525784600791AC2/$File/EPA-SAB-11-003_Response_05-20-2011.pdf

APPENDIX C – 5

EXCERPTS

REVIEW OF THE ENVIRONMENTAL PROTECTION AGENCY'S DRAFT IRIS ASSESSMENT OF FORMALDEHYDE

Committee to Review EPA's Draft IRIS Assessment of Formaldehyde

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This project was supported by Contract EP-C-09-003 between the National Academy of Sciences and U.S. Environmental Protection Agency. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

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Contents

TABLES

formaldehyde exposure and the three kinds of cancer, EPA's decision to calculate unit risk values for them appears to be defensible on the basis of the agency's cancer guidelines. However, EPA should provide a clear description of the criteria that it used to select the specific cancers and demonstrate a systematic application of the criteria. The calculation of the unit risk values is a complex process, involves many sources of uncertainty and variability, and is influenced by the low-dose extrapolation used (for example, linear vs threshold). The committee therefore recommends that EPA conduct an independent analysis of the dose-response models to confirm the degree to which the models fit the data appropriately. EPA is encouraged to consider the use of alternative extrapolation models for the analysis of the cancer data; this is especially important given the use of a single study, the inconsistencies in the exposure measures, and the uncertainties associated with the selected cancers.

THE FORMALDEHYDE IRIS ASSESSMENT: THE PATH FORWARD

The committee recognizes that the completion of the formaldehyde IRIS assessment is awaited by diverse stakeholders, and it has tried to be judicious in its recommendations of specific changes noted in its report. However, the committee concludes that the following general recommendations are critical to address in the revision of the draft assessment. First, rigorous editing is needed to reduce the volume of the text substantially and address the redundancies and inconsistencies; reducing the text could greatly enhance the clarity of the document. Second, Chapter 1 of the draft assessment needs to discuss more fully the methods of the assessment. The committee is recommending not the addition of long descriptions of EPA guidelines but rather clear concise statements of criteria used to exclude, include, and advance studies for derivation of the RfCs and unit risk estimates. Third, standardized evidence tables that provide the methods and results of each study are needed for all health outcomes; if appropriate tables were used, long descriptions of the studies could be moved to an appendix or deleted. Fourth, all critical studies need to be thoroughly evaluated for strengths and weaknesses by using uniform approaches; the findings of these evaluations could be summarized in tables to ensure transparency. Fifth, the rationales for selection of studies that are used to calculate RfCs and unit risks need to be articulated clearly. Sixth, the weight-of-evidence descriptions need to indicate the various determinants of "weight." The reader needs to be able to understand what elements (such as consistency) were emphasized in synthesizing the evidence.

The committee is concerned about the persistence of problems encountered with IRIS assessments over the years, especially given the multiple groups that have highlighted them, and encourages EPA to address the problems with development of the draft assessments that have been identified. The committee recognizes that revision of the approach will involve an extensive effort by EPA staff and others, and it is not recommending that EPA delay the revision of the

formaldehyde assessment to implement a new approach. However, models for conducting IRIS assessments more effectively and efficiently are available, and the committee provides several examples in the present report. Thus, EPA might be able to make changes in its process relatively quickly by selecting and adapting existing approaches. As exemplified by the recent revision of the approach used for the National Ambient Air Quality Standards, this task is not insurmountable. If the methodologic issues are not addressed, future assessments may still have the same general and avoidable problems that are highlighted here.

7

A Roadmap for Revision

In reviewing the draft assessment *Toxicological Review of Formaldehyde-Inhalation Assessment: In Support of Summary Information on the Integrated Risk Information System (IRIS)*, the committee initially evaluated the general methodology (Chapter 2) and then considered the dosimetry and toxicology of formaldehyde (Chapter 3) and the review of the evidence and selection of studies related to noncancer and cancer outcomes (Chapters 4 and 5). Finally, the committee addressed the calculation of the reference concentrations (RfCs) for noncancer effects and the unit risks for cancer and the treatment of uncertainty and variability (Chapter 6). In this chapter, the committee provides general recommendations for changes that are needed to bring the draft to closure. On the basis of "lessons learned" from the formaldehyde assessment, the committee offers some suggestions for improvements in the IRIS development process that might help the Environmental Protection Agency (EPA) if it decides to modify the process. As noted in Chapter 2, the committee distinguishes between the process used to generate the draft IRIS assessment (that is, the development process) and the overall process that includes the multiple layers of review. The committee is focused on the development of the draft IRIS assessment.

CRITICAL REVISIONS OF THE CURRENT DRAFT IRIS ASSESSMENT OF FORMALDEHYDE

The formaldehyde draft IRIS assessment has been under development for more than a decade (see Chapter 1, Figure 1-3), and its completion is awaited by diverse stakeholders. Here, the committee offers general recommendations—in addition to its specific recommendations in Chapters 3-6—for the revisions that are most critical for bringing the document to closure. Although the committee suggests addressing some of the fundamental aspects of the approach to generating the draft assessment later in this chapter, it is not recommending that the assessment for formaldehyde await the possible development of a revised ap-

proach. The following recommendations are viewed as critical overall changes needed to complete the draft IRIS assessment:

- To enhance the clarity of the document, the draft IRIS assessment needs rigorous editing to reduce the volume of text substantially and address redundancy and inconsistency. Long descriptions of particular studies, for example, should be replaced with informative evidence tables. When study details are appropriate, they could be provided in appendixes.
- Chapter 1 needs to be expanded to describe more fully the methods of the assessment, including a description of search strategies used to identify studies with the exclusion and inclusion criteria clearly articulated and a better description of the outcomes of the searches (a model for displaying the results of literature searches is provided later in this chapter) and clear descriptions of the weight-of-evidence approaches used for the various noncancer outcomes. The committee emphasizes that it is not recommending the addition of long descriptions of EPA guidelines to the introduction, but rather clear concise statements of criteria used to exclude, include, and advance studies for derivation of the RfCs and unit risk estimates.
- Standardized evidence tables for all health outcomes need to be developed. If there were appropriate tables, long text descriptions of studies could be moved to an appendix or deleted.
- All critical studies need to be thoroughly evaluated with standardized approaches that are clearly formulated and based on the type of research, for example, observational epidemiologic or animal bioassays. The findings of the reviews might be presented in tables to ensure transparency. The present chapter provides general guidance on approaches to reviewing the critical types of evidence.
- The rationales for the selection of the studies that are advanced for consideration in calculating the RfCs and unit risks need to be expanded. All candidate RfCs should be evaluated together with the aid of graphic displays that incorporate selected information on attributes relevant to the database.
- Strengthened, more integrative, and more transparent discussions of weight of evidence are needed. The discussions would benefit from more rigorous and systematic coverage of the various determinants of weight of evidence, such as consistency.

FUTURE ASSESSMENTS AND THE IRIS PROCESS

This committee's review of the draft IRIS assessment of formaldehyde identified both specific and general limitations of the document that need to be addressed through revision. The persistence of limitations of the IRIS assessment methods and reports is of concern, particularly in light of the continued evolution of risk-assessment methods and the growing societal and legislative pressure to evaluate many more chemicals in an expedient manner. Multiple

groups have recently voiced suggestions for improving the process. The seminal "Red Book," the National Research Council (NRC) report *Risk Assessment in the Federal Government: Managing the Process*, was published in 1983 (NRC 1983). That report provided the still-used four-element framework for risk assessment: hazard identification, dose-response assessment, exposure assessment, and risk characterization. Most recently, in the "Silver Book," *Science and Decisions: Advancing Risk Assessment*, an NRC committee extended the framework of the Red Book in an effort to make risk assessments more useful for decision-making (NRC 2009). Those and other reports have consistently highlighted the necessity for comprehensive assessment of evidence and characterization of uncertainty and variability, and the Silver Book emphasizes assessment of uncertainty and variability appropriate to the decision to be made.

Science and Decisions: Advancing Risk Assessment made several recommendations directly relevant to developing IRIS assessments, including the draft formaldehyde assessment. First, it called for the development of guidance related to the handling of uncertainty and variability, that is, clear definitions and methods. Second, it urged a unified dose-response assessment framework for chemicals that would link understanding of disease processes, modes of action, and human heterogeneity among cancer and noncancer outcomes. Thus, it suggested an expansion of cancer dose-response assessments to reflect variability and uncertainty more fully and for noncancer dose-response assessments to reflect analysis of the probability of adverse responses at particular exposures. Although that is an ambitious undertaking, steps toward a unifying framework would benefit future IRIS assessments. Third, the Silver Book recommended that EPA assess its capacity for risk assessment and take steps to ensure that it is able to carry out its challenging risk-assessment agenda. For some IRIS assessments, EPA appears to have difficulty in assembling the needed multidisciplinary teams.

The committee recognizes that EPA has initiated a plan to revise the overall IRIS process and issued a memorandum that provided a brief description of the steps (EPA 2009a). Figure 7-1 illustrates the steps outlined in that memorandum. The committee is concerned that little information is provided on what it sees as the most critical step, that is, completion of a draft IRIS assessment. In the flow diagram, six steps are devoted to the review process, and thus the focus of the revision appears to be on the steps after the assessment has been generated. Although EPA may be revising its approaches for completing the draft assessment (Step 1 in Figure 7-1), the committee could not locate any other information on the revision of the IRIS process. Therefore, the committee offers some suggestions on the development process.

In providing guidance on revisions of the IRIS development process (that is, Step 1 as illustrated in Figure 7-1), the committee begins with a discussion of the current state of science regarding reviews of evidence and cites several examples that provide potential models for IRIS assessments. The

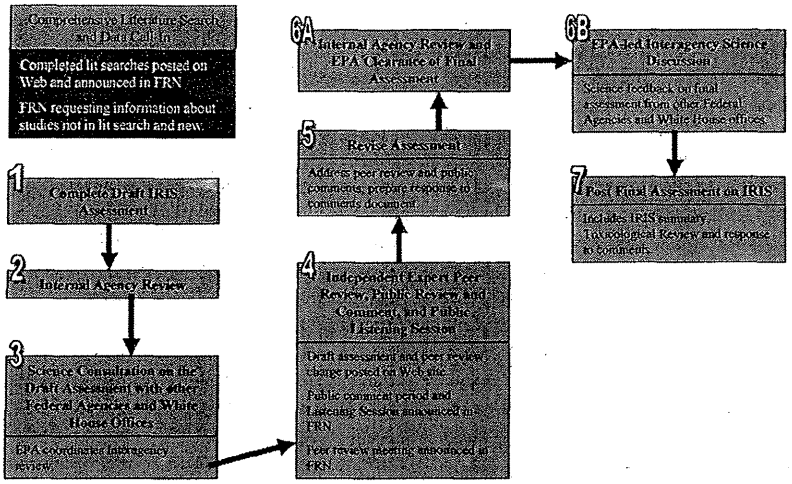

FIGURE 7-1 New IRIS assessment process. Abbreviations: FRN, Federal Register Notice; IRIS, Integrated Risk Information System; and EPA, Environmental Protection Agency. Source: EPA 2009a.

committee also describes the approach now followed in reviewing and synthesizing evidence related to the National Ambient Air Quality Standards (NAAQSs), a process that has been modified over the last 2 years. It is provided as an informative example of how the agency was able to revise an entrenched process in a relatively short time, not as an example of a specific process that should be adopted for the IRIS process. Finally, the committee offers some suggestions for improving the IRIS development process, providing a "roadmap" of the specific items for consideration.

An Overview of the Development of the Draft IRIS Assessment

In Chapter 2, the committee provided its own diagram (Figure 2-1) describing the steps used to generate the draft IRIS assessment. For the purpose of offering committee comments on ways to improve those steps, that figure has been expanded to indicate the key outcomes at each step (Figure 7-2). For each of the steps, the figure identifies the key questions addressed in the process. At the broadest level, the steps include systematic review of evidence, hazard identification using a weight-of-evidence approach, and dose-response assessment.

The systematic review process is undertaken to identify all relevant literature on the agent of interest, to evaluate the identified studies, and possibly to

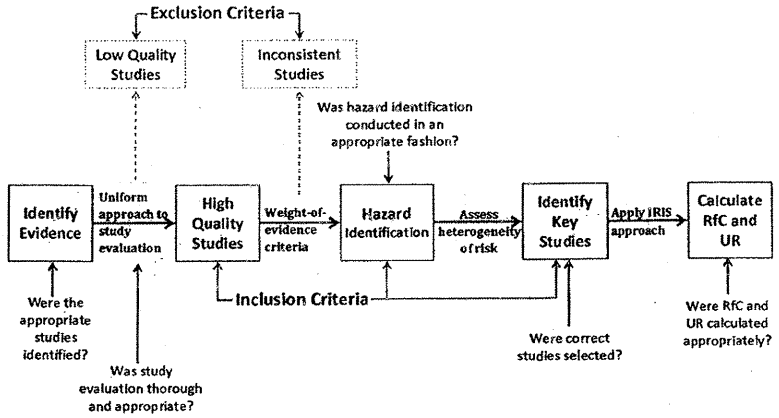

FIGURE 7-2 Elements of the key steps in the development of a draft IRIS assessment. Abbreviations: IRIS, Integrated Risk Information System; RfC, reference concentration; and UR, unit risk.

provide a qualitative or quantitative synthesis of the literature. Chapter 1 of the draft IRIS assessment of formaldehyde provides a brief general description of the process followed by EPA, including the approach to searching the literature. However, neither Chapter 1 nor other chapters of the draft provide a sufficiently detailed description of the approach taken in evaluating individual studies. In discussing particular epidemiologic studies, a systematic approach to study evaluation is not provided. Consequently, some of the key methodologic points are inconsistently mentioned, such as information bias and confounding.

For hazard identification, the general guidance is also found in Chapter 1 of the draft IRIS assessment. The approach to conducting hazard identification is critical for the integrity of the IRIS process. The various guidelines cited in Chapter 1 provide a general indication of the approach to be taken to hazard identification but do not offer a clear template for carrying it out. For the formaldehyde assessment, hazard identification is particularly challenging because the outcomes include cancer and multiple noncancer outcomes. The various EPA guidelines themselves have not been harmonized, and they provide only general guidance. Ultimately, the quality of the studies reviewed and the strength of evidence provided by the studies for deriving RfCs and unit risks need to be clearly presented. More formulaic approaches are followed for calculation of RfCs and unit risks. The key issue is whether the calculations were conducted appropriately and according to accepted assessment procedures.

Brief Review of Established Best Practices

The following sections highlight some best practices of current approaches to evidence-based reviews, hazard identification, and dose-response assessment that could provide EPA guidance if it decides to address some of the fundamental issues identified by the committee. The discussion is meant not to be comprehensive or to provide all perspectives on the topics but simply to highlight some important aspects of the approaches. The committee recognizes that some of the concepts and approaches discussed below are elementary and are addressed in some of EPA's guidelines. However, the current state of the formaldehyde draft IRIS assessment suggests that there might be a problem with the practical implementation of the guidelines in completing the IRIS assessments. Therefore, the committee highlights aspects that it finds most critical.

Current Approaches to Evidence-Based Reviews

Public-health decision-making has a long history of using comprehensive reviews as the foundation for evaluating evidence and selecting policy options. The landmark 1964 report of the U.S. surgeon general on tobacco and disease is exemplary (DHEW 1964). It used a transparent method that involved a critical survey of all relevant literature by a neutral panel of experts and an explicit framework for assessing the strength of evidence for causation that was equivalent to hazard identification (Table 7-1).

The tradition of comprehensive, evidence-based reviews has been continued in the surgeon general's reports. The 2004 surgeon general's report, which marked the 40th anniversary of the first report, highlighted the approach for causal inference used in previous reports and provided an updated and standardized four-level system for describing strength of evidence (DHHS 2004) (Table 7-2).

The same systematic approaches have become fundamental in many fields of clinical medicine and public health. The paradigm of "evidence-based medicine" involves the systematic review of evidence as the basis of guidelines. The international Cochrane Collaboration engages thousands of researchers and clinicians throughout the world to carry out reviews. In the United States, the Agency for Healthcare Research and Quality supports 14 evidence-based practice centers to conduct reviews related to healthcare.

There are also numerous reports from NRC committees and the Institute of Medicine (IOM) that exemplify the use of systematic reviews in evaluating evidence. Examples include reviews of the possible adverse responses associated with Agent Orange, vaccines, asbestos, arsenic in drinking water, and secondhand smoke. A 2008 IOM report, *Improving the Presumptive Disability Decision-Making Process for Veterans*, proposed a comprehensive new scheme for

TABLE 7-1 Criteria for Determining Causality

Criterion	Definition
Consistency	Persistent association among different studies in different populations
Strength of association	Magnitude of the association
Specificity	Linkage of specific exposure to specific outcome
Temporality	Exposure comes before effect
Coherence, plausibility, analogy	Coherence of the various lines of evidence with a causal relationship
Biologic gradient	Presence of increasing effect with increasing exposure (dose-response relationship)
Experiment	Observations from "natural experiments," such as cessation of exposure (for example, quitting smoking)

Source: DHHS 2004.

TABLE 7-2 Hierarchy for Classifying Strength of Causal Inferences on the Basis of Available Evidence

A. Evidence is *sufficient* to infer a causal relationship.

B. Evidence is *suggestive but not sufficient* to infer a causal relationship.

C. Evidence is *inadequate* to infer the presence or absence of a causal relationship (evidence that is sparse, of poor quality, or conflicting).

D. Evidence is *suggestive of no causal relationship.*

Source: DHHS 2004.

evaluating evidence that an exposure sustained in military service had contributed to disease (IOM 2008); the report offers relevant coverage of the practice of causal inference.

This brief and necessarily selective coverage of evidence reviews and evaluations shows that models are available that have proved successful in practice. They have several common elements: transparent and explicitly documented methods, consistent and critical evaluation of all relevant literature, application of a standardized approach for grading the strength of evidence, and clear and consistent summative language. Finally, highlighting features and limitations of the studies for use in quantitative assessments seems especially important for IRIS literature reviews.

A state-of-the-art literature review is essential for ensuring that the process of gathering evidence is comprehensive, transparent, and balanced. The committee suggests that EPA develop a detailed search strategy with search terms related to the specific questions that are addressed by the literature review. The yield of articles from searches can best be displayed graphically, documenting how initial search findings are narrowed to the articles in the final review selection on the basis of inclusion and exclusion criteria. Figure 7-3 provides an example of the selection process in a systematic review of a drug for lung disease. The progression from the initial 3,153 identified articles to the 11 reviewed is transparent. Although this example comes from an epidemiologic meta-analysis, a similar transparent process in which search terms, databases, and resources are listed and study selection is carefully tracked may be useful at all stages of the development of the IRIS assessment.

After studies are identified for review, the next step is to summarize the details and findings in evidence tables. Typically, such tables provide a link to the references, details of the study populations and methods, and key findings. They are prepared in a rigorous fashion with quality-assurance measures, such as using multiple abstractors (at least for a sample) and checking all numbers abstracted. If prepared correctly, the tables eliminate the need for long descriptions of studies and result in shorter text. Some draft IRIS assessments have begun to use a tabular format for systematic and concise presentation of evidence, and the committee encourages EPA to refine and expand that format as it revises the formaldehyde draft IRIS assessment and begins work on others.

The methods and findings of the studies are then evaluated with a standardized approach. Templates are useful for this purpose to ensure uniformity of approach, particularly if multiple reviewers are involved. Such standardized approaches are applied whether the research is epidemiologic (observational), experimental (randomized clinical trials), or toxicologic (animal bioassays). For example, for an observational epidemiologic study, a template for evaluation should consider the following:

- Approach used to identify the study population and the potential for selection bias.
- Study population characteristics and the generalizability of findings to other populations.
- Approach used for exposure assessment and the potential for information bias, whether differential (nonrandom) or nondifferential (random).
- Approach used for outcome identification and any potential bias.
- Appropriateness of analytic methods used.
- Potential for confounding to have influenced the findings.
- Precision of estimates of effect.
- Availability of an exposure metric that is used to model the severity of adverse response associated with a gradient of exposures.

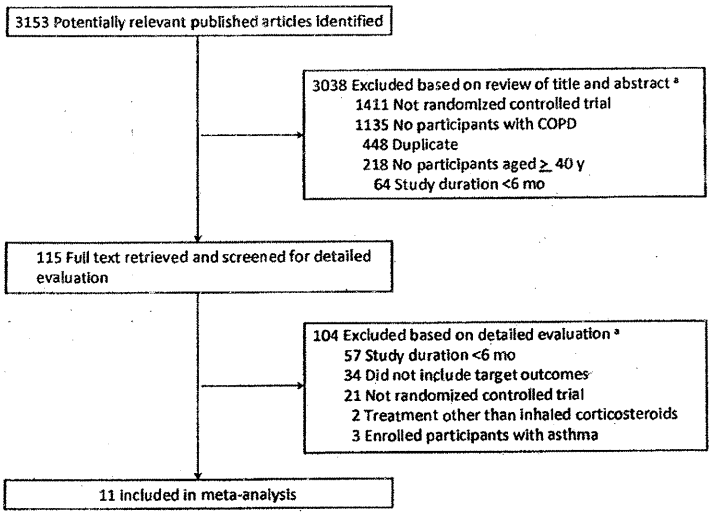

FIGURE 7-3 Example of an article-selection process. [a]Articles could be excluded for more than one reason; therefore, summed exclusions exceed total. Abbreviation: COPD, chronic obstructive pulmonary disease. Source: Drummond et al. 2008. Reprinted with permission; copyright 2008, American Medical Association.

Similarly, a template for evaluation of a toxicology study in laboratory animals should consider the species and sex of animals studied, dosing information (dose spacing, dose duration, and route of exposure), end points considered, and the relevance of the end points to human end points of concern.

Current Approaches to Hazard Identification

Hazard identification involves answering the question, Does the agent cause the adverse effect? (NRC 1983, 2009). Numerous approaches have been used for this purpose, and there is an extensive literature on causal inference, both on its philosophic underpinnings and on methods for evaluating the strength of evidence of causation. All approaches have in common a systematic identification of relevant evidence, criteria for evaluating the strength of evidence, and language for describing the strength of evidence of causation. The topic of causal inference and its role in decision-making was recently covered in the 2008 IOM report on evaluation of the presumptive decision-making process noted above. The 2004 report of the U.S. surgeon general on smoking and health (DHHS 2004) provided an updated review of the methods used in that series of reports.

The review approach for hazard identification embodies the elements described above and uses the criteria for evidence evaluation that have their origins in the 1964 report of the U.S. surgeon general (DHEW 1964) and the writings of Austin Bradford Hill, commonly known as the Hill criteria (see Table 7-1; Hill 1965). The criteria are not rigid and are not applied in a check-list manner; in fact, none is required for inferring a causal relationship, except for temporality inasmuch as exposure to the causal agent must precede the associated effect. The conclusion of causal inference is a clear statement on the strength of evidence of causation. For the purpose of hazard identification, such statements should follow a standardized classification to avoid ambiguity and to ensure comparability among different agents and outcomes.

Beyond the surgeon general's reports used here as an example, there are numerous examples of systematic approaches to hazard identification, including the monographs on carcinogenicity of the International Agency for Research on Cancer and the National Toxicology Program.[1] They have the same elements of systematic gathering and review of all lines of evidence and classification of the strength of evidence in a uniform and hierarchic structure.

Current Approaches to Dose-Response Assessment

The topic of dose-response assessment was covered in *Science and Decisions* (NRC 2009), which reviewed the current paradigm and called for a unified framework, bringing commonality to approaches for cancer and noncancer end points. That report also provides guidance on enhancing methods used to characterize uncertainty and variability. The present committee supports those recommendations but offers additional suggestions on the complementary coverage of the use of meta-analysis and pooled analysis in dose-response assessment.

IRIS assessments should address the following critical questions: Which studies should be included for derivation of reference values for noncancer outcomes and unit risks for cancer outcomes? Which dose-response models should be used for deriving those values? The latter question is related to model uncertainty in quantitative risk assessment and is not addressed here in this report. The former question is related to a fundamental issue of filtering the literature to identify the studies that provide the best dose-response information. A related question arises about how to combine information among studies because multiple studies may provide sufficient dose-response data. For this section, the committee assumes that the previously described evidence-based review has identified studies with adequate dose-response information to support some quantification of risk associated with exposure.

As suggested above, it would be unusual for a single study to trump all other studies providing information for setting reference values and unit risks. The combination of the analysis outcomes of different studies falls under the

[1]See http://monographs.iarc.fr/index.php and http://ntp.niehs.nih.gov/.

general description of meta-analysis (Normand 1999). The combination and synthesis of results of different studies appears central to an IRIS assessment, but such analyses require careful framing.

Stroup and colleagues (2000) provide a summary of recommendations for reporting meta-analyses of epidemiologic studies. Their proposal includes a table with a proposed check list that has broad categories for reporting, including background (such as problem definition and study population), search strategy (such as searchers, databases, and registries used), methods, results (such as graphic and tabular summaries, study description, and statistical uncertainty), discussion (such as bias and quality of included studies), and conclusion (such as generalization of conclusions and alternative explanations). Their recommendations on methods warrant specific consideration with reference to the development of an IRIS assessment, particularly those on evaluation and assessment of study relevance, rationale for selection and coding of studies, confounding, study quality, heterogeneity, and statistical methods. For the latter, key issues include the selection of models, the clarity with which findings are presented, and the availability of sufficient details to facilitate replication.

In combining study information, it is important that studies provide information on the same quantitative outcome, are conducted under similar conditions, and are of similar quality. If studies are of different quality, this might be addressed by weighting.

The simplest form of combining study information involves the aggregation of p values among a set of independent studies of the same null hypothesis. That simple approach might have appeal for establishing the relationship between some risk factor and an adverse outcome, but it is not useful for establishing exposure levels for a hazard. Thus, effect-size estimation among studies is usually of more interest for risk-estimation purposes and causality assessment. In this situation, a given effect is estimated for each study, and a combined estimate is obtained as a weighted average of study-specific effects in which the weights are inversely related to the precision associated with the estimation of each study-specific effect.

The question is whether EPA should routinely conduct meta-analysis for its IRIS assessments. Implicitly, the development of an IRIS assessment involves many of the steps associated with meta-analysis, including the collection and assessment of background literature. Assuming the availability of independent studies of the same end point and a comprehensive and unbiased inclusion of studies, questions addressed by a meta-analysis may be of great interest. Is there evidence of a homogeneous effect among studies? If not, can one understand the source of heterogeneity? If it is determined that a combined estimate is of interest (for example, an estimate of lifetime cancer risk based on combining study-specific estimates of this risk), a weighted estimate might be derived and reported.

Case Study: Revision of the Approach to Evidence Review and Risk Assessment for National Ambient Air Quality Standards

Approaches to evidence review and risk assessment vary within EPA. The recently revised approach used for NAAQSs offers an example that is particularly relevant because it represents a major change in an approach taken by one group in the National Center for Environmental Assessment. (EPA 2009b, 2010a,b)

Under Section 109 of the Clean Air Act, EPA is required to consider revisions of the NAAQSs for specified criteria air pollutants—currently particulate matter (PM), ozone, nitrogen dioxide, sulfur dioxide, carbon monoxide, and lead—every 5 years. Through 2009, the process for revision involved the development of two related documents that were both reviewed by the Clean Air Scientific Advisory Committee (CASAC) and made available for public comment. The first, the criteria document, was an encyclopedic compilation, sometimes several thousand pages long, of most scientific publications on the criteria pollutant that had been published since the previous review. Multiple authors contributed to the document, and there was generally little synthesis of the evidence, which was not accomplished in a systematic manner.

The other document was referred to as the staff paper. It was written by a different team in the Office of Air Quality Policy and Standards, and it identified the key scientific advances in the criteria document that were relevant to revising the NAAQSs. In the context of those advances, it offered the array of policy options around retaining or revising the NAAQSs that could be justified by recent research evidence. The linkages between the criteria document and the staff paper were general and not transparent.

The identified limitations of the process led to a proposal for its revision, and it took 2 years to complete the changes in the process. The new process replaces the criteria document with an integrated science assessment and a staff paper that includes a policy assessment. For the one pollutant, PM, that has nearly completed the full sequence, a risk and exposure analysis was also included.

The new documents address limitations of those used previously. The integrated science assessment is an evidence-based review that targets new studies as before. However, review methods are explicitly stated, and studies are reviewed in an informative and purposeful manner rather than in encyclopedic fashion. A main purpose of the integrated science assessment is to assess whether adverse health effects are causally linked to the pollutant under review. The integrated science assessment offers a five-category grading of strength of evidence on each outcome and follows the general weight-of-evidence approaches long used in public health. The intent is to base the risk and exposure analysis on effects for which causality is inferred or those at lower levels if they have particular public-health significance. The risk and exposure analysis brings

together the quantitative information on risk and exposure and provides estimates of the current burden of attributable morbidity and mortality and the estimates of avoidable and residual morbidity and mortality under various scenarios of changes in the NAAQS. Standard descriptors for uncertainty are now in place.

The policy assessment develops policy options on the basis of the findings of the integrated science assessment and the risk and exposure analysis. The policy assessment for the PM NAAQS is framed around a series of policy-relevant questions, such as, Does the available scientific evidence, as reflected in the integrated science assessment, support or call into question the adequacy of the protection afforded by the current 24-hr PM_{10} standard against effects associated with exposures to thoracic coarse particles? Evidence-based answers to the questions are provided with a reasonably standardized terminology for uncertainty.

For the most recent reassessment of the PM NAAQS, EPA staff and CASAC found the process to be effective; it led to greater transparency in evidence review and development of policy options than the prior process (Samet 2010). As noted above, the present committee sees the revision of the NAAQS review process as a useful example of how the agency was able to revise an entrenched process in a relatively short time.

Reframing the Development of the IRIS Assessment

The committee was given the broad charge of reviewing the formaldehyde draft IRIS assessment and also asked to consider some specific questions. In addressing those questions, the committee found, as documented in Chapter 2, that some problems with the draft arose because of the processes and methods used to develop the assessment. Other committees have noted some of the same problems. Accordingly, the committee suggests here steps that EPA could take to improve IRIS assessment through the implementation of methods that would better reflect current practices. The committee offers a roadmap for changes in the development process if EPA concludes that such changes are needed. The term *roadmap* is used because the topics that need to be addressed are set out, but detailed guidance is not provided because that is seen as beyond the committee's charge. The committee's discussion of a reframing of the IRIS development process is based on its generic representation provided in Figure 7-2. The committee recognizes that the changes suggested would involve a multiyear process and extensive effort by the staff of the National Center for Environmental Assessment and input and review by the EPA Science Advisory Board and others. The recent revision of the NAAQS review process provides an example of an overhauling of an EPA evidence-review and risk-assessment process that took about 2 years.

In the judgment of the present and past committees, consideration needs to be given to how each step of the process could be improved and gains made in transparency and efficiency. Models for conducting IRIS reviews more effectively and efficiently are available. For each of the various components (Figure 7-2), methods have been developed, and there are exemplary approaches in assessments carried out elsewhere in EPA and by other organizations. In addition, there are relevant examples of evidence-based algorithms that EPA could draw on. Guidelines and protocols for the conduct of evidence-based reviews are available, as are guidelines for inference as to the strength of evidence of association and causation. Thus, EPA may be able to make changes in the assessment process relatively quickly by drawing on appropriate experts and selecting and adapting existing approaches.

One major, overarching issue is the use of weight of evidence in hazard identification. The committee recognizes that the terminology is embedded in various EPA guidelines (see Appendix B) and has proved useful. The determination of weight of evidence relies heavily on expert judgment. As called for by others, EPA might direct effort at better understanding how weight-of-evidence determinations are made with a goal of improving the process (White et al. 2009).

The committee highlights below what it considers critical for the development of a scientifically sound IRIS assessment. Although many elements are basic and have been addressed in the numerous EPA guidelines, implementation does not appear to be systematic or uniform in the development of the IRIS assessments.

General Guidance for the Overall Process

- Elaborate an overall, documented, and quality-controlled process for IRIS assessments.
- Ensure standardization of review and evaluation approaches among contributors and teams of contributors; for example, include standard approaches for reviews of various types of studies to ensure uniformity.
- Assess disciplinary structure of teams needed to conduct the assessments.

Evidence Identification: Literature Collection and Collation Phase

- Select outcomes on the basis of available evidence and understanding of mode of action.
- Establish standard protocols for evidence identification.
- Develop a template for description of the search approach.
- Use a database, such as the Health and Environmental Research Online (HERO) database, to capture study information and relevant quantitative data.

Evidence Evaluation: Hazard Identification and Dose-Response Modeling

- Standardize the presentation of reviewed studies in tabular or graphic form to capture the key dimensions of study characteristics, weight of evidence, and utility as a basis for deriving reference values and unit risks.
- Develop templates for evidence tables, forest plots, or other displays.
- Establish protocols for review of major types of studies, such as epidemiologic and bioassay.

Weight-of-Evidence Evaluation: Synthesis of Evidence for Hazard Identification

- Review use of existing weight-of-evidence guidelines.
- Standardize approach to using weight-of-evidence guidelines.
- Conduct agency workshops on approaches to implementing weight-of-evidence guidelines.
- Develop uniform language to describe strength of evidence on noncancer effects.
- Expand and harmonize the approach for characterizing uncertainty and variability.
- To the extent possible, unify consideration of outcomes around common modes of action rather than considering multiple outcomes separately.

Selection of Studies for Derivation of Reference Values and Unit Risks

- Establish clear guidelines for study selection.
  - o Balance strengths and weaknesses.
  - o Weigh human vs experimental evidence.
  - o Determine whether combining estimates among studies is warranted.

Calculation of Reference Values and Unit Risks

- Describe and justify assumptions and models used. This step includes review of dosimetry models and the implications of the models for uncertainty factors; determination of appropriate points of departure (such as benchmark dose, no-observed-adverse-effect level, and lowest observed-adverse-effect level), and assessment of the analyses that underlie the points of departure.
- Provide explanation of the risk-estimation modeling processes (for example, a statistical or biologic model fit to the data) that are used to develop a unit risk estimate.

- Assess the sensitivity of derived estimates to model assumptions and end points selected. This step should include appropriate tabular and graphic displays to illustrate the range of the estimates and the effect of uncertainty factors on the estimates.
- Provide adequate documentation for conclusions and estimation of reference values and unit risks. As noted by the committee throughout the present report, sufficient support for conclusions in the formaldehyde draft IRIS assessment is often lacking. Given that the development of specific IRIS assessments and their conclusions are of interest to many stakeholders, it is important that they provide sufficient references and supporting documentation for their conclusions. Detailed appendixes, which might be made available only electronically, should be provided when appropriate.

REFERENCES

DHEW (U.S. Deaprtment of Health Education and Welfare). 1964. Smoking and Health. Report of the Advisory Committee to the Surgeon General. Public Health Service Publication No. 1103. Washington, DC: U.S. Government Printing Office [online]. Available: http://profiles.nlm.nih.gov/NN/B/B/M/Q/_/nnbbmq.pdf [accessed Feb. 1, 2011].

DHHS (U.S. Department of Health and Human Services). 2004. The Health Consequences of Smoking: A Report of the Surgeon General. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta, GA [online]. Available: http://www.cdc.gov/tobacco/data_statistics/sgr/2004/complete_report/index.htm [accessed Nov. 22, 2010].

Drummond, M.B., E.C. Dasenbrook, M.W. Pitz, D.J. Murphy, and E. Fan. 2008. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: A systematic review and meta-analysis. JAMA. 300(20):2407-2416.

EPA (U.S. Environmental Protection Agency). 2009a. New Process for Development of Integrated Risk Information System Health Assessments. Memorandum to Assistant Administrators, General Counsel, Inspector General, Chief Financial Officer, Chief of Staff, Associate Administrators, and Regional Administrators, from Lisa P. Jackson, the Administrator, U.S. Environmental Protection Agency, Washington, DC. May 21, 2009 [online]. Available: http://www.epa.gov/iris/pdfs/IRIS_PROCESS_MEMO.5.21.09.PDF [accessed Nov. 23, 2010].

EPA (U.S. Environmental Protection Agency). 2009b. Integrated Science Assessment for Particulate Matter (Final Report). EPA/600/R-08/139F. National Center for Environmental Assessment-RTP Division, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC. December 2009 [online]. Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546 [accessed March 2, 2011].

EPA (U.S. Environmental Protection Agency). 2010a. Quantitative Health Risk Assessment for Particulate Matter (Final Report). EPA-452/R-10-005. Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC. June 2010

Appendix B

Weight-of-Evidence Descriptions from U.S. Environmental Protection Agency Guidelines

The text in this appendix was excerpted directly from the indicated guidelines of the U.S. Environmental Protection Agency (EPA).

GUIDELINES FOR MUTAGENICITY RISK ASSESSMENT

The evidence for a chemical's ability to produce mutations and to interact with the germinal target is integrated into a weight-of-evidence judgment that the agent may pose a hazard as a potential human germ-cell mutagen. All information bearing on the subject, whether indicative of potential concern or not, must be evaluated. Whatever evidence may exist from humans must also be factored into the assessment.

All germ-cell stages are important in evaluating chemicals because some chemicals have been shown to be positive in postgonial stages but not in gonia (Russell et al., 1984). When human exposures occur, effects on postgonial stages should be weighted by the relative sensitivity and the duration of the stages. Chemicals may show positive effects for some endpoints and in some test systems, but negative responses in others. Each review must take into account the limitations in the testing and in the types of responses that may exist.

To provide guidance as to the categorization of the weight of evidence, a classification scheme is presented to illustrate, in a simplified sense, the strength of the information bearing on the potential for human germ-cell mutagenicity. It is not possible to illustrate all potential combinations of evidence, and considerable judgment must be exercised in reaching conclusions. In addition, certain responses in tests that do not measure direct mutagenic end points (e.g., SCE induction in mammalian germ cells) may provide a basis for raising the weight

of evidence from one category to another. The categories are presented in decreasing order of strength of evidence.

1. Positive data derived from human germ-cell mutagenicity studies, when available, will constitute the highest level of evidence for human mutagenicity.
2. Valid positive results from studies on heritable mutational events (of any kind) in mammalian germ cells.
3. Valid positive results from mammalian germ-cell chromosome aberration studies that do not include an intergeneration test.
4. Sufficient evidence for a chemical's interaction with mammalian germ cells, together with valid positive mutagenicity test results from two assay systems, at least one of which is mammalian (in vitro or in vivo). The positive results may both be for gene mutations or both for chromosome aberrations; if one is for gene mutations and the other for chromosome aberrations, both must be from mammalian systems.
5. Suggestive evidence for a chemical's interaction with mammalian germ cells, together with valid positive mutagenicity evidence from two assay systems as described under 4, above. Alternatively, positive mutagenicity evidence of less strength than defined under 4, above, when combined with sufficient evidence for a chemical's interaction with mammalian germ cells.
6. Positive mutagenicity test results of less strength than defined under 4, combined with suggestive evidence for a chemical's interaction with mammalian germ cells.
7. Although definitive proof of nonmutagenicity is not possible, a chemical could be classified operationally as a nonmutagen for human germ cells if it gives valid negative test results for all endpoints of concern.
8. Inadequate evidence bearing on either mutagenicity or chemical interaction with mammalian germ cells (EPA 1986, Pp 9-10).

METHODS FOR DERIVATION OF INHALATION REFERENCE CONCENTRATIONS AND APPLICATION OF INHALATION DOSIMETRY

The culmination of the hazard identification phase of any risk assessment involves integrating a diverse data collection into a cohesive, biologically plausible toxicity "picture"; that is, to develop the weight of evidence that the chemical poses a hazard to humans. The salient points from each of the laboratory animal and human studies in the entire data base should be summarized as should the analysis devoted to examining the variation or consistency among factors (usually related to the mechanism of action), in order to establish the likely outcome for exposure to this chemical. From this analysis, an appropriate animal model or additional factors pertinent to human extrapolation may be identified.

The utility of a given study is often related to the nature and quality of the other available data. For example, clinical pharmacokinetic studies may validate that the target organ or disease in laboratory animals is likely to be the same effect observed in the exposed human population. However, if a cohort study describing the nature of the dose-response relationship were available, the clinical description would rarely give additional information. An apparent conflict may arise in the analysis when an association is observed in toxicologic but not epidemiologic data, or vice versa. The analysis then should focus on reasons for the apparent difference in order to resolve the discrepancy. For example, the epidemiologic data may have contained other exposures not accounted for, or the laboratory animal species tested may have been inappropriate for the mechanism of action. A framework for approaching data summary is provided in Table 2-6. Table 2-7 provides the specific uses of various types of human data in such an approach. These guidelines have evolved from criteria used to establish causal significance, such as those developed by the American Thoracic Society (1985) to assess the causal significance of an air toxicant and a health effect. The criteria for establishing causal significance can be found in Appendix C. In general, the following factors enhance the weight of evidence on a chemical:

- Clear evidence of a dose-response relationship;
- Similar effects across sex, strain, species, exposure routes, or in multiple experiments;
- Biologically plausible relationship between metabolism data, the postulated mechanism of action, and the effect of concern;
- Similar toxicity exhibited by structurally related compounds;
- Some correlation between the observed chemical toxicity and human evidence.

The greater the weight of evidence, the greater the confidence in the conclusion derived. Developing improved weight-of-evidence schemes for various noncancer health effect categories has been the focus of efforts by the Agency to improve health risk assessment methodologies (Perlin and McCormack, 1988).

Another difficulty encountered in this summarizing process is that certain studies may produce apparently positive or negative results, yet may be flawed. The flaws may have arisen from inappropriate design or execution in performance (e.g., lack of statistical power or adjustment of dosage during the course of the study to avoid undesirable toxic effects). The treatment of flawed results is critical; although there is something to be learned from every study, the extent that a study should be used is dependent on the nature of the flaw (Society of Toxicology, 1982). A flawed negative study could only provide a false sense of security, whereas a flawed positive study may contribute to some limited understanding. Although there is no substitute for good science, grey areas such as this are ultimately a matter of scientific judgment. The risk assessor will have to decide what is and is not useful within the framework outlined earlier.

Studies meeting the criteria detailed in Sections 2.1.1 and 2.1.2 (epidemiologic, nonepidemiologic data), and experimental studies on laboratory animals that fit into this weight-of- evidence framework are used in the quantitative dose-response assessment discussed in Chapter 4 (EPA 1994, Pp 2-42 to 2-46).

GUIDELINES FOR DEVELOPMENTAL TOXICITY RISK ASSESSMENT

The 1989 Proposed Amendments described important considerations in determining the relative weight of various kinds of data in estimating the risk of developmental toxicity in humans. The intent of the proposed weight-of-evidence (WOE) scheme was that it not be used in isolation, but be used as the first step in the risk assessment process, to be integrated with dose-response information and the exposure assessment.

The WOE scheme was the subject of a considerable number of public comments, and was one of the major concerns of the SAB. The concern of public commentors was that the reference to human developmental toxicity in this scheme suggested that a chemical could be prematurely designated, and perhaps labeled, as causing developmental toxicity in humans prior to the completion of the risk assessment process. The SAB suggested that the intended use of this scheme was not consistent with the use of the term "weight of evidence" in other contexts, since WOE is usually thought of as an evaluation of the total composite of information available to make a judgment about risk. In addition, the SAB Committee proposed that the Agency consider development of a more conceptual approach using decision analytical techniques to predict the relationships among various outcomes.

In the final Guidelines, the terminology used in the WOE scheme has been completely changed and retitled "Characterization of the Health-Related Database." The intended purpose of the scheme is to provide a framework and criteria for making a decision on whether or not sufficient data are available to conduct a risk assessment. This decision is based on the available data, whether animal or human, and does not necessarily imply human hazard. This decision process is part of, but not the complete, WOE evaluation, which also takes into account the RfDDT or RfCDT and the human exposure information, culminating in risk characterization.

The final Guidelines also place strong emphasis on the integration of the dose-response evaluation with hazard information in characterizing the sufficiency of the health-related database. In line with this approach, the Guidelines have been reorganized to combine hazard identification and dose-response evaluation. Finally, the SAB comments on developing a conceptual matrix provide an interesting challenge, but current data indicate that the relationships among endpoints of developmental toxicity are not consistent across chemicals or species. The Agency is currently supporting modeling efforts to further explore the relationship among various development toxicity endpoints and the

development of biologically based dose-response models that consider multiple effects (EPA 1991, Pp 69-70).

A REVIEW OF THE REFERENCE DOSE AND REFERENCE CONCENTRATION PROCESSES

A weight-of-evidence approach such as that provided in EPA's RfC Methodology (U.S. EPA, 1994) or in EPA's proposed guidelines for carcinogen risk assessment (U.S. EPA, 1999a) should be used in assessing the database for an agent. This approach requires a critical evaluation of the entire body of available data for consistency and biological plausibility. Potentially relevant studies should be judged for quality and studies of high quality given much more weight than those of lower quality. When both epidemiological and experimental data are available, similarity of effects between humans and animals is given more weight. If the mechanism or mode of action is well characterized, this information is used in the interpretation of observed effects in either human or animal studies. Weight of evidence is not to be interpreted as simply tallying the number of positive and negative studies, nor does it imply an averaging of the doses or exposures identified in individual studies that may be suitable as points of departure (PODs) for risk assessment. The study or studies used for the POD are identified by an informed and expert evaluation of all the available evidence (EPA 2002b, Pp 4-11 to 4-12).

GUIDELINES FOR CARCINOGEN RISK ASSESSMENT

The cancer guidelines emphasize the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents. This is accomplished in a single integrative step after assessing all of the individual lines of evidence, which is in contrast to the step-wise approach in the 1986 cancer guidelines. Evidence considered includes tumor findings, or lack thereof, in humans and laboratory animals; an agent's chemical and physical properties; its structure-activity relationships (SARs) as compared with other carcinogenic agents; and studies addressing potential carcinogenic processes and mode(s) of action, either *in vivo* or *in vitro*. Data from epidemiologic studies are generally preferred for characterizing human cancer hazard and risk. However, all of the information discussed above could provide valuable insights into the possible mode(s) of action and likelihood of human cancer hazard and risk. The cancer guidelines recognize the growing sophistication of research methods, particularly in their ability to reveal the modes of action of carcinogenic agents at cellular and subcellular levels as well as toxicokinetic processes.

Weighing of the evidence includes addressing not only the likelihood of human carcinogenic effects of the agent but also the conditions under which such effects may be expressed, to the extent that these are revealed in the toxicological and other biologically important features of the agent.

The weight of evidence narrative to characterize hazard summarizes the results of the hazard assessment and provides a conclusion with regard to human carcinogenic potential. The narrative explains the kinds of evidence available and how they fit together in drawing conclusions, and it points out significant issues/strengths/limitations of the data and conclusions. Because the narrative also summarizes the mode of action information, it sets the stage for the discussion of the rationale underlying a recommended approach to dose-response assessment.

In order to provide some measure of clarity and consistency in an otherwise free-form, narrative characterization, standard descriptors are used as part of the hazard narrative to express the conclusion regarding the weight of evidence for carcinogenic hazard potential. There are five recommended standard hazard descriptors: "*Carcinogenic to Humans*," "*Likely to Be Carcinogenic to Humans*," "*Suggestive Evidence of Carcinogenic Potential*," "*Inadequate Information to Assess Carcinogenic Potential*," and "*Not Likely to Be Carcinogenic to Humans*." Each standard descriptor may be applicable to a wide variety of data sets and weights of evidence and is presented only in the context of a weight of evidence narrative. Furthermore, as described in Section 2.5 of these cancer guidelines, more than one conclusion may be reached for an agent (EPA 2005b, Pp 1-11 to 1-12).

The *weight of evidence narrative* is a short summary (one to two pages) that explains an agent's human carcinogenic potential and the conditions that characterize its expression. It should be sufficiently complete to be able to stand alone, highlighting the key issues and decisions that were the basis for the evaluation of the agent's potential hazard. It should be sufficiently clear and transparent to be useful to risk managers and non-expert readers. It may be useful to summarize all of the significant components and conclusions in the first paragraph of the narrative and to explain complex issues in more depth in the rest of the narrative.

The weight of the evidence should be presented as a narrative laying out the complexity of information that is essential to understanding the hazard and its dependence on the quality, quantity, and type(s) of data available, as well as the circumstances of exposure or the traits of an exposed population that may be required for expression of cancer. For example, the narrative can clearly state to what extent the determination was based on data from human exposure, from animal experiments, from some combination of the two, or from other data. Similarly, information on mode of action can specify to what extent the data are from *in vivo* or *in vitro* exposures or based on similarities to other chemicals. The extent to which an agent's mode of action occurs only on reaching a minimum dose or a minimum duration should also be presented. A hazard might also be expressed disproportionately in individuals possessing a specific gene; such characterizations may follow from a better understanding of the human genome. Furthermore, route of exposure should be used to qualify a hazard if, for example, an agent is not absorbed by some routes. Similarly, a hazard can be attribut-

able to exposures during a susceptible lifestage on the basis of our understanding of human development.

The weight of evidence-of-evidence narrative should highlight:

- the quality and quantity of the data;
- all key decisions and the basis for these major decisions; and
- any data, analyses, or assumptions that are unusual for or new to EPA.

To capture this complexity, a weight of evidence narrative generally includes

- conclusions about human carcinogenic potential (choice of descriptor(s), described below),
- a summary of the key evidence supporting these conclusions (for each descriptor used), including information on the type(s) of data (human and/or animal, *in vivo* and/or *in vitro*) used to support the conclusion(s),
- available information on the epidemiologic or experimental conditions that characterize expression of carcinogenicity (e.g., if carcinogenicity is possible only by one exposure route or only above a certain human exposure level),
- a summary of potential modes of action and how they reinforce the conclusions,
- indications of any susceptible populations or lifestages, when available, and
- a summary of the key default options invoked when the available information is inconclusive.

To provide some measure of clarity and consistency in an otherwise free-form narrative, the weight of evidence descriptors are included in the first sentence of the narrative. Choosing a descriptor is a matter of judgment and cannot be reduced to a formula. Each descriptor may be applicable to a wide variety of potential data sets and weights of evidence. These descriptors and narratives are intended to permit sufficient flexibility to accommodate new scientific understanding and new testing methods as they are developed and accepted by the scientific community and the public. Descriptors represent points along a continuum of evidence; consequently, there are gradations and borderline cases that are clarified by the full narrative. Descriptors, as well as an introductory paragraph, are a short summary of the complete narrative that preserves the complexity that is an essential part of the hazard characterization. Users of these cancer guidelines and of the risk assessments that result from the use of these cancer guidelines should consider the entire range of information included in the narrative rather than focusing simply on the descriptor.

In borderline cases, the narrative explains the case for choosing one descriptor and discusses the arguments for considering but not choosing another.

For example, between "suggestive" and "likely" or between "suggestive" and "inadequate," the explanation clearly communicates the information needed to consider appropriately the agent's carcinogenic potential in subsequent decisions.

Multiple descriptors can be used for a single agent, for example, when carcinogenesis is dose- or route-dependent. For example, if an agent causes point-of-contact tumors by one exposure route but adequate testing is negative by another route, then the agent could be described as likely to be carcinogenic by the first route but not likely to be carcinogenic by the second. Another example is when the mode of action is sufficiently understood to conclude that a key event in tumor development would not occur below a certain dose range. In this case, the agent could be described as likely to be carcinogenic above a certain dose range but not likely to be carcinogenic below that range.

Descriptors can be selected for an agent that has not been tested in a cancer bioassay if sufficient other information, e.g., toxicokinetic and mode of action information, is available to make a strong, convincing, and logical case through scientific inference. For example, if an agent is one of a well-defined class of agents that are understood to operate through a common mode of action and if that agent has the same mode of action, then in the narrative the untested agent would have the same descriptor as the class. Another example is when an untested agent's effects are understood to be caused by a human metabolite, in which case in the narrative the untested agent could have the same descriptor as the metabolite. As new testing methods are developed and used, assessments may increasingly be based on inferences from toxicokinetic and mode of action information in the absence of tumor studies in animals or humans.

When a well-studied agent produces tumors only at a point of initial contact, the descriptor generally applies only to the exposure route producing tumors unless the mode of action is relevant to other routes. The rationale for this conclusion would be explained in the narrative.

When tumors occur at a site other than the point of initial contact, the descriptor generally applies to all exposure routes that have not been adequately tested at sufficient doses. An exception occurs when there is convincing information, e.g., toxicokinetic data that absorption does not occur by another route.

When the response differs qualitatively as well as quantitatively with dose, this information should be part of the characterization of the hazard. In some cases reaching a certain dose range can be a precondition for effects to occur, as when cancer is secondary to another toxic effect that appears only above a certain dose. In other cases exposure duration can be a precondition for hazard if effects occur only after exposure is sustained for a certain duration. These considerations differ from the issues of relative absorption or potency at different dose levels because they may represent a discontinuity in a dose-response function.

When multiple bioassays are inconclusive, mode of action data are likely to hold the key to resolution of the more appropriate descriptor. When bioassays

are few, further bioassays to replicate a study's results or to investigate the potential for effects in another sex, strain, or species may be useful.

When there are few pertinent data, the descriptor makes a statement about the database, for example, "Inadequate Information to Assess Carcinogenic Potential," or a database that provides "Suggestive Evidence of Carcinogenic Potential." With more information, the descriptor expresses a conclusion about the agent's carcinogenic potential to humans. If the conclusion is positive, the agent could be described as "Likely to Be Carcinogenic to Humans" or, with strong evidence, "Carcinogenic to Humans." If the conclusion is negative, the agent could be described as "Not Likely to Be Carcinogenic to Humans."

Although the term "likely" can have a probabilistic connotation in other contexts, its use as a weight of evidence descriptor does not correspond to a quantifiable probability of whether the chemical is carcinogenic. This is because the data that support cancer assessments generally are not suitable for numerical calculations of the probability that an agent is a carcinogen. Other health agencies have expressed a comparable weight of evidence using terms such as "Reasonably Anticipated to Be a Human Carcinogen" (NTP) or "Probably Carcinogenic to Humans" (International Agency for Research on Cancer).

The following descriptors can be used as an introduction to the weight of evidence narrative. The examples presented in the discussion of the descriptors are illustrative. The examples are neither a checklist nor a limitation for the descriptor. The complete weight of evidence narrative, rather than the descriptor alone, provides the conclusions and the basis for them.

"Carcinogenic to Humans"

This descriptor indicates strong evidence of human carcinogenicity. It covers different combinations of evidence.

- This descriptor is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer.
- Exceptionally, this descriptor may be equally appropriate with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence. It can be used when all of the following conditions are met: (a) there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, and (b) there is extensive evidence of carcinogenicity in animals, and (c) the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, and (d) there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information. In this case, the narrative includes a summary of both the experimental and epidemiologic information on mode of action and also an indication of the

relative weight that each source of information carries, e.g., based on human information, based on limited human and extensive animal experiments.

"Likely to Be Carcinogenic to Humans"

This descriptor is appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "Carcinogenic to Humans." Adequate evidence consistent with this descriptor covers a broad spectrum. As stated previously, the use of the term "likely" as a weight of evidence descriptor does not correspond to a quantifiable probability. The examples below are meant to represent the broad range of data combinations that are covered by this descriptor; they are illustrative and provide neither a checklist nor a limitation for the data that might support use of this descriptor. Moreover, additional information, e.g., on mode of action, might change the choice of descriptor for the illustrated examples. Supporting data for this descriptor may include:

- an agent demonstrating a plausible (but not definitively causal) association between human exposure and cancer, in most cases with some supporting biological, experimental evidence, though not necessarily carcinogenicity data from animal experiments;
- an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans;
- a positive tumor study that raises additional biological concerns beyond that of a statistically significant result, for example, a high degree of malignancy, or an early age at onset;
- a rare animal tumor response in a single experiment that is assumed to be relevant to humans; or
- a positive tumor study that is strengthened by other lines of evidence, for example, either plausible (but not definitively causal) association between human exposure and cancer or evidence that the agent or an important metabolite causes events generally known to be associated with tumor formation (such as DNA reactivity or effects on cell growth control) likely to be related to the tumor response in this case.

"Suggestive Evidence of Carcinogenic Potential"

This descriptor of the database is appropriate when the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. This descriptor covers a spectrum of evidence associated with varying levels of concern for carcinogenicity, ranging from a positive cancer result in the only

study on an agent to a single positive cancer result in an extensive database that includes negative studies in other species. Depending on the extent of the database, additional studies may or may not provide further insights. Some examples include:

- a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor "Likely to Be Carcinogenic to Humans." The study generally would not be contradicted by other studies of equal quality in the same population group or experimental system (see discussions of *conflicting evidence* and *differing results*, below);
- a small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background tumors and not due to the agent being assessed. (When there is a high background rate of a specific tumor in animals of a particular sex and strain, then there may be biological factors operating independently of the agent being assessed that could be responsible for the development of the observed tumors.) In this case, the reasons for determining that the tumors are not due to the agent are explained;
- evidence of a positive response in a study whose power, design, or conduct limits the ability to draw a confident conclusion (but does not make the study fatally flawed), but where the carcinogenic potential is strengthened by other lines of evidence (such as structure-activity relationships); or
- a statistically significant increase at one dose only, but no significant response at the other doses and no overall trend.

"Inadequate Information to Assess Carcinogenic Potential"

This descriptor of the database is appropriate when available data are judged inadequate for applying one of the other descriptors. Additional studies generally would be expected to provide further insights. Some examples include:

- little or no pertinent information;
- conflicting evidence, that is, some studies provide evidence of carcinogenicity but other studies of equal quality in the same sex and strain are negative. *Differing results*, that is, positive results in some studies and negative results in one or more different experimental systems, do not constitute *conflicting evidence,* as the term is used here. Depending on the overall weight of evidence, differing results can be considered either suggestive evidence or likely evidence; or negative results that are not sufficiently robust for the descriptor, "Not Likely to Be Carcinogenic to Humans."

• negative results that are not sufficiently robust for the descriptor, "Not Likely to Be Carcinogenic to Humans."

"Not Likely to Be Carcinogenic to Humans"

This descriptor is appropriate when the available data are considered robust for deciding that there is no basis for human hazard concern. In some instances, there can be positive results in experimental animals when there is strong, consistent evidence that each mode of action in experimental animals does not operate in humans. In other cases, there can be convincing evidence in both humans and animals that the agent is not carcinogenic. The judgment may be based on data such as:

• animal evidence that demonstrates lack of carcinogenic effect in both sexes in well designed and well-conducted studies in at least two appropriate animal species (in the absence of other animal or human data suggesting a potential for cancer effects),

• convincing and extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans,

• convincing evidence that carcinogenic effects are not likely by a particular exposure route (see Section 2.3), or

• convincing evidence that carcinogenic effects are not likely below a defined dose range. A descriptor of "not likely" applies only to the circumstances supported by the data. For example, an agent may be "Not Likely to Be Carcinogenic" by one route but not necessarily by another. In those cases that have positive animal experiment(s) but the results are judged to be not relevant to humans, the narrative discusses why the results are not relevant.

Multiple Descriptors

More than one descriptor can be used when an agent's effects differ by dose or exposure route. For example, an agent may be "Carcinogenic to Humans" by one exposure route but "Not Likely to Be Carcinogenic" by a route by which it is not absorbed. Also, an agent could be "Likely to Be Carcinogenic" above a specified dose but "Not Likely to Be Carcinogenic" below that dose because a key event in tumor formation does not occur below that dose (EPA 2005b, Pp 2-49 to 2-58).

A FRAMEWORK FOR ASSESSING HEALTH RISKS OF ENVIRONMENTAL EXPOSURES TO CHILDREN

The WOE approach requires a critical evaluation (expert judgment) of all available data for consistency and biological plausibility. Criteria for this as-

sessment are not presented here; rather, considerations important for the WOE are described. The key to WOE conclusions is the provision of a clear justification for decisions. Finally, the extent of the database is summarized, and assumptions made in the assessment are explicitly detailed. Further details about EPA's WOE approach can be found in the *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b), and *Supplemental Guidance for Assessing Cancer Susceptibility from Early Life Exposure to Carcinogens* (U.S. EPA, 2005c). *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002b, Section 4.3.2.1.) and *Determination of the Appropriate FQPA Safety Factor(s) on Tolerance Assessment* (U.S. EPA, 2002c, Section III) provide additional detail on the WOE.

Key themes for the consideration of toxicity data in a WOE assessment, as adapted from Gray et al. (2001), are shown in Figure 4-5. This figure focuses on judging animal studies within a WOE assessment. However, if adequate human studies are available they would be given more weight. The process for evaluating these considerations is described in the following subsections. In this process, the quality of potentially relevant studies is judged, modifiers and interactions are detailed, outcomes across species are compared, TK and TD data are examined and weighed for comparisons across species, and the uncertainties and data gaps are determined. SARs with other chemicals or chemical classes are explored to determine the extent to which these data can inform the assessment via an MOA discussion or reduce uncertainties.

GUIDELINES FOR NEUROTOXICITY RISK ASSESSMENT

The interpretation of data as indicative of a potential neurotoxic effect involves the evaluation of the validity of the database. This approach and these terms have been adapted from the literature on human psychological testing (Sette, 1987; Sette and MacPhail, 1992), where they have long been used to evaluate the level of confidence in different measures of intelligence or other abilities, aptitudes, or feelings. There are four principal questions that should be addressed: whether the effects result from exposure (content validity); whether the effects are adverse or toxicologically significant (construct validity); whether there are correlative measures among behavioral, physiological, neurochemical, and morphological endpoints (concurrent validity); and whether the effects are predictive of what will happen under various conditions (predictive validity). Addressing these issues can provide a useful framework for evaluating either human or animal studies or the weight of evidence for a chemical (Sette, 1987; Sette and MacPhail, 1992). The next sections indicate the extent to which chemically induced changes can be interpreted as providing evidence of neurotoxicity.

The qualitative characterization of neurotoxic hazard can be based on either human or animal data (Anger, 1984; Reiter, 1987; U.S. EPA, 1994). Such data can result from accidental, inappropriate, or controlled experimental exposures. This section describes many of the general and some of the specific characteristics of human studies and reports of neurotoxicity. It then describes some features of animal studies of neuroanatomical, neurochemical, neurophysiological, and behavioral effects relevant to risk assessment. The process of characterizing the sufficiency or insufficiency of neurotoxic effects for risk assessment is described in section 3.3. Additional sources of information relevant to hazard characterization, such as comparisons of molecular structure among compounds and in vitro screening methods, are also discussed.

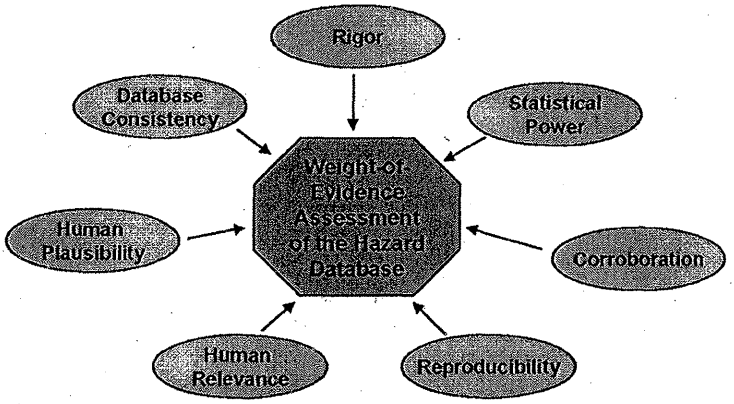

FIGURE 4-5 Conceptual view of a weight of evidence (WOE) assessment. This figure illustrates the critical considerations within a WOE assessment of toxicity data. *Rigor* is the degree of proper conduct and analysis of a study; greater weight is generally given to more rigorous studies. *Statistical Power* is the ability of a study to detect effects of a given magnitude. *Corroboration* means that specific effects are replicated in similar studies, similar effects are observed under varied conditions and /or similar effects are observed in multiple laboratories. *Reproducibility* means that an effect is observed in multiple species by various routes of exposure. *Relevance to Humans* means that similar effects are observed in humans or in a species taxonomically related to humans or at doses similar to those expected in humans. *Plausibility to Humans* is the determination of whether a similar metabolism, mechanisms of damage and repair, and molecular target of response could be expected to occur in humans, based on an evaluation of the biologic mechanism of a toxic response in animals. *Database Consistency* is the extent to which all of the data are similar in outcome and dose (exposure-response) and are operating under a single biologically plausible assumption (mode of action). Source: Adapted from Gray et al. 2001, EPA 2006, Pp 29-30.

The hazard characterization should:

a. Identify strengths and limitations of the database:
- Epidemiological studies (case reports, cross-sectional, case-control, cohort, or human laboratory exposure studies);
- Animal studies (including structural or neuropathological, neurochemical, neurophysiological, behavioral or neurological, or developmental endpoints).

b. Evaluate the validity of the database:
- Content validity (effects result from exposure);
- Construct validity (effects are adverse or toxicologically significant);
- Concurrent validity (correlative measures among behavioral, physiological, neurochemical, or morphological endpoints);
- Predictive validity (effects are predictive of what will happen under various conditions).

c. Identify and describe key toxicological studies.

d. Describe the type of effects:
- Structural (neuroanatomical alternations);
- Functional (neurochemical, neurophysiological, behavioral alterations).

e. Describe the nature of the effects (irreversible, reversible, transient, progressive, delayed, residual, or latent).

f. Describe how much is known about how (through what biological mechanism) the chemical produces adverse effects.

g. Discuss other health endpoints of concern.

h. Comment on any nonpositive data in humans or animals.

I. Discuss the dose-response data (epidemiological or animal) available for further dose-response analysis.

j. Discuss the route, level, timing, and duration of exposure in studies demonstrating neurotoxicity as compared to expected human exposures.

k. Summarize the hazard characterization:
- Confidence in conclusions;
- Alternative conclusions also supported by the data;
- Significant data gaps; and
- Highlights of major assumptions.

REFERENCES

American Thoracic Society. 1985. Guidelines as to what constitutes an adverse respiratory health effect, with special reference to epidemiologic studies of air pollution. Am. Rev. Respir. Dis. 131(4):666-668.

Anger, W.K. 1984. Neurobehavioral testing of chemicals: Impact on recommended standards. Neurobehav. Toxicol. Teratol. 6(2):147-153.

EPA (U.S. Environmental Protection Agency). 1986. Guidelines for Mutagenicity Risk Assessment. U.S. Environmental Protection Agency [online]. Available: http://www.epa.gov/osa/mmoaframework/pdfs/MUTAGEN2.PDF [accessed Nov. 19, 2010].

EPA (U.S. Environmental Protection Agency). 1991. Guidelines for Developmental Toxicity Risk Assessment. U.S. Environmental Protection Agency [online]. Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23162 [accessed Nov. 19, 2010].

EPA (U.S. Environmental Protection Agency). 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. U.S. Environmental Protection Agency [online]. Available: http://www.epa.gov/raf/publications/methods-derivation-inhalation-ref.htm [accessed Nov. 19, 2010].

EPA (U.S. Environmental Protection Agency). 1998. Guidelines for Neurotoxicity Risk Assessment. U.S. Environmental Protection Agency [online]. Available: http://www.epa.gov/raf/publications/pdfs/NEUROTOX.PDF [accessed Dec. 16, 2010].

EPA (U.S. Environmental Protection Agency). 1999a. Guidelines for Carcinogen Risk Assessment [Review Draft]. NCEA-F-0644. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC. July 1999 [online]. Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54932#Download [accessed Mar. 17, 2011].

EPA (U.S. Environmental Protection Agency). 2002b. A Review of the Reference Dose and Reference Concentration Process. U.S. Environmental Protection Agency [online]. Available: http://www.epa.gov/iris/RFD_FINAL1.pdf [accessed Nov. 19, 2010].

EPA (U.S. Environmental Protection Agency). 2002c. Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment. Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, DC. February 28, 2002 [online]. Available: http://www.epa.gov/oppfead1/trac/science/determ.pdf [accessed Mar. 17, 2011].

EPA (U.S. Environmental Protection Agency). 2005b. Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency [online]. Available: http://www.epa.gov/osa/mmoaframework/pdfs/CANCER-GUIDELINES-FINAL-3-25-05%5B1%5D.pdf [accessed Nov. 19, 2010].

EPA (U.S. Environmental Protection Agency). 2005c. Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens. EPA/630/R-03/003F. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC. March 2005 [online]. Available: http://www.epa.gov/ttn/atw/childrens_supplement_final.pdf [accessed Mar. 17, 2011].

EPA (U.S. Environmental Protection Agency). 2006. A Framework for Assessing Health Risks of Environmental Exposures to Children. U.S. Environmental Protection Agency [online]. Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=158363 [accessed Nov. 19, 2010].

Gray, G.M., S.I. Baskin, G. Charnley, J.T. Cohen, L.S. Gold, N.I. Kerkvliet, H.M. Koenig, S.C. Lewis, R.M. McClain, L.R. Rhomberg, J.W. Snyder, and L.B. Weekley. 2001. The Annapolis accords on the use of toxicology in risk assessment and decision-making: An Annapolis Center Workshop report. Toxicol. Mech. Methods 11(3):225-231.

APPENDIX C – 6

EXCERPTS

DRAFT—DO NOT CITE OR QUOTE

EPA/635/R-11/002A
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EPA

TOXICOLOGICAL REVIEW

OF

LIBBY AMPHIBOLE ASBESTOS

In Support of Summary Information on the Integrated Risk Information System (IRIS)

August 2011

(Note: This document is an assessment of the noncancer and cancer health effects associated with the inhalation route of exposure only)

NOTICE

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U.S. Environmental Protection Agency
Washington, DC

1. INTRODUCTION

This document presents background information and justification for the Integrated Risk Information System (IRIS) Summary of the hazard and exposure-response assessment of Libby Amphibole asbestos,[1] a mixture of amphibole fibers identified in the Rainy Creek complex and present in ore from the vermiculite mine near Libby, MT. IRIS Summaries may include oral reference dose (RfD) and inhalation reference concentration (RfC) values for chronic and other exposure durations, and a carcinogenicity assessment. This assessment reviews the potential hazards, both cancer and noncancer health effects, from exposure to Libby Amphibole asbestos and provides quantitative information for use in risk assessments: an RfC for noncancer and an inhalation unit risk addressing cancer risk. Libby Amphibole asbestos-specific data are not available to support RfD or cancer slope factor derivations for oral exposures.

An RfC is typically defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." In the case of Libby Amphibole asbestos, the RfC is expressed in terms of the lifetime exposure in units of fibers per cubic centimeter of air (fibers/cc) in units of the fibers as measured by phase contrast microscopy (PCM). The inhalation RfC for Libby Amphibole asbestos considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects) that may arise after inhalation of Libby Amphibole asbestos. In this assessment, the estimates of hazard are derived from modeling cumulative exposures from human data, and thus for exposures of less than a lifetime the risk assessor should calculate a lifetime average concentration to compare to the RfC.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question, and quantitative estimates of risk from inhalation exposures are derived. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are derived from the application of a low-

[1] The term "Libby Amphibole asbestos" is used in this document to identify the mixture of amphibole mineral fibers of varying elemental composition (e.g., winchite, richterite, tremolite, etc.) that have been identified in the Rainy Creek complex near Libby, MT. It is further described in Section 2.2.

dose extrapolation procedure from human data. An inhalation unit risk (IUR) is typically defined as a plausible upper bound on the estimate of cancer risk per $\mu g/m^3$ air breathed for 70 years. For Libby Amphibole asbestos, the RfC is expressed as a Lifetime Daily Exposure in fibers/cc (in units of the fibers as measured by PCM), and the IUR is expressed as cancer risk per fibers/cc (in units of the fibers as measured by PCM).

Development of these hazard identification and exposure-response assessments for Libby Amphibole asbestos has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). U.S. Environmental Protection Agency (EPA) Guidelines and Risk Assessment Forum technical panel reports that may have been used in the development of this assessment include the following: *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986c), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988b), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991a), *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998), *Science Policy Council Handbook: Risk Characterization* (U.S. EPA, 2000c), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000a), *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000d), *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 2006d), and *A Framework for Assessing Health Risks of Environmental Exposures to Children* (U.S. EPA, 2006b).

The literature search strategy employed for this assessment is based on EPA's National Center for Environmental Assessment's Health and Environmental Research Outline database tool (which includes PubMed, MEDLINE, Web of Science, JSTOR, and other literature sources). The key search terms included the following: Libby Amphibole, tremolite, asbestos, richterite, winchite, amphibole, and Libby, MT. The relevant literature was reviewed through

July 2011. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document.

1.1. RELATED ASSESSMENTS

1.1.1. IRIS Assessment for Asbestos (U.S. EPA, 1988a)

The IRIS assessment for asbestos was posted online in IRIS in 1988 and includes an IUR of 0.23 excess cancers per 1 fiber/cc (U.S. EPA, 1988a) (this unit risk is given in units of the fibers as measured by PCM). The IRIS IUR for general asbestos is derived by estimation of excess cancers for a continuous lifetime exposure and is based on the central tendency—not the upper bound—of the risk estimates (U.S. EPA, 1988a) and is applicable to exposures across a range of exposure environments and types of asbestos (CAS Number 1332-21-4). Although other cancers have been associated with asbestos (e.g., laryngeal, stomach, ovarian) (Straif et al., 2009), the IRIS IUR for asbestos accounts for only lung cancer and mesothelioma. Additionally, pleural and pulmonary effects from asbestos exposure (e.g., localized pleural thickening, asbestosis, and reduced lung function) are well documented, though, currently, there is no RfC for these noncancer health effects.

The derivation of the unit risk for general asbestos is based on the *Airborne Asbestos Health Assessment Update* (AAHAU) (U.S. EPA, 1986a). The AAHAU provides various cancer potency factors and mathematical models of lung cancer and mesothelioma mortality based on synthesis of data from occupational studies and presents estimates of lifetime cancer risk for continuous environmental exposures (0.0001 fiber/cc and 0.01 fiber/cc) (U.S. EPA, 1986a) (see Table 6-3). For both lung cancer and mesothelioma, life-table analysis was used to generate risk estimates based on the number of years of exposure and the age at onset of exposure. Although various exposure scenarios were presented, the unit risk is based on a lifetime continuous exposure from birth. The final asbestos IUR is 0.23 excess cancer per 1 fiber/cc continuous exposure[2] and was established by the EPA Carcinogen Risk Assessment Verification Endeavor workgroup and posted on the IRIS database in 1988 (U.S. EPA, 1988a) (see Table 1-1).

[2]An IUR of 0.23 can be interpreted as a 23% increase in lifetime risk of dying from mesothelioma or lung cancer with each 1 fiber/cc increase in continuous lifetime exposure.

Table 1-1. Derivation of the current IRIS inhalation unit risk for asbestos from the lifetime risk tables in the AAHAU

Gender	Excess deaths per 100,000[a]			Risk	Unit risk
	Mesothelioma	Lung cancer	Total		
Female	183	35	218.5	2.18×10	
Male	129	114	242.2	2.42×10	
All	156	74	230.3	2.30×10	0.23

[a]Data are for exposure at 0.01 fibers/cc for a lifetime.
AAHAU = Airborne Asbestos Health Assessment Update.
Source: U.S. EPA (1988a).

1.1.2. EPA Health Assessment for Vermiculite (1991b)

An EPA health assessment for vermiculite reviewed available health data, including studies on workers who mined and processed ore with no significant amphibole fiber content. The cancer and noncancer health effects observed in the Libby, MT worker cohort were not seen in studies of workers exposed to vermiculite from mines with similar exposure to vermiculite but much lower exposures to asbestos fibers. Therefore, it was concluded that the health effects observed from the materials mined from Zonolite Mountain near Libby, MT, were most likely due to amphibole fibers not the vermiculite itself (U.S. EPA, 1991b). At the time, EPA recommended the application of the IRIS IUR for asbestos fibers (0.23 per fiber/cc) in addressing potential risk of the amphibole fibers entrained in vermiculite mined in Libby, MT.

1.2. LIBBY AMPHIBOLE ASBESTOS-SPECIFIC HUMAN HEALTH ASSESSMENT

Libby Amphibole asbestos is a complex mixture of amphibole fibers—both mineralogically and morphologically (see Section 2.2). The mixture primarily includes tremolite, winchite, and richterite fibers with trace amounts of magnesioriebeckite, edenite, and magnesio-arfvedsonite. These fibers exhibit a complete range of morphologies from prismatic crystals to asbestiform fibers (Meeker et al., 2003). Epidemiologic studies of workers exposed to Libby Amphibole asbestos fibers indicate increased lung cancer and mesothelioma, as well as asbestosis, and other nonmalignant respiratory diseases (Larson et al., 2010b; Larson et al., 2010a; Moolgavkar et al., 2010; Rohs et al., 2008; Sullivan, 2007; McDonald et al., 2004, 2002;

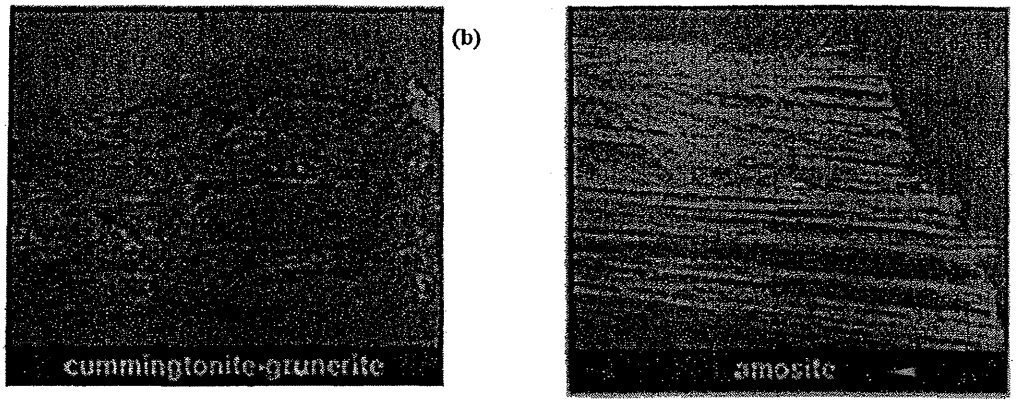


Figure 2-6. Comparison of crystalline forms amphibole minerals. Panel A shows a specimen identified as an amphibole mineral in the cummingtonite-grunerite solid solution series, although crystalline in form, the habit of formation did not favor formation of individual particles and fibers, hence its appearance as 'massive'. Panel B shows an amphibole mineral with very similar elemental composition but formed in a habit where very long fibers were allowed to form—hence the asbestiform appearance.

Source: Adapted from Bailey (2006).

may be elongated, but differ from the crystals described above as at least one face of the structure is the cleavage plane—not the face of a formed crystal.

With respect to classifying mineral field samples, geologists applied descriptive terms appropriate for viewing samples simply or at low magnification (e.g., field glass). The geologic terms for fiber morphology for classification of field samples is based on the macroscopic appearance of the crystals and fibers (e.g., acicular "needle-like in form") (AGI, 2005). In this framework, asbestos and asbestiform fibers are defined as long, slender, hair-like fibers visible to the naked eye (see Figure 2-6). This is a hallmark of commercially mined asbestos which is sought after for numerous applications because of its high tensile strength, heat resistance and in some cases, can be woven. Although these terms were used to describe fibers in hand samples and identify commercially valuable asbestos they are only applicable at the macroscopic level. It is important to realize that material defined as commercial asbestos, mined, milled, and manufactured into products not only contained these visible fibers, but many smaller fibers and single crystals which were not visible to the naked eye (Dement and Harris, 1979). As further

explained in Section 3, only these smaller fibers can enter the lung and transport to the pleura where the health effects of asbestos are best characterized. Therefore, for the purposes of this assessment (i.e., examining the health effects of asbestos fibers), consideration must be given to how these microscopic fibers are defined. For this purpose, terms intended for describing field samples may need to set aside, or redefined when applied at the microscopic level.

Currently there are several technologies commonly used to view and identify mineral structures at high magnification using light microscopes or electron microscopy. As standard analytical methods were developed for counting mineral fibers, structures and matrices using these instruments, analytical definitions to describe fibers and structures were developed. Phase contrast microscopy (PCM) was developed to detect fibers in occupational settings and has been widely used to assess worker exposure (see Text Box 2-1). The definition of a PCM-fiber is based purely on its dimensions. The standardization of the PCM method (i.e., NIOSH 7400) and its importance in applying health standards in occupational settings, results the common usage of the term 'fiber' to refer to those objects counted in the PCM analytical method (NIOSH, 1994a). However, this method cannot define the material or morphology of the viewed fiber. Thus PCM-fibers may be any material, and if they are mineral fibers may be any fiber morphology. If the nature of the fiber needs to be defined, NIOSH Method 7402 employs electron microscopy to determine if the fibers viewed by PCM are mineral fibers, and can establish the mineral composition (NIOSH, 1994b). This method does not recount the fibers, but, rather, it identifies what proportion of the fibers are mineral fibers, with an elemental composition consistent with asbestos, which is then used to adjust the PCM-fiber count. Although the PCM-fiber definition was not based on either mineralogy or an understanding of which fibers might be biologically relevant, this definition has become the basis of existing health standards (e.g., MSHA, 2008; OSHA, 1994; U.S. EPA, 1988a).

Text Box 2-1. Fibers Viewed by Light Microscopy

The collection of fibers on an air filter and visually counted under a phase contrast microscope (PCM) was first described in 1934 by the Dutch physicist Frits Zernike. The specification of a fiber as > 5 μm in length and a length-to-diameter ratio (fiber aspect ratio) of at least 3:1 resulted from this method. As a light microscope technique, the PCM method cannot distinguish mineral fibers from other fibers.

The U.S. Public Health Service developed and tested a standard air sampling method based on PCM detection by National Institute for Occupational Safety and Health (NIOSH) Method #7400). The NIOSH method specifies the analyst count fibers > 5 μm in length with an aspect ratio of at least 3:1. Results from PCM analysis are reported as fibers per cubic centimeter of air (f/cc).

Electron microscopy can view objects at much higher magnification and can be coupled with other techniques which can identify the mineralogy (see Text Box 2-2). X-ray diffraction (XRD) may be used with the above techniques to differentiate crystalline structure of minerals in solid materials and provides information on the availability of the total mineral present. Thus, XRD can determine the mineral composition of the material analyzed, identifying its solid solution series and classifying the mineral per standardized nomenclature for amphibole minerals (see Section 2.1.1.1).

With the advent of the use of electron microscopy to identify mineral particles, there has been an attempt to resolve the traditional dimensional fiber definition(s), by describing the particles examined by electron microscopy and X-ray diffraction in terms that are both geologically and mineralogically relevant. Structures viewed by electron microscopy may be described as having parallel sides, and considered 'fibers'. Where long, thin, curving fibers are viewed they may be described as 'asbestiform'. Structures with nonparallel sides can be considered acicular or prismatic, depending on their proportions. Thus, the descriptive terms used by geologists have migrated into the analytical field. However, the habit of formation of a single structure viewed by electron microscopy cannot be determined, and, while descriptive, these terms may not correlate to the geologic and commercial definitions of these terms. Therefore, the use of these definitions to describe individual particles viewed by TEM can be problematic (Meeker et al., 2003). Important characteristics such as crystal structure and surface chemistry cannot be adequately categorized solely with visually determined definitions developed for the classification of field samples.

Text Box 2-2. Minerals Viewed by Electron Microscopy

Electron microscopy employs electrons—rather than light—to visualize the specimen. Furthermore, instead of using glass lenses to focus the light wavelengths, electromagnetic lenses are used to focus electrons for their study. The analytical techniques included in electron microscopy for asbestos testing are TEM, scanning electron microscopy (SEM), and scanning transmission electron microscopy (STEM). TEM produces two-dimensional (2-D) images that generally use a magnification factor of about 500 to 500,000×. SEM produces three-dimensional (3-D) images that generally result in about 10 to 300,000× magnification. STEM can produce both 2-D and 3-D images that generally result in about 10 to 500,000× magnification.

The ISO 10312 method for analyzing air filters enumerates structures much smaller than the PCM fibers, with an minimum length requirement of 0.5 µm. Additionally, structures with an aspect ratio of at least 5:1 are considered fibers, rather than 3:1 as with PCM analysis. The ISO 10312 method also defines other structures (fiber bundles, clusters, and matrices) that are included in the structure count. Therefore, the term 'structure' rather than 'fiber' is used when presenting air sampling results from the ISO 10312 method, where structures per cc of air (s/cc) are reported.

3. FIBER TOXICOKINETICS

There are no published data on the toxicokinetics of Libby Amphibole asbestos.[8] However, to help inform the reader as to the expected toxicokinetics of Libby Amphibole asbestos, this section contains a general summary description of toxicokinetics of fibers. A more detailed discussion of fiber toxicokinetics is beyond the scope of this document and is reviewed elsewhere (NIOSH, 2011; ICRP, 1994).

The principal components of fiber toxicokinetics in mammalian systems are (1) deposition at the lung epithelial surface, and (2) clearance from the lung due to physical and biological mechanisms (including both translocation from the lung to other tissues [including the pleura]), and elimination from the body (see Figure 3-1).

Libby Amphibole asbestos includes fibers with a range of mineral compositions including amphibole fibers primarily identified as richterite, winchite, and tremolite (see Section 2.2). Although the fiber size varies somewhat from sample to sample, a large percentage (~45%) is less than 5 μm long in bulk samples examined from the Libby mine site (Meeker et al., 2003). Limited data from air samples taken in the workplace also document a large percentage of fibers (including both respirable[9] fibers as well as fibers <5 μm-long) (see Section 4.1.1.2 and Table 4-3). The importance of the size of fibers and how they deposit following inhalation is described below. Due to a lack of data specific to Libby Amphibole asbestos, these deposition steps are discussed for general forms of asbestos. The main route of human exposure to mineral fibers is through inhalation, although other routes of exposure play a role. Exposure of pulmonary tissue to fibers via the inhalation route depends on the fiber concentration in the breathing zone, the physical (aerodynamic) characteristics of the fibers, and the anatomy and physiology of the respiratory tract. Ingestion is another pathway of human exposure and occurs mainly through the swallowing of material removed from the lungs via mucociliary clearance or drinking water contaminated with asbestos, or eating, drinking, or smoking in asbestos-contaminated work environments (Condie, 1983). Handling asbestos can result in

[8]The term "Libby Amphibole asbestos" is used in this document to identify the mixture of amphibole mineral fibers of varying elemental composition (e.g., winchite, richterite, tremolite, etc.) that have been identified in the Rainy Creek complex near Libby, MT. It is further described in Section 2.2.

[9]Respirable fibers are those that can be inhaled into the lower lung where gas exchange occurs and are defined by their aerodynamic diameter ($d_a \leq 3$ μm; NIOSH) (2011).

4. HAZARD IDENTIFICATION OF LIBBY AMPHIBOLE ASBESTOS

Several human studies are available that provide evidence for the hazard identification of Libby Amphibole asbestos.[11] This discussion focuses primarily on data derived from studies of people exposed to Libby Amphibole asbestos—either at work or in the community. The adverse health effects in humans are supported by the available Libby Amphibole asbestos experimental animal and laboratory studies. Libby Amphibole asbestos contains winchite (84%), with lesser amounts of richterite (11%) and tremolite (6%) with trace amounts of magnesioriebeckite, edenite, and magnesio-arfvedsonite (Meeker et al., 2003) (see Section 2.2.3 for a more complete discussion). Adverse health effects from tremolite exposure have been reported in both human communities and laboratory animals; these effects are consistent with the human health effects reported for Libby Amphibole asbestos. Studies examining the health effects of exposure to winchite or richterite alone were not available in the published literature. The presentation of noncancer and cancer health effects provides a comprehensive review of adverse health effects observed from exposures to Libby Amphibole asbestos.

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY

The Libby Amphibole asbestos epidemiologic database includes studies conducted in occupational settings examining exposures to workers and community-based studies, which can include exposures to workers, exposures to family members of workers, and exposures from environmental sources. Occupational epidemiology studies exist for two worksites where workers were exposed to Libby Amphibole asbestos. These worksites include the mine and mill at the Zonolite Mountain operations near Libby, MT, and a vermiculite processing plant in Marysville, OH. Worker cohorts from each site and the study results are described in Section 4.1.1. Community-based studies include community health consultations for Libby, MT conducted by the Agency for Toxic Substances and Disease Registry (ATSDR), including an evaluation of cancer mortality data, and a health screening of current and former area residents—including workers—that collected medical and exposure histories, chest X-rays, and pulmonary function tests (ATSDR, 2001b, 2000) (see Section 4.1.2). ATSDR, in conjunction

[11] The term "Libby Amphibole asbestos" is used in this document to identify the mixture of amphibole mineral fibers of varying elemental composition (e.g., winchite, richterite, tremolite, etc.) that have been identified in the Rainy Creek complex near Libby, MT. It is further described in Section 2.2.

with state health departments, also conducted health consultations for 28 other communities around vermiculite processing plants that were potentially exposed to Libby Amphibole asbestos (see Section 4.1.4). These health consultations consisted of analyses of cancer incidence or mortality data; results from nine of these studies are currently available.

No occupational studies are available for exposure to tremolite, richterite, or winchite mineral fibers individually or as a mixture exposure, other than Libby Amphibole asbestos. Communities, however, have been exposed to tremolite and other mineral fibers from natural soils and outcroppings. Tremolite asbestos-containing soil has been used in whitewash in interior wall coatings in parts of Turkey and Greece. Studies in these areas published as early as 1979 reported an increased risk of pleural and peritoneal malignant mesothelioma (Sichletidis et al., 1992; Baris et al., 1987; Langer et al., 1987; Baris et al., 1979). More recent studies of communities exposed to tremolite and chrysotile fibers report excess lung cancer and mesothelioma (1.3- and 6.9-fold, respectively) (Hasanoglu et al., 2006). Other studies reported pleural anomalies in residents exposed to naturally occurring asbestos, which includes actinolite, tremolite, and anthophyllite (Metintas et al., 2005; Zeren et al., 2000). Clinical observations include a bilateral increase in pleural calcification accompanied by restrictive lung function as the disease progresses, a condition known as "Metsovo lung," named after a town in Greece (Constantopoulos et al., 1985). In one community, the prevalence of pleural calcification was 46% (of 268 residents), increasing with age to 80% in residents over 70 (Langer et al., 1987). Both tremolite and chrysotile were identified in bronchoalveolar lavage fluid of 65 residents from different areas of Turkey who were environmentally exposed (Dumortier et al., 1998). The health effects observed in communities with environmental and residential exposure to tremolite are consistent with health effects documented for workers exposed to commercial forms of asbestos.

4.1.1. Studies of Libby, MT Vermiculite Mining Operation Workers

Several studies of mortality from specific diseases among workers in the Libby, MT mining operations have been conducted, beginning in the 1980s with the studies by McDonald et al. (1986a) and Amandus and Wheeler. (1987). McDonald et al. (2004, 2002) published an update with mortality data through 1999, and Sullivan (2007) updated the cohort originally described by Amandus and Wheeler (1987) (referred to in this assessment as the Libby worker

Larson et al. (2010b) evaluated multiple causes of death, and, therefore, more than one cause of death can be coded for an individual. A total of 104 lung or bronchus cancer deaths were observed, for an SMR of 1.6 (95% CI: 1.3, 2.0) using an external comparison of United States cause of death data from 1960 to 2002 (Larson et al., 2010b). A higher risk was seen in the higher cumulative exposure categories using Cox proportional hazards modeling with an internal referent group: relative risk 1.0 (referent), 1.1 (95% CI: 0.6, 2.1), 1.7 (95% CI: 1.0, 3.0), and 3.2 (95% CI: 1.8, 5.3) respectively, for <1.4 (referent), 1.4 to <8.6, 8.6 to <44.0 and ≥44.0 fibers/cc-years. Larson et al. (2010b) used data from a health screening program conducted in Libby by ATSDR in 2000–2001 (described in Section 4.1.2.2) pertaining to smoking history to estimate that the proportion of smokers ranged from 50% to 66% in the unexposed group (defined as exposure <8.6 fibers/cc-years) and between 66% and 85% among the exposed (defined as ≥8.6 fibers/cc-years). Larson et al. (2010b) used these estimates in a Monte Carlo simulation to estimate the potential bias in lung cancer risks that could have been introduced by differences in smoking patterns. The bias-adjustment factor ($RR_{unadjusted}/RR_{adjusted}$ = 1.3) reduced the overall RR estimate for lung cancer from 2.4 to 2.0.

4.1.1.3.2. *Mesothelioma*

Data pertaining to mesothelioma risk from the available studies are summarized in Table 4-5. McDonald et al. (2004) presented dose-response modeling of mesothelioma risk based on 12 cases. Using Poisson regression, the mesothelioma mortality rate across increasing categories of exposure was compared to the rate in the lowest exposure category. Note that the referent group was also at excess risk of dying from mesothelioma; that is, one to three cases of mesothelioma were observed in the referent group, depending on the exposure index. Three exposure indices were used in analysis: average intensity over the first 5 years of employment, cumulative exposure, and residence-weighted cumulative exposure. Because of the requirement for 5 years of employment data, 199 individuals (including three mesothelioma cases) were excluded from the analysis of average intensity. The residence-weighted cumulative exposure was based on the summation of exposure by year, weighted by years since the exposure. This metric gives greater weight to exposures that occurred a longer time ago. Although evidence of an excess risk of dying from mesothelioma was seen in all groups, there was little evidence of increasing RR with increasing average intensity or cumulative exposure. For the

al., 2010b; Sullivan, 2007; McDonald et al., 2004)[16] observed increasing risks with increasing cumulative exposure exposures when analyzed using tertiles or quartiles, or as a continuous measure. Increased risks are also seen in the studies reporting analyses using an external referent group, i.e., standardized mortality ratios (Sullivan, 2007; Amandus and Wheeler, 1987; McDonald et al., 1986a). Radiographic evidence of small opacities (evidence of parenchymal damage) and pleural thickening (both discrete and diffuse) has also been shown in studies of Libby workers (Larson et al., 2010a; Whitehouse, 2004; Amandus et al., 1987b; McDonald et al., 1986b).

4.1.2. Libby, MT Community Studies

In addition to worker exposures, the operations of the Zonolite Mountain mine are believed to have resulted in both home exposures and community exposures. Potential pathways of exposure (discussed below) range from release of airborne fibers into the community, take-home exposure from mine workers (e.g., clothing), and recreational activities including gardening and childhood play activities. Due to a potential for a broader community concern, ATSDR conducted several studies and health actions responding to potential asbestos contamination in the Libby, MT area.

4.1.2.1. *Geographic Mortality Analysis*

ATSDR conducted a location-specific analysis of mortality risks and a community health screening for asbestos in the Libby area (see Table 4-8). The mortality analysis was based on death certificate data from 1979–1998, with geocoding of current residence at time of death. The six geographic areas used in the analysis were defined as the Libby city limits (1.1 square miles around the downtown); the extended boundary of Libby (2.2 square miles around the downtown); the boundary based on air modeling (16 square miles, based on computer modeling of asbestos fiber distribution); the medical screening boundary (25 square miles, including the town of Libby and areas along the Kootenai River); the Libby valley (65 square miles); and central Lincoln County (314 square miles, based on a 10-mile radius around downtown Libby) (ATSDR, 2000).

[16]See also reanalysis of Sullivan (2007) data by Moolgavar et al. (2010).

The 1990 population estimates were 2,531, 3,694, 4,300, 6,072, 8,617, and 9,512, respectively, for these six areas. Age-standardized SMRs were calculated using underlying cause-of-death information obtained from death certificates issued during the study period for 413 of 419 identified decedents, and Montana and U.S. populations were used as reference groups. Increased SMRs were observed for both asbestosis and pulmonary circulation diseases (see Table 4-8). The SMR for lung cancer ranged from 0.9–1.1 and 0.8–1.0 in the analyses for each of the six geographic boundaries using Montana and U.S. reference rates, respectively. In addition, four deaths due to mesothelioma were observed during the study period. These analyses did not distinguish between deaths among workers and deaths among other community members.

4.1.2.2. *Community Screening—Respiratory Health*

The ATSDR community health screening was conducted from July–November 2000 and July–September 2001 with 7,307 total participants (ATSDR, 2001b) (see Table 4-9). Eligibility was based on residence, work, or other presence in Libby for at least 6 months before 1991. The total population eligible for screening is not known; the population of Libby, MT in 2000 was approximately 10,000. In addition to a standardized interview regarding medical history, symptoms, work history, and other potential exposures, clinical tests included spirometry (forced expiratory volume in one second [FEV1] and FVC) and chest X-rays (for participants aged 18 years and older). Moderate to severe restriction (defined by the researchers as FVC <70% predicted value) was observed in 2.2% of the men and 1.6% of women but was not observed in individuals less than age 18.

Two board-certified radiologists (B readers) examined each radiograph, and a third reader was used in cases of disagreement. Readers were aware that the radiographs were from participants in the Libby, MT health screening but were not made aware of exposure histories and other characteristics (Peipins et al., 2004a; Price, 2004; Peipins et al., 2003). The radiographs revealed pleural abnormalities in 17.9% of participants, with prevalence increasing with increasing number of "exposure pathways" (defined on the basis of potential work and residential exposure to asbestos within Libby and from other sources) (see Table 4-9). Detailed results of an analysis excluding the former Libby workers cohort were not presented, but the authors noted that the relationship between number of exposure pathways and increasing

Table 4-8. Cancer mortality and nonmalignant respiratory disease mortality in the Libby, MT community

Reference(s)	Inclusion criteria and design details	Results
ATSDR (2000)	1979–1998, underlying cause of death from death certificates; geocoding of street locations (residence at time of death) within six geographic boundaries (ranging from 2,532 residents in Libby city limits to 9,521 in central Lincoln County in 1990). Inquiries to postmaster were required because of P.O. Box address for 8% (n = 32); information on 47 of 91 residents of elderly care facilities resulted in reclassification of 16 of 47 (34%) to nonresidents of Libby. U.S. Census data corresponding to the same six geographic boundaries of Libby, MT. 419 decedents identified, 418 death certificates obtained, 413 with geocoding. Age-standardized SMRs based on Montana and U.S. comparison rates. Asbestosis SMRs were somewhat higher using the U.S. referent group, but choice of referent group had little difference on SMRs for most diseases. Four deaths from mesothelioma observed in the study area.	Lung cancer (n = 82) SMR (95% CI) Comparison area (Montana reference rates): Libby city limits 1.1 (0.8, 1.5) Extended Libby boundary 1.1 (0.8, 1.5) Air modeling 1.0 (0.8, 1.4) Medical screening 0.9 (0.7, 1.2) Libby valley 0.9 (0.7, 1.2) Central Lincoln County 0.9 (0.7, 1.1) Pancreatic cancer (n = 10) SMR (95% CI) Comparison area (Montana reference rates): Libby city limits 1.0 (0.5, 2.1) Extended Libby boundary 0.9 (0.4, 1.7) Air modeling 0.7 (0.3, 1.4) Medical screening 0.7 (0.3, 1.2) Libby valley 0.6 (0.3, 1.0) Central Lincoln County 0.5 (0.3, 1.0) Asbestosis (n = 11) SMR (95% CI) Comparison area (Montana reference rates): Libby city limits 40.8 (13.2, 95.3) Extended Libby boundary 47.3 (18.9, 97.5) Air modeling 44.3 (19.1, 87.2) Medical screening 40.6 (18.5, 77.1) Libby valley 38.7 (19.3, 69.2) Central Lincoln County 36.3 (18.1, 64.9) Comparison area (U.S. reference rates): Libby city limits 63.5 (20.5, 148) Extended Libby boundary 74.9 (30.0, 154) Air modeling 71.0 (30.6, 140) Medical screening 66.1 (30.2, 125) Libby valley 63.7 (31.7, 114) Central Lincoln County 59.8 (29.8, 107) Pulmonary circulation (n = 14) SMR (95% CI) Comparison area (Montana reference rates): Libby city limits 2.3 (1.1, 4.4) Extended Libby boundary 1.9 (0.9, 3.7) Air modeling 1.8 (0.9, 3.3) Medical screening 1.6 (0.8, 2.9) Libby valley 1.6 (0.9, 2.7) Central Lincoln County 1.5 (0.8, 2.5)

Table 4-9. Pulmonary function and chest radiographic studies in the Libby, MT community

Reference(s)	Inclusion criteria and design details	Results
Peipins et al. (2003); ATSDR (2001b)	Resided, worked, attended school, or participated in other activities in Libby for at least 6 months before 1991 (including mine employees and contractors). Health screening between July and November 2000. Conducted interviews (n = 6,149, 60% of Libby residents based on 2000 Census data) and chest X-rays (n = 5,590, 18 years and older), and determined spirometry—forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC1), and ratio (FEV1/FVC). 19 "exposure pathways" including Libby mining company work, contractor work, dust exposure at other jobs, vermiculite exposure at other jobs, potential asbestos exposure at other jobs or in the military, cohabitation with Libby mining company worker, and residential and recreational use of vermiculite. Chest X-rays read by 1980 ILO classifications (3 views; posterior-anterior, right- and left- anterior oblique). Peipins et al. (2003) similar to (ATSDR, 2001b) except longer screening period (July–November 2000 and July–September 2001). Conducted interviews (n = 7,307) and chest X-rays (n = 6,668).	Peipins (2003) and ATSDR (2001b): Pleural abnormalities seen in 17.9% of participants; increasing prevalence with increasing number of exposure pathways (6.7% among those with no specific pathways, 34.6% among those with 12 or more pathways). ATSDR (2001b): Moderate-to-severe FVC1 restriction (FVC <70% predicted): 2.2% of men >17 years old; 1.6% of women >17 years old; 0.0% of men or women <18 years old. Also includes data on self-reported lung diseases and symptoms.
Weill et al. (2011)	Participants in the ATSDR community health screening (see first row in table). Analysis limited to ages 25 to 90 years, excluding individuals with history of other asbestos-related work exposures, with spirometry, consensus reading of chest X-ray, smoking data, and exposure pathway data (n = 4,397). Analysis based on five exposure categories: (1) W.R. Grace worker, (2) other vermiculite worker (contractor work), (3) other dusty occupation, (4) household (combination of three household categories), and (5) environmental ("no" to work and household exposures in Categories 1–6). Chest X-rays read by 1980 ILO classifications (frontal view).	Profusion ≥1/0 / Plaque / DPT/CAO Prevalence (%), ages 25 to 40 years: 1) W.R. Grace 0.0 / 20.0 / 5.0 2) Other 0.8 / 0.8 / 0.0 3) Dusty 0.0 / 3.8 / 0.4 4) Household 0.0 / 2.2 / 0.0 5) Environment 0.0 / 0.4 / 0.0 Prevalence (%), ages 41 to 50 years: 1) W.R. Grace 0.0 / 26.2 / 5.0 2) Other 0.5 / 7.8 / 1.0 3) Dusty 0.0 / 2.8 / 0.9 4) Household 0.0 / 11.1 / 0.4 5) Environment 0.0 / 1.9 / 0.2 Prevalence (%), ages 51 to 60 years: 1) W.R. Grace 3.2 / 34.9 / 3.2 2) Other 0.6 / 13.7 / 0.6 3) Dusty 0.6 / 12.6 / 0.0 4) Household 1.0 / 20.1 / 1.5 5) Environment 0.0 / 7.7 / 0.9 Prevalence (%), ages 61 to 90 years: 1) W.R. Grace 11.1 / 45.7 / 8.6 2) Other 0.6 / 24.8 / 8.5 3) Dusty 1.1 / 21.9 / 3.3 4) Household 2.4 / 38.3 / 5.7 5) Environment 1.3 / 12.7 / 2.2

Table 4-9. Pulmonary function and chest radiographic studies in the Libby, MT community (continued)

Reference(s)	Inclusion criteria and design details	Results
Vinikoor et al. (2010)	Participants in the ATSDR community health screening (see first row in table). Analysis limited to n = 1,003 ages 10–29 years at time of health screening (≤age 18 in 1990 when the mining/milling operations closed). Excluded if worked for W.R. Grace, or for a contractor of W.R. Grace, exposed to dust at other jobs, or exposed to vermiculite at other jobs. Exposure characterized by 6 activities (never, sometimes, or frequently participated in 1–2 or ≥3 activities). Analysis of history of respiratory symptoms and spirometry data (obstructive, restrictive, or mixed).	Little difference across exposure levels in prevalence of physician-diagnosed lung disease or abnormal spirometry. Odds Ratio (95% CI) seen between ≥3 activities and Usual cough 2.93 (0.93, 9.25) Shortness of breath 1.32 (0.51, 3.42) Bloody phlegm 1.49 (0.41, 5.43)

OR = odds ratio; DPT = diffuse pleural thickening; CAO = costophrenic angle obliteration.

prevalence of pleural abnormalities was somewhat attenuated with this exclusion. The prevalence of pleural anomalies decreased from approximately 35% to 30% in individuals with 12 or more exposure pathways when these workers were excluded from the analysis. Among individuals with no definable exposure pathways, the prevalence of pleural anomalies was 6.7%, which is higher than reported in other population studies (Peipins et al., 2004a; Price, 2004). The direct comparability between study estimates is difficult to make; the possibility of over- or underascertainment of findings from the X-rays based on knowledge of conditions in Libby was not assessed in this study. No information is provided regarding analyses excluding all potential work-related asbestos exposures.

Weill et al. (2011) used the ATSDR community health screening data to analyze the prevalence of X-ray abnormalities in relation to age, smoking history, and types of exposures. From the 6,668 participants with chest X-rays, 1,327 individuals with a history of asbestos-related work (other than with the Grace mining or related vermiculite operations) were excluded, along with 817 excluded based on age (<25 or >90 years) or lack of spirometric data, smoking data, or exposure pathway data. An additional 127 were excluded because a consensus agreement (2 out of 3 readers) was not reached regarding the X-ray findings, leaving n = 4,397 in the analysis. Analysis was based on five exposure categories: (1) Grace worker (n = 255), (2) other vermiculite worker (e.g., secondary contractor worker for Grace or other jobs with vermiculite exposure (n = 664), (3) other dusty occupation (e.g., plumber, dry wall finisher,

carpenter, roofer, electrician, welder, shipyard work or ship construction or repair (n = 831), (4) household, including household with other vermiculite or dusty work (lived with a Grace worker combination of three household categories) (n = 880), and (5) environmental ("no" to work and household exposures in Categories 1–4) (n = 1,894). The frontal views (posterior-anterior) of the chest X-rays were used in this analysis [in contrast to the use of frontal and oblique views in Peipins et al. (2003)]. As expected, lung function (FEV_1, FVC, and FEV_1/FVC) was lower among ever smokers compared with never smokers (within each age group) and decreased with age (within each smoking category). The prevalence of X-ray abnormalities (plaques, or diffuse pleural thickening, and/or costophrenic angle obliteration) also generally increased with age (divided into 25–40, 41–50, 51–60, and 61–90 years) within each of the exposure categories (see Table 4-9), with the highest prevalence seen among Grace workers. For a given age, the prevalence among those with environmental exposure only (i.e., no household or occupational exposures) was similar to the prevalence among those with non-Grace occupational or household exposures in the next youngest age category. The prevalence among the household contact category was similar or higher than the prevalence among the other vermiculite and dusty job categories. This household contact category includes individuals who lived with a Grace worker with no personal history of vermiculite or dust work (n = 594) and those who also had a history of other vermiculite (n = 114) or dusty (n = 172) jobs. The authors noted the prevalence rates were similar among these groups, and so the analysis was based on the combination of these three groups. Mean FVCs (±SE) percentage predicted were 78.76 (±3.64), 82.16 (±3.34), 95.63 (±0.76), and 103.15 (±0.25), respectively, in those with diffuse pleural thickening and/or costophrenic angle obliteration, profusion ≥1/0, other pleural abnormalities, and no pleural abnormalties. The strongest effects of diffuse pleural thickening and/or costophrenic angle obliteration on FVC were seen among men who had never smoked (–23.77, $p < 0.05$), with smaller effects seen among men who had smoked (–9.77, $p < 0.05$) and women who had smoked (–6.73, $p < 0.05$).

Vinikoor et al. (2010) used the 2000–2001 health screening data to examine respiratory symptoms and spirometry results among 1,224 adolescents and young adults who were 18 years or younger in 1990 when the mining/milling operations closed. At the time of the health screening, the ages in this group ranged from 10 to 29 years. Exclusion criteria for this analysis included previous work for W.R. Grace, work for a contractor of W.R. Grace, exposure to dust at

other jobs, or exposure to vermiculite at other jobs. The total number of exclusions was 221, leaving 1,003 in the analysis. The potential for vermiculite exposure was classified based on responses to questions about six activities (handling vermiculite insulation, participation in recreational activities along the vermiculite-contaminated gravel road leading to the mine, playing at the ball fields near the expansion plant, playing in or around the vermiculite piles, heating the vermiculite to "pop" it, and other activities involving vermiculite). The medical history questionnaire included information on three respiratory symptoms: usually have a cough (n = 108, 10.8%); troubled by shortness of breath when walking up a slight hill or when hurrying on level ground (n = 145, 14.5%); coughed up phlegm that was bloody in the past year (n = 59, 5.9%). A question on history of physician-diagnosed lung disease (n = 51, 5.1%) was also included. The spirometry results were classified as normal in 896 (90.5%), obstructive in 62 (6.3%), restrictive in 30 (3.0%), and mixed in 2 (0.2%). Information on smoking history was also collected in the questionnaire: 15.8% and 7.3% were classified as current and former smokers, respectively. Approximately half of the participants lived with someone who smoked. The analyses adjusted for age, sex, personal smoking history, and living with a smoker. For usually having a cough, the odds ratios (ORs) were 1.0 (referent), 1.88 (95% CI: 0.71, 5.00), 2.00 (95% CI: 0.76, 5.28) and 2.93 (95% CI: 0.93, 9.25) for never, sometimes, frequently participated in 1–2 activities, and frequently participated in ≥3 activities, respectively. For shortness of breath, the corresponding ORs across those exposure categories were 1.0 (referent), 1.16 (95% CI: 0.55, 2.44), 1.27 (95% CI: 0.61, 2.63) and 1.32 (95% CI: 0.51, 3.42), and for presence of bloody phlegm in the past year the ORs were 1.0 (referent), 0.85 (95% CI: 0.31, 2.38), 1.09 (0.41, 2.98), and 1.49 (95% CI: 0.41, 5.43). For history of physician-diagnosed lung disease and abnormal spirometry results, there was little difference in the odds ratios across the exposure categories: for lung disease, the ORs were 1.0 (referent), 1.95 (95% CI: 0.57, 6.71), 1.51 (95% CI: 0.43, 5.24) and 1.72 (95% CI: 0.36, 8.32) for the categories of never, sometimes, frequently participated in 1–2 activities, and frequently participated in ≥3 activities, respectively. For abnormal spirometry (i.e., obstructive, restrictive, or mixed, n = 94 cases), the ORs were 1.0 (referent), 1.34 (95% CI: 0.60, 2.96), 1.20 (95% CI: 0.53, 2.70) and 1.33 (95% CI: 0.42, 4.19) across these exposure groups.

Two other studies examining autoimmune disease and autoantibodies in residents of Libby, Montana are described in Section 4.3.

4.1.2.3. *Other Reports of Asbestos-Related Disease Among Libby, MT Residents*

Whitehouse et al. (2008) recently reviewed 11 cases of mesothelioma diagnosed between 1993 and 2006 in residents in or around Libby, MT ($n = 9$) and in family members of workers in the mining operations ($n = 2$). Three cases were men who might have had occupational asbestos exposure through construction work (Case 1), working in the U.S. Coast Guard and as a carpenter (Case 5), or through railroad work involving sealing railcars in Libby (Case 7). One case was a woman whose father had worked at the mine for 2 years; although the family lived 100 miles east of Libby, her exposure may have come through her work doing the family laundry, which included laundering her father's work clothes. The other seven cases (four women, three men) had lived or worked in Libby for 6–54 years, and had no known occupational or family-related exposure to asbestos. Medical records were obtained for all 11 patients; pathology reports were obtained for 10 of the 11 patients. The Centers for Disease Control estimated the death rate from mesothelioma, using 1999 to 2005 data, as approximately 14 per million per year (CDC, 2009), approximately five times higher than the rate estimated by Whitehouse et al. (2008) for the Libby area population based on the estimated population of 9,500 for Lincoln County and 15 years (or 150,000 person-years) covered by the analysis. Whitehouse et al. (2008) stated that a W.R. Grace unpublished report of measures taken in 1975 indicated that exposure levels of 1.1 fibers/cc were found in Libby, and 1.5 fibers/cc were found near the mill and railroad facilities. Because the mining and milling operations continued to 1990, and because of the expected latency period for mesothelioma, Whitehouse et al. (2008) suggests that additional cases can be expected to occur within this population.

4.1.2.4. *Summary of Respiratory Health Effects in Libby, MT Community Studies*

The geographic-based mortality analysis of 1997–1998 mortality data indicates that asbestosis-related mortality is substantially increased in Libby, MT, and the surrounding area, with rates 40 times higher compared with Montana rates and 60–70 times higher compared with U.S. rates (ATSDR, 2000). These data provide evidence of the disease burden within the community; however, because this analysis did not distinguish between deaths among workers and deaths among other community members, it is not possible based on these data to estimate the risk of asbestos-related mortality experienced by residents who were not employed at the mining or milling operations. The community health screening studies provide more detailed

information regarding exposure pathways in addition to occupation (ATSDR, 2001b). Data from the ATSDR community health screening study indicate that the prevalence of pleural abnormalities, identified by radiographic examination, increases substantially with increasing number of exposure pathways (Peipins et al., 2003). In addition, the prevalence of some self-reported respiratory symptoms among 10 to 29-year-old adolescents and young adults was associated with certain exposure pathways. These participants were ≤ age 18 in 1990 when the mining/milling operations closed (Vinikoor et al., 2010). A better understanding of the community health effects and the examination of the potential progression of adverse health effect in this community would benefit from additional research to establish the clinical significance of these findings. The observation by Whitehouse et al. (2008) of cases of mesothelioma among individuals with no direct occupational exposure to the mining and milling operations indicates the need for continued surveillance for this rare cancer.

4.1.3. Marysville, OH Vermiculite Processing Plant Worker Studies

Libby vermiculite was used in the production of numerous commercial products, including as a potting soil amender and a carrier for pesticides and herbicides. A Marysville, OH plant that used Libby vermiculite in the production of fertilizer beginning around 1960 to 1980 is the location of the two related studies described in this section.

The processing facility had eight main departments, employing approximately 530 workers, with 232 employed in production and packaging of the fertilizer and 99 in maintenance; other divisions included research, the front office, and the polyform plant (Lockey, 1985). Six departments were located at the main facility (trionizing, packaging, warehouse, plant maintenance, central maintenance, and front offices). Research and development and a polyform fertilizer plant were located separately, approximately one-quarter mile from the main facility. In the trionizing section of the plant, the vermiculite ore was received by rail or truck, unloaded into a hopper, and transported to the expansion furnaces. After expansion, the vermiculite was blended with other materials (e.g., urea, potash, herbicides), packaged, and stored. Changes to the expander type and dust-control measures began in 1967, with substantial improvement in dust control occurring throughout the 1970s.

Information about exposure assessment at the Marysville, OH plant is summarized in the final row of Table 4-1. Industrial hygiene monitoring at the plant began in 1972. Lockey et al.

Weinberg, 2011). Although limited, the data described in Section 4.2 suggest an increase in inflammatory response following exposure to Libby Amphibole asbestos and tremolite asbestos similar to that observed for other durable mineral fibers [reviewed in Mossman et al. (2007)]. Whether this inflammatory response then leads to cancer is unknown. Studies examining other types of asbestos (e.g., crocidolite, chrysotile, and amosite) have demonstrated an increase in chronic inflammation as well as respiratory cancer related to exposure [reviewed in Kamp and Weitzman (1999)]. Chronic inflammation has also been linked to genotoxicity and mutagenicity following exposure to some particles and fibers (Driscoll et al., 1997; 1996; 1995). The evidence described above suggests chronic inflammation is observed following Libby Amphibole asbestos and tremolite asbestos exposure; however, the role of inflammation and whether it leads to lung cancer or mesothelioma following exposure to Libby Amphibole asbestos is unknown.

ROS production has been measured in response to both Libby Amphibole asbestos and tremolite asbestos exposure. Blake et al. (2007) demonstrated an increase in the production of superoxide anion following exposure to Libby Amphibole asbestos. Blake et al. (2007) also demonstrated that total superoxide dismutase was inhibited, along with a decrease in intracellular glutathione, both of which are associated with increased levels of ROS. These results are supported by a recent study in human mesothelial cells (Hillegass et al., 2010) (described in Section 4.4 and Appendix D). Increased ROS production was also observed in human airway epithelial cells following exposure to Libby Amphibole asbestos (Duncan et al., 2010) (described in Section 4.4 and Appendix D). This increase in ROS and decrease in glutathione are common effects following exposure to asbestos fibers and particulate matter. Although ROS production is relevant to humans, based on similar human responses as compared to animals, information on the specifics of ROS production following exposure to Libby Amphibole asbestos is limited to the available data described here. Therefore, the role of ROS production in lung cancer and mesothelioma following exposure to Libby Amphibole asbestos is unknown.

4.3. OTHER DURATION OR ENDPOINT-SPECIFIC STUDIES

4.3.1. Immunological

Two epidemiology studies have examined the potential role of Libby Amphibole asbestos and autoimmunity. Noonan et al. (2006) used the data from the community health screening to examine self-reported history of autoimmune diseases (rheumatoid arthritis, scleroderma, or

lupus) in relation to the asbestos exposure pathways described above (see Table 4-17). To provide more specificity in the self-reported history of these diseases, a follow-up questionnaire was mailed to participants to confirm the initial report and obtain clarifying information regarding the type of disease, whether the condition had been diagnosed by a physician, and whether the participant was currently taking medication for the disease. Responses were obtained from 208 (42%) of the 494 individuals who had reported these conditions. Of these 208 responses, 129 repeated the initial report of the diagnosis of rheumatoid arthritis, and 161 repeated the initial report of the diagnosis of one of the three diseases (rheumatoid arthritis, scleroderma, or lupus). Among people aged 65 and over ($n = 34$ rheumatoid arthritis cases, determined using responses from the follow-up questionnaire), a two- to threefold increase in risk was observed in association with several measures reflecting potential exposure to asbestos (e.g., asbestos exposure in the military) or specifically to Libby Amphibole asbestos (e.g., past work in mining and milling operations, use of vermiculite in gardening, and frequent playing on vermiculite piles when young). Restricted forced vital capacity, presence of parenchymal abnormalities, playing on vermiculite piles, and other dust or vermiculite exposures were also associated with rheumatoid arthritis in the group younger than 65 ($n = 95$ cases). Restricted forced vital capacity was defined as FVC <80% predicted and a ratio of FEV1 to FVC ≥70% predicted. For all participants, an increased risk of rheumatoid arthritis was observed with increasing number of exposure pathways. RRs of 1.0, 1.02, 1.79, 2.51, and 3.98 were observed for 0 (referent), 1, 2–3, 4–5, and 6 or more pathways, respectively (trend $p < 0.001$, adjusting for restrictive spirometry, parenchymal abnormalities, and smoking history). Although the information gathered in the follow-up questionnaire and repeated reports of certain diagnoses decreased the false-positive reports of disease, considerable misclassification (over-reporting and under-reporting) is likely, given the relatively low confirmation rate of self-reports of physician-diagnosed rheumatoid arthritis (and other autoimmune diseases) seen in other studies (Karlson et al., 2003; Rasch et al., 2003; Ling et al., 2000).

Another study examined serological measures of autoantibodies in 50 residents of Libby, MT, and a comparison group of residents of Missoula, Montana (Pfau et al., 2005); (see Table 4-17). The Libby residents were recruited for a study of genetic susceptibility to

Table 4-17. Autoimmune-related studies in the Libby, MT community

Reference(s)	Inclusion criteria and design details	Results
Noonan et al. (2006)	Nested case-control study among 7,307 participants in 2000–2001 community health screening. Conducted interviews, gathered self-reported history of rheumatoid arthritis, scleroderma, or lupus. Follow-up questionnaire mailed to participants concerning self-report of "physician-diagnosis" of these diseases and medication use.	Association with work in Libby mining/milling operations (ages 65 and older): Rheumatoid arthritis OR: 3.2 (95% CI: 1.3, 8.0) Rheumatoid arthritis, lupus, scleroderma OR: 2.1 (95% CI: 0.90, 4.1) Risk increased with increasing number of asbestos exposure pathways.
Pfau et al. (2005)	Libby residents (n = 50) recruited for study of genetic susceptibility to asbestos-related lung disease. Missoula, MT comparison group (n = 50), recruited for study of immune function; age and sex-matched to Libby participants. Serum samples obtained; IgA levels, prevalence of antinuclear, anti-dsDNA antibodies, anti-RF antibodies, and anti-Sm, RNP, SS-A, SS-B, and Scl-70 antibodies determined.	Increased prevalence of high titer (≥1:320) antinuclear antibodies in Libby sample (22%) compared to Missoula sample (6%). Similar increases for rheumatoid factor, anti-RNP, anti-Scl-60, anti-Sm, anti-R_o (SSA), and anti-La (SSB) antibodies observed in Libby sample.

asbestos-related lung disease, and the Missoula residents were participants in a study of immune function The Libby sample exhibited an increased prevalence (22%) of high-titer (≥1:320) antinuclear antibodies when compared to the Missoula sample (6%), and similar increases were seen in the Libby sample for rheumatoid factor, anti-RNP, anti-Scl-60, anti-Sm, anti-R_o (SSA), and anti-La (SSB) antibodies. Although neither sample was randomly selected from the community residents, an individual's interest in participating in a gene and lung disease study likely would not be influenced by the presence of autoimmune disease or autoantibodies in that individual.

Hamilton et al. (2004), Blake et al. (2008), and Pfau et al. (2008) examined the role of asbestos in autoimmunity in laboratory animal or in vitro studies. Blake et al. (2008) performed in vitro assays with Libby Amphibole asbestos (see Section 4.4), and both studies performed the in vivo assays with tremolite. C57BL/6 mice were instilled intratracheally for a total of two doses each of 60-μg saline and wollastonite or Korean tremolite sonicated in sterile PBS, given 1 week apart in the first 2 weeks of a 7-month experiment. Sera from mice exposed to tremolite showed antibody binding colocalized with SSA/Ro52 on the surface of apoptotic blebs (Blake et al., 2008). In Pfau et al. (2008), by 26 weeks, the tremolite-exposed animals had a significantly

Tremolite and Libby Amphibole asbestos exposure led to increases in both fibrosis and tumorigenicity in all but one animal study, supporting a possible role for proliferation in response to these fibers. However, there are limited data to demonstrate that increased cytotoxicity and cellular proliferation following exposure to Libby Amphibole asbestos leads to lung cancer or mesothelioma.

Summary. The review of these studies clearly highlights the need for more controlled studies examining Libby Amphibole asbestos in comparison with other forms of asbestos and for examining multiple endpoints—including ROS production, DNA damage, and pro-inflammatory gene expression alterations—to improve understanding of mechanisms involved in cancer and other health effects. Data gaps still remain to determine specific mechanisms involved in Libby Amphibole asbestos-induced disease. Studies that examined cellular response to tremolite also found that tremolite exposure may lead to increased ROS production, toxicity, and genotoxicity (Okayasu et al., 1999; Wagner et al., 1982). As with the in vivo studies, the definition of fibers and how the exposures were measured varies among studies.

4.5. SYNTHESIS OF MAJOR NONCANCER EFFECTS

The predominant noncancer health effects observed following inhalation exposure to Libby Amphibole asbestos are effects on the lungs and pleural lining surrounding the lungs. Recent studies have also examined noncancer health effects following exposure to Libby Amphibole asbestos in other systems, including autoimmune effects and cardiovascular disease. These effects have been observed primarily in studies of exposed workers and community members and are supported by laboratory animal studies.

4.5.1. Pulmonary Effects

4.5.1.1. *Pulmonary Fibrosis (Asbestosis)*

Asbestosis is the interstitial pneumonitis and fibrosis caused by inhalation of asbestos fibers and is characterized by a diffuse increase of collagen in the alveolar walls (fibrosis) and the presence of asbestos fibers, either free or coated with a proteinaceous material and iron (asbestos bodies). Fibrosis results from a sequence of events following lung injury, which includes inflammatory cell migration, edema, cellular proliferation, and accumulation of collagen. Asbestosis is associated with dyspnea, bibasilar rales, and changes in pulmonary

function: a restrictive pattern, mixed restrictive-obstructive pattern, and/or decreased diffusing capacity (ATS, 2004). Radiographic evidence of small opacities in the lung is direct evidence of scarring of the lung tissue and as the fibrotic scarring of lung tissue consistent with mineral dust and mineral fiber toxicity. The scarring of the parenchymal tissue of the lung contributes to measured changes in pulmonary function, including obstructive pulmonary deficits from narrowing airways, restrictive pulmonary deficits from impacting the elasticity of the lung as well as decrements in gas exchange.

Workers exposed to Libby Amphibole asbestos from vermiculite mining and processing facilities in Libby, MT, as well as plant workers in Marysville, OH, where vermiculite ore was exfoliated and processed, have an increased prevalence of small opacities on chest X-rays, which is indicative of fibrotic damage to the parenchymal tissue of the lung (Rohs et al., 2008; Amandus et al., 1987b; McDonald et al., 1986b; Lockey et al., 1984). These findings are consistent with a diagnosis of asbestosis, and the studies are described in detail in Section 4.1.1.4.2. Significant increases in asbestosis as the primary cause-of-death have been documented in studies of the Libby worker cohort report (see Table 4.6 for details) (Larson et al., 2010b; Sullivan, 2007; Amandus and Wheeler, 1987; McDonald et al., 1986a). For both asbestosis mortality and radiographic signs of asbestos (small opacities), positive exposure-response relationships are described where these effects are greater with greater cumulative exposure to Libby Amphibole asbestos.

Deficits in pulmonary function consistent with pulmonary fibrosis have been reported in individuals exposed to Libby Amphibole asbestos. The initial study of the Marysville, OH cohort measured but reported no change in pulmonary function (Lockey et al., 1984). Pulmonary function was not reported for the cohort follow-up, although prevalence of pleural and parenchymal abnormalities was increased (Rohs et al., 2008). Although studies of the occupational Libby worker cohort do not include assessment of pulmonary function (Amandus et al., 1987b; McDonald et al., 1986b) data from the ATSDR community screening, which included workers, provide support for functional effects from parenchymal changes. The original report of the health screening data indicated moderate-to-severe pulmonary restriction in 2.2% of men (Peipins et al., 2003; ATSDR, 2001b). A recent reanalysis of these data show that for study participants with small opacities viewed on the radiographs (grade 1/0 or greater), and DPT the mean FVC is reduced to 78.76 (±3.64), 82.16 (±3.34), respectively of the expected value (Weill

et al., 2011). A mean FVC of 95.63 (±0.76) was reported for those with other pleural abnormalities versus 103.15 (±0.25) in participants with no radiographic abnormalities. The strongest effects of diffuse pleural thickening and/or costophrenic angle obliteration on FVC were seen among men who had never smoked (–23.77, $p < 0.05$), with smaller effects seen among men who had smoked (–9.77, $p < 0.05$) and women who had smoked (–6.73, $p < 0.05$). Laboratory animal and mechanistic studies of Libby Amphibole asbestos are consistent with the noncancer health effects observed in both Libby workers and community members. Pleural fibrosis was increased in hamsters after intrapleural injections of Libby Amphibole asbestos (Smith, 1978). More recent studies have demonstrated increased collagen deposition consistent with fibrosis following intratracheal instillation of Libby Amphibole asbestos fibers in mice (Padilla-Carlin et al., 2011; Shannahan et al., 2011a; Shannahan et al., 2011b; Smartt et al., 2010; Putnam et al., 2008). Pulmonary fibrosis, inflammation, and granulomas were observed after tremolite inhalation exposure in Wistar rats (Bernstein et al., 2005; Bernstein et al., 2003) and intratracheal instillation in albino Swiss mice (Sahu et al., 1975). Davis et al. (1985) also reported pulmonary effects after inhalation exposure in Wistar rats including increases in peribronchiolar fibrosis, alveolar wall thickening, and interstitial fibrosis.

4.5.1.2. *Other Nonmalignant Respiratory Diseases*

Mortality studies of the Libby workers indicate that there is increased mortality, not only from asbestosis, but other respiratory diseases. Deaths attributed to chronic obstructive respiratory disease and deaths attributed to "other" nonmalignant respiratory disease were elevated more than twofold (see Table 4-6) (Larson et al., 2010b; Sullivan, 2007). These diseases are consistent with asbestos toxicity, and the evidence of a positive exposure-response relationship for mortality from all nonmalignant respiratory diseases, supports this association.

4.5.2. Pleural Effects

Pleural thickening that is caused by mineral fiber exposure includes two distinct biological lesions: discrete pleural plaques in the parietal pleura and diffuse pleural thickening of the visceral pleura. Both forms of pleural thickening can be viewed on standard radiographs. However, the two are not always clearly distinguishable on X-rays, and smaller lesions may not be detected. High resolution computed tomography is a method that can distinguish between the

lesions, as well as detect smaller lesions than are visible on X-rays. Pleural thickening may restrict lung function, increase breathlessness with exercise, and contribute to chronic chest pain. The potential for health effects and severity of health effects are increased with the extent and thickness of the pleural lesions.

Data from the ATSDR community health screening study indicate that the prevalence of pleural abnormalities, identified by radiographic examination, increases substantially with increasing number of exposure pathways (Peipins et al., 2003). A reanalysis of these data also considered age, smoking history, and types of exposures. Increased pleural thickening is reported for Libby workers, those with other vermiculite work and those in "dusty trades." Increased LPT is reported in both those exposed only as household contacts or through environmental exposure pathways, with greater incidence by age (38.3 and 12.7%, respectively, in the 61–90 age group) (Weill et al., 2011). DPT is reported at lower rates with 5.9 and 2.2%, respectively, in these exposure groups in the highest age bracket evaluated (age 61–90).

Increased pleural thickening is reported for both of the studied worker cohorts, with evidence of positive exposure response relationships (Larson et al., 2010a; Rohs et al., 2008; Amandus et al., 1987b; McDonald et al., 1986b; Lockey et al., 1984). Both McDonald et al. (1986b) and Amandus et al. (1987b) indicate age is also a predictor of pleural thickening in exposed individuals, which may reflect the effects of time from first exposure. Smoking data were limited on the Libby workers and analyses do not indicate clear relationships between smoking and pleural thickening (Amandus et al., 1987b; McDonald et al., 1986b). Pleural thickening in workers at the Scott Plant (Marysville, OH) was associated with hire on or before 1973 and age at time of interview but was not associated with BMI or smoking history (ever smoked) (Rohs et al., 2008).

4.5.3. Other Noncancer Health Effects (Cardiovascular Toxicity, Autoimmune Effects)

There is limited research available on noncancer health effects occurring outside the respiratory system. Larson et al. (2010b) examined cardiovascular disease-related mortality in the cohort of exposed workers from Libby (see Section 4.1.1.4.3). Mechanistic studies have examined the potential role of iron and the associated inflammation for both the respiratory and cardiovascular disease (Shannahan et al., 2011b). Two studies examined the association between asbestos exposure and autoimmune disease (Noonan et al., 2006) or autoantiboides and other

immune markers (Pfau et al., 2005) (see Table 4-17). Limitations in the number, scope, and design of these studies make it difficult to reach conclusions as to the role of asbestos exposure in either cardiovascular disease or autoimmune disease.

4.5.4. Libby Amphibole Asbestos Summary of Noncancer Health Effects

The studies in humans summarized in Section 4.1 have documented an increase in mortality from nonmalignant respiratory disease, including asbestosis, in workers exposed to Libby Amphibole asbestos (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004; Amandus and Wheeler, 1987). Radiographic evidence of pleural thickening and interstitial damage (small opacities) are also well documented among employees of the Libby vermiculite mining operations (Larson et al., 2010a; Amandus et al., 1987b; McDonald et al., 1986b). Additional studies have documented an increase in radiographic changes in the pleura and parenchyma among employees of a manufacturing facility in Marysville, OH that used Libby vermiculite ore contaminated with Libby Amphibole asbestos (Rohs et al., 2008; Lockey et al., 1984). Positive exposure-response relationships for these health effects for both occupational cohorts studied, as well as the observed latency, support an association between exposure to Libby Amphibole asbestos and these pleuro-pulmonary effects. Studies of community members exposed to Libby Amphibole asbestos have documented similar pleural abnormalities and pulmonary deficits consistent with parenchymal damage (Weill et al., 2011; Whitehouse, 2004; Peipins et al., 2003). Although limited, animal studies support the toxicity of Libby Amphibole asbestos to pleural and pulmonary tissues. Developing research supports a role of inflammatory processes in the toxic action of Libby Amphibole asbestos, consistent with the observed health effects (Duncan et al., 2010; Hamilton et al., 2004). Taken together, the strong evidence in human studies, defined exposure response relationships, and supportive animal studies provide compelling evidence that exposure to Libby Amphibole asbestos causes nonmalignant respiratory disease, including asbestosis, pleural thickening, and deficits in pulmonary function associated with mineral fiber exposures. Existing data regarding cardiovascular effects and the potential for autoimmune disease are limited.

4.5.5. Mode-of-Action Information (Noncancer)

The precise mechanisms causing toxic injury from inhalation exposure to Libby Amphibole asbestos have not been established. However, nearly all-durable mineral fibers with dimensional characteristics that allow penetration to the terminal bronchioles and alveoli of the lung have the capacity to induce pathologic response in the lung and pleural cavity (ATSDR, 2001a; Witschi and Last, 1996). The physical-chemical attributes of mineral fibers are important in determining the type of toxicity observed. Fiber dimension (width and length), density, and other characteristics such as chemical composition, surface area, solubility in physiological fluids, and durability all play important roles in both the type of toxicity observed and the biologically significant dose. Fibrosis results from a sequence of events following lung injury, which includes inflammatory cell migration, edema, cellular proliferation, and accumulation of collagen. Fibers do migrate to the pleural space, and it has been hypothesized that a similar cascade of inflammatory events may contribute to fibrotic lesions in the visceral pleura. Thickening of the visceral pleura is more often localized to lobes of the lung with pronounced parenchymal changes, and it has also been hypothesized that the inflammatory and fibrogenic processes within the lung parenchyma in response to asbestos fibers may influence the fibrogenic process in the visceral pleura. The etiology of parietal plaques is largely unknown with respect to mineral fiber exposure.

There is currently insufficient evidence to establish the noncancer mode of action for Libby Amphibole asbestos. Limited in vitro studies have demonstrated oxidative stress following Libby Amphibole asbestos exposures in various cell types (Duncan et al., 2010; Hillegass et al., 2010; Pietruska et al., 2010; Blake et al., 2007). Libby Amphibole asbestos fibers increased intracellular ROS in both murine macrophages and human epithelial cells (Duncan et al., 2010; Blake et al., 2007). Surface iron, inflammatory marker gene expression was increased following exposure to Libby Amphibole asbestos in human epithelial cells (Shannahan et al., 2011b; Duncan et al., 2010; Pietruska et al., 2010) (see Table 4-18). Tremolite studies demonstrate cytotoxicity in various cell culture systems (see Table 4-19).

The initial stages of any fibrotic response involve cellular proliferation, which may be compensatory for cell death due to cytotoxicity. Analysis of cellular proliferation has demonstrated both increases and decreases following exposure to asbestos fibers in vitro and in vivo depending on the specific fiber or cell type (Mossman et al., 1985; Topping and Nettesheim,

1980). Other studies have focused on the activation of cell-signaling pathways that lead to cellular proliferation following exposure to asbestos (Scapoli et al., 2004; Shukla et al., 2003; Ding et al., 1999; Zanella et al., 1996).

Although slightly increased compared to controls, cytotoxicity in murine macrophage cells exposed to Libby Amphibole asbestos was decreased compared to other fiber types (Blake et al., 2008). Cytotoxicity was slightly, but statistically significantly, increased compared to an unexposed control at 24 hours post exposure to Libby Amphibole asbestos, while crocidolite exposure resulted in even higher levels of cytotoxicity. No other in vitro study examined cytotoxicity following exposure to Libby Amphibole asbestos, although an increase in apoptosis was demonstrated in this same cell system (Blake et al., 2008). Recent studies in mice exposed to Libby Amphibole asbestos demonstrated increased collagen deposition and collagen gene expression, markers of fibrosis (Smartt et al., 2010; Putnam et al., 2008). Short-term studies in rats also demonstrated an increased inflammatory response (Padilla-Carlin et al., 2011; Shannahan et al., 2011a; Shannahan et al., 2011b). Tremolite and Libby Amphibole asbestos exposure led to increases in both fibrosis in all but one animal study, supporting a role for proliferation in response to these fibers. Taken together with studies on other asbestos fibers, these data suggest that a cytotoxicity and cell proliferation may play a role in the noncancer health effects following exposure to Libby Amphibole asbestos.

Although continued research demonstrates that the Libby Amphibole asbestos has biologic activity consistent with the inflammatory action and cytotoxic effects seen with other forms of asbestos, the data are not sufficient to establish a mode of action for the pleura-pulmonary effects of exposure to Libby Amphibole asbestos.

4.6. EVALUATION OF CARCINOGENICITY

4.6.1. Summary of Overall Weight of Evidence

Under the EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), Libby Amphibole asbestos is *carcinogenic to humans* following inhalation exposure based on epidemiologic evidence that shows a convincing association between exposure to Libby Amphibole asbestos fibers and increased lung cancer and mesothelioma mortality (Larson et al., 2010b; Moolgavkar et al., 2010; Sullivan, 2007; McDonald et al., 2004; Amandus and Wheeler, 1987; McDonald et al., 1986a). These results are further supported by animal studies that

Table 5-2. Summary of rationale for identifying candidate principal studies on Libby Amphibole asbestos for RfC development

Attribute	Preferred characteristics for candidate principal studies for the Libby Amphibole Asbestos RfC
Relevance of exposure paradigm	Studies of subchronic or chronic duration are preferred over studies of acute exposure duration because most relevant environmental exposure scenarios are expected to address chronic exposure scenarios (potentially including both continuous exposure from ambient conditions and episodic activity-related exposures). Measures of cumulative exposure are a widely used metric to address asbestos risk. It is consistent with the expectation that toxic responses will reflect an accumulative effect of asbestos inhaled and deposited in tissues over time. Additionally mean exposure, exposure duration, and time from first exposure (TSFE) have all been reported as predictors of health effects from asbestos exposure. Cumulative exposure has the advantage that it reflects both duration and intensity (e.g., mean level) of asbestos exposure. Relatively lower exposure intensities that may represent conditions more similar to environmental exposures are preferred as there may be less uncertainty in extrapolation of the results to lower exposure levels. Results from studies with high exposure intensity or cumulative exposure are, other things being comparable, judged less relevant for environmental risk assessment compared to studies defining effects at lower levels of exposure. Some biological processes (e.g., potential decrease in effectiveness of particle clearance processes) may more strongly influence responses at very high levels of exposure and be less relevant at lower levels. Thus, exposure conditions with lower level exposures may remove some of the uncertainty in estimating health effects from environmental exposures.
Study design characteristics	Sufficient follow-up time for outcomes to develop (which can depend on the health outcome being addressed). Study size and participation rates that are adequate to detect and quantify health outcomes being studied are preferred, with no indications of bias in study population selection. Use of a study design or analytic approach, which adequately addresses the relevant sources of potential confounding, including age, sex, smoking, and exposure to other risk factors (such as non-Libby asbestos).

Table 5-2. Summary of rationale for identifying candidate principal studies on Libby Amphibole asbestos for RfC development (continued)

Measurement of exposure	Emphasis is placed on the specificity of exposure assessment in time and place with a preference for greater detail where possible. Exposure measurements that are site- and task-specific provide appropriate exposure information, and individual, rather than area samples are preferred where available. Measurement techniques that are more specific to the agent of concern are preferred over less specific analytical methods. Better characterization of fibers is preferred. For asbestos fibers, TEM analysis, which can identify the mineral fibers present, provides the most specific information; PCM identifies fibers as defined by that method (NIOSH 7400) and, thus, is useful but do not confirm the mineral nature of the counted fibers. Total dust measurements are the least informative of those available. Stronger studies will often be based upon knowledge of individual work histories (job titles/tasks with consideration of changes over time); however, appropriate group-based exposure estimates may also be relevant. Exposure reconstruction and estimating exposures based on air sampling from other time periods and/or operations are less preferred methods of exposure estimation.
Measurement of effect(s)	Emphasis is placed on the more sensitive health outcome endpoints that are available. For parenchymal and pleural effects considered here, the radiographic abnormalities are more sensitive than the corresponding mortality causes. An RfC is intended to be a level at which no category of adverse health outcome would occur. Pleural and parenchymal abnormalities assessed using good quality radiographs or high-resolution computed tomography (HRCT) and independently evaluated multiple qualified readers according to ILO standards. Evaluation of radiographs should not be influenced by knowledge of exposure status.

intensity exposures for the Marysville cohort and corresponding lower cumulative exposures are advantages of this study, considering there are uncertainties inherent in exposure-response data and extrapolating from the high intensity occupation exposures to lower level exposures often seen in community and environmental exposures.

5.2.1.2.1. *Evaluation of study design in candidate studies*

The candidate principal studies differed in the study populations, in terms of follow-up time, study size and participation, and available information (see Table 5-1). The study sizes are similar for the two Libby worker studies (n = 184 and n= 244, respectively) (Amandus et al., 1987b; McDonald et al., 1986b) and the Marysville update (n = 280) (Rohs et al., 2008).

Adequate follow-up time allows for the health effect to manifest prior to sampling. In the case of pleural abnormalities, there is some variability with latency based on intensity of

exposure as well as the nature of the pleural lesion where discrete pleural plaques have a shorter latency than diffuse thickening of the visceral pleura. Larson et al. (2010a) studied the latency for individuals in the Libby worker cohort, reporting a median latency of 8.6 years for localized pleural thickening versus 27 years for diffuse pleural thickening and 19 years for minimal signs of small opacities (parenchymal changes).[24] Lockey et al. (1984) report the mean employment duration for their exposure groups from 6.6 to 13.3 years at the time of their study (but do not assess time since first exposure (TSFE); thus, it is unclear whether in the first examination these workers had sufficient follow-up to assess the radiographic changes, especially diffuse pleural thickening and small opacities. The Rohs et al. (2008) report includes 24 more years of follow-up time and is preferred over the early Lockey et al. (1984) study on this basis.

Both studies of the Libby workers report duration of employment and average age of the participants, but not TSFE. The McDonald et al. (1986b) study included both current and former workers—these former workers likely have longer time from first exposure compared with current workers. The study included all current plant employees (164 men, 9 women). However, there was a lower participation rate in former employees (80 of 110 eligible former employees agreed to provide chest radiographs). Additionally, X-rays for all study participants were taken in the same year, providing similar quality X-rays between past and current employees. In contrast, Amandus et al. (1987b) only considered workers employed during 1975 to 1982 and relied on available radiographs regardless of year (radiographs were available for 93% of employees). Because workers terminated prior to 1975 were excluded from the study, older individuals, and individuals with longer TSFE were less likely to be included than in the study by McDonald et al. (1986b), which included former workers. Both Libby worker studies do report radiographic abnormalities, so the follow-up is adequate for some effects to be documented; however, compared with the Rohs et al. (2008) study, the Libby worker studies have shorter follow-up times.

[24] Individual latency for visible LPT in Libby exposed workers was evaluated in 84 workers with radiographic evidence of pleural and/or parenchymal changes (Larson et al., 2010a). By examining historical radiographs, researchers were able to identify the first appearance of the lesions, although it is recognized that retrospective design of this study likely identified lesions at earlier time points, as the readers were aware of the later X-rays (Larson et al., 2010a). It is acknowledged that some of the workers at Libby may have been exposed through the community prior to working, and in fact, one individual had the first pleural change noted at 9 years of age, prior to occupational exposure (Larson et al., 2010a). Where data on prior exposures were available, workers with no prior exposure had an average latency of 9.4 years versus 5.1 years for workers with potential exposures prior to hire ($N = 63$ and 31, respectively).

Among Marysville workers, there were very few employees who declined to participate in the earlier study by Lockey et al. (1984), where 512 out of 530 employees were included, but there is potential for selection bias in the follow-up by Rohs et al. (2008), where only 280 employees out of the original cohort were evaluated. Rohs et al. (2008) state that employees hired in 1973 or earlier (when exposure estimates were more uncertain) were more likely to participate compared to employees hired after 1973, and while the range of cumulative Libby Amphibole asbestos exposure was similar between participants and nonparticipants, participants did have higher mean cumulative exposure estimates. While it is accurate that exposure levels were uncertain before sampling began at Marysville in 1972, it is also accurate that exposures were much lower beginning in 1974, when additional industrial hygiene controls were implemented. Thus, persons hired ≤1973 had higher exposure (if less perfectly measured), while those hired ≥1974 had lower exposure, and likely less disease (under an assumption of an exposure-response effect). Thus, we might assume that the prevalence rates in nonparticipants are likely lower than in participants. The self-selection to participate in the study is dependent on the exposure, thus leading to dependent censoring and potential selection bias (see Section 4.1.3 for a discussion of this potential selection bias). However, Rohs et al. (2008) conducted a sensitivity analysis assuming that all living nonparticipants had no pleural changes and report a similar significant trend of increased pleural changes by exposure quartile. In contrast, participation rates for the Libby worker studies were much higher (see above), and there is no indication of potential bias in selection of these study participants (Amandus et al., 1987b; McDonald et al., 1986b).

Both studies of Libby workers also evaluated age and smoking as potential confounders of the association between Libby Amphibole asbestos exposure and radiographic abnormalities. McDonald et al. (1986b) report that both age and cumulative exposure are significant predictors of small opacities and pleural abnormalities in the study of current and former workers, providing regression coefficients for cumulative exposure, age, and smoking status. Amandus et al. (1987b) report that although cumulative exposure and age are both significant predictors for small opacities, cumulative exposure was not significantly related to pleural abnormalities when age is included in the model, thus limiting the usefulness of these data for RfC derivation based on pleural abnormalities. Neither study of Libby workers addressed gender, body mass index

(BMI), or time from first exposure, although both studies excluded workers with other asbestos/dusty trade occupations.

With respect to the Marysville, OH worker cohort, Lockey et al. (1984) only matched on age in their analysis. The follow-up examination by Rohs et al. (2008) included information on several important covariates, including age, gender, hire date, prior exposure to asbestos, BMI, and smoking history. Hire date and age were significantly associated with the prevalence of pleural abnormalities, and results are presented considering these covariates.

5.2.1.3. *Evaluation of Exposure Assessment in Candidate Studies*

For both the O.M. Scott facility in Marysville, OH and the Libby, MT facilities, exposure estimates rely primarily on fiber counts using phase contrast microscopy (PCM) and reconstruction of earlier exposures from company records, employee interviews, and the professional judgment of the researchers estimating historical exposures (Amandus et al., 1987a; McDonald et al., 1986a; Lockey et al., 1984). Work histories for the Libby worker cohort were extracted from company employment records, while work histories for the Marysville cohort were self-reported.

The two studies of workers in Libby, MT used similar exposure estimation, based on the same fiber measurements and work records (Amandus et al., 1987b; McDonald et al., 1986a). As discussed in Section 4.1.1.2, exposures prior to 1968 are not based on fiber measurements by PCM and, thus, are more uncertain that later exposure estimates.[25] The study population of McDonald et al. (1986b) included current and former workers, with 26% of participants over 60 and 40% of participants between 40–59 years of age at the time of their X-ray in 1983. Although tenure and dates of employment are not reported, exposure estimates for this study group would include the less-certain exposure estimates prior to 1968 (McDonald et al., 1986a). However, Amandus et al. (1987b) studied workers still employed during 1975–1982 (i.e., excluding those terminated prior to 1975) who had at least 5 years of employment. The average tenure of the study participants was 14 years. Although both studies have the limitation of less-certain exposure estimates prior to 1968, based on study design, the Amandus et al. (1987b)

[25] Exposures in the dry mill at Libby, MT, prior to 1967 were estimated from total dust measurements based on site—specific conversion ratios. Exposures for all other location operations prior to 1968 were estimated because no air sampling data were available (Amandus et al., 1987a; McDonald et al., 1986b).

study group includes a greater proportion of more recent workers. However, neither researcher assessed these uncertainties nor the impact of early exposure estimates on the apparent exposure-response relationship.

Another source of uncertainty in exposure estimates for this cohort is possible community/nonoccupational exposures. Members of the Libby worker cohort may have lived in Libby prior to/after employment and resided in Libby and surrounding areas during employment. In both cases, there may have been community exposures to Libby Amphibole asbestos that are not captured in occupational-based cumulative exposure metrics. This unmeasured nonoccupational exposure may be low relative to the estimated occupational exposures, but is, nevertheless, a source of uncertainty in estimating the exposure-response relationship.

The quality of the exposure assessment also changed over time in the Marysville cohort (Rohs et al., 2008; Lockey, 1985). Industrial hygiene measurements based on PCM analysis are available for the O.M. Scott facility beginning in 1972, although personal breathing zone samples were not available until 1976 (Rohs et al., 2008). Thus, exposure levels for all job tasks prior to 1972 are estimates from later sampling events. Additionally, air sampling data were not available for several job tasks until the late 1970s. For example, air-sampling data were only available for two of seven job tasks in the trionizing department beginning in 1973 (expander and dryer). All others have dates of 1976 or later [see Table 10, Lockey (1985)]. The installation of exposure control equipment in 1974 adds to the uncertainty in early exposures estimated from sampling in later years. There is uncertainty when the Libby ore was first used in the facility. Company records indicated that the date was between 1957 and 1960, and the University of Cincinnati used the best-available information from focus group interviews to assign the first usage of Libby ore in 1959 (see Appendix F).

EPA has collaborated with the University of Cincinnati research team to better evaluate historical exposures at the O.M. Scott facility in Marysville, OH (see Appendix F). Although no air-sampling results were found prior to 1972, additional information on plant processes from other records and employee interviews has resulted in updated exposure estimates (see Section 5.2.3.1). These refined estimates of the historical exposure improve exposure characterization for the Marysville worker cohort over previous publications.

5.2.1.3.1. *Evaluation of outcome assessment in candidate studies*

In all four candidate studies, outcomes were assessed using chest radiographs independently evaluated by multiple readers. However, there were differences in the standards used for evaluation of radiographic changes, as well as timing and quality of the radiographs. The two studies in Libby workers (Amandus et al., 1987b; McDonald et al., 1986b) used similar outcome-assessment procedures, with radiographs evaluated by three readers according to 1980 ILO standards. Two different sets of standards were used to evaluate radiographs in the Marysville cohort. The first study used modified 1971 ILO standards (modifications not stipulated) (Lockey et al., 1984), while the follow-up study used the updated 2000 ILO standards (Rohs et al., 2008).

Radiograph quality may also impact outcome assessment. In McDonald et al. (1986b), which used radiographs taken in 1983 specifically for the study, 7% of films were classed as "poor quality" (some technical defect impairing the pneumoconiosis classification) and 0.4% as "unreadable." Amandus et al. (1987b), which used available radiographs taken over a wide time period (1975 to 1982), report that the proportion of films rated as "poor quality" ranged from 14.7% to 22.8% depending on the reader. In the Marysville cohort, Lockey et al. (1984) state that "...radiographs that could not be interpreted because of poor quality were repeated" (p. 953). Rohs et al. (2008) do not report the percentage of films rated as "poor quality" but do note that 7 out of 298 (2.3%) radiographs taken were considered unreadable.

5.2.1.3.2. *Selection of principal cohort*

Based on the criteria set out in Table 5-2 and the above evaluation, the update of the Marysville, OH worker cohort (Rohs et al., 2008) is the preferred cohort. The main advantages of the Marysville, OH worker cohort over the two studies of pleural and lung abnormalities in the workers in Libby, MT are:

1) Adequate follow-up time and the availability of time from first exposure data for evaluation,

2) Minimal exposure to Libby Amphibole asbestos outside of the workplace,

3) Better quality radiographs, and use of the most recent ILO reading guidelines in the cohort update,

4) Data are more appropriate for low-dose extrapolation—a lower range of cumulative exposures for the study participants (n = 280), compared to Libby workers,

5) The data allow consideration of more covariates and potential confounders (e.g., BMI, smoking status, age),

6) The presence of a demonstrated exposure-response relationship for Libby amphibole asbestos exposure and radiographic abnormalities—in contrast to the study by Amandus et al. (1987b), which does not support an exposure-response relationship for pleural abnormalities based on the cumulative exposure metric (when age is included as a covariate).

The disadvantages of the Marysville, OH cohort compared to the two studies of pleural and lung abnormalities in the workers in Libby, MT are:

1) Approximately 70% of the Marysville, OH cohort were hired before 1972 when there were no measured exposure data [Rohs et al. (2008), and Lockey et al. (1984) study].

2) Participants in Rohs et al. (2008) were self-selected, with greater participation among older employees and those who began work prior to 1973 when exposures were relatively higher. This is a potential source of bias in study population selection analyzed by Rohs et al. (see Section 4.1.3).

3) Exposure estimates are based on self-reported work histories. In this case, there is some uncertainty in the employment history, and some individuals had extensive overtime work. Employment history was self-reported during interviews with each individual for the original study (i.e., Lockey et al., 1984), and errors in this process could affect assigned Libby Amphibole asbestos exposure estimates for this cohort.

5.2.1.4. *Selection of Critical Effect*

There are several endpoints that are suitable for consideration for the derivation of an RfC for Libby Amphibole asbestos where health effects data and exposure information are available in the principal study (Rohs et al., 2008; Lockey et al., 1984): (1) parenchymal changes viewed as small opacities in the lung; (2) blunting of the costophrenic angle (measured between the rib cage and the diaphragm); or (3) pleural thickening (both localized and diffuse). Each of these effects is an irreversible pathological lesion (ATS, 2004). As the available epidemiologic

studies describe these endpoints as viewed on standard X-rays (see Text Box 5-1), it is important to understand the distinction between what is viewed on the radiograph versus the underlying biologic lesion. The following discussion reviews the health effects associated with each of these radiographic abnormalities observed in workers exposed to Libby Amphibole asbestos.

Text Box 5-1. Radiographic Abnormalities of the Lung and Pleura

Parenchymal changes in the lung (small opacities): The small opacities viewed within the lung (interstitial changes) are indicative of pneumoconiosis and are associated with exposure to not only mineral fibers, but also mineral dust and silica. The radiographic signs of pneumoconiosis begin as small localized areas of scarring in the lung tissue and can progress to significant scarring and lung function deficits. The ILO standards provide a scheme for grading the severity of the small opacities; the size, shape, and profusion of the small opacities are recorded, as well as the affected zone of the lung (ILO, 2002).

Obliteration of the costophrenic angle: The costophrenic angle (CPA) is measured as the angle between the ribcage and the diaphragm on a posterior anterior-viewed radiograph (the costophrenic recess). When CPA blunting or obliteration is noted on a radiograph, it is recorded as present or absent (ILO, 2002). Obliteration of the CPA may occur in the absence of other radiographic signs.

Pleural thickening: The pleural lining around the lungs (visceral pleura) and along the chest wall and diaphragm (parietal pleura) may thicken due to fibrosis and collagen deposits. Pleural thickening (all sites) is reported as either localized pleural thickening (LPT) or diffuse pleural thickening (DPT). DPT of the chest wall may be reported as in-profile or face on, and is recorded on the lateral chest wall "only in the presence of and in continuity with, an obliterated costophrenic angle" (ILO, 2002). Localized pleural thickening may also be viewed in-profile or face-on and is generally a pleural plaque (parietal). Calcification is noted where present (ILO, 2002).

5.2.2. Evaluation of Radiographic Lesions as Potential Critical Effects

5.2.2.1. *Health Effects of Parenchymal Changes as Small Opacities Viewed on Standard Radiographs*

Radiographic evidence of small opacities in the lung is evidence of fibrotic scarring of lung tissue consistent with mineral dust and mineral fiber toxicity. The scarring of the parenchymal tissue of the lung contributes to measured changes in pulmonary function, including obstructive pulmonary deficits from narrowing airways, restrictive pulmonary deficits from impacting the elasticity of the lung as well as decrements in gas exchange. However, although data across the mineral fiber literature strongly support a finding of functional deficits where small opacities are visible on radiographs, the data also indicate that deficits in pulmonary function (consistent with interstitial fibrosis) are seen before these changes are detected by

radiographic examination. Thus, changes in lung function may occur before the fibrotic lesions can be detected on standard radiographs (ATS, 2004; Broderick et al., 1992). For example, decreased Carbon monoxide (CO) diffusion is a sign of reduced gas exchange in the pulmonary region of the lung and is observed in workers exposed to other types of asbestos even when small opacities are absent on radiographs. Similarly, obstructive deficits in lung function may be observed without radiographic signs for fibrotic lesions of small opacities. As decreased diffusion and obstructive deficits are mechanistically linked to changes in the parenchymal tissue these data suggest radiographs may not be sensitive enough to detect and protect against small localized lesions in parenchymal tissue of the lung. Radiographic evidence of small opacities indicates interstitial damage of the lung paremchyma, is associated with decreased pulmonary function and considered evidence of an adverse health effect. Thus, small opacities are an appropriate endpoint for RfC derivation. However, as there is evidence of functional changes in lung function from lesions not detectable on conventional radiographs, more sensitive endpoints should be considered.

5.2.2.2. *Health Effects of Diffuse Pleural Thickening (DPT) Viewed on Standard Radiographs*

DPT is a fibrotic lesion (often described as a basket weave of collagen) in the visceral pleura that encases each lobe of the lungs. The fibrotic lesion restricts the ability of the lung to expand mechanically, as well as by reducing the available volume (where thickening has progressed) (Jones et al., 1988) and DPT is strongly associated with reduced lung function (ATS, 2004). There are consistent reports of impaired lung function associated with DPT in asbestos-exposed populations (Broderick et al., 1992; Kilburn and Warshaw, 1991; Bourbeau et al., 1990). A cross-sectional study of men (n = 1,298) exposed to asbestos through various trades (e.g., boiler makers, welders, plumbers/pipefitters) included chest radiographs and spirometry (Kilburn and Warshaw, 1991). When considering the effect of DPT (with costophrenic angle [CPA] blunting) on radiographic function, FVC, FEV1, and FEF25-75[26] were all significantly reduced (85, 79, and 66% of predicted values, respectively) as compared with individuals with calcification or plaques only in men with no signs of small opacities (ILO

[26] Forced Vital Capacity (FVC); Forced Expiratory Volume in 1 second (FEV1) and Percent FVC (FEV%) = [(100 × FEV1) ÷ FVC, FEF25-75, is the expiratory flow between 25% and 75% of the FEV.]

profusion score of 0/0 or 0/1) ($p < 0.0001$). The relationship between pleural fibrosis and FVC was studied in asbestos-exposed sheet metal workers ($N = 1,211$) where not only the type of thickening (discrete versus diffuse) (ILO, 1980) but also CPA involvement and the location of the thickening were taken into consideration (Broderick et al., 1992). Univariate analysis indicated FVC was decreased by both DPT (with CPA blunting) and circumscribed thickening, diaphragm involvement, CPA involvement, and the extent of the thickening (Broderick et al., 1992). Multivariate linear regression, allowing for control of potential confounders, found decreased FVC was significantly related to DPT, plaques, CPA involvement, and extent of the thickening, but not diaphragmatic involvement (Broderick et al., 1992).

The mechanisms for reduced lung volume in individuals with asbestos-related DPT have been examined by measuring lung function and changes in diaphragm length, rib-cage dimensions, and subphrenic volume in 26 patients during breathing (Singh et al., 1999). DPT reduced both total lung capacity and FVC with corresponding decreases in rib-cage expansion and movement of the diaphragm, consistent with the restrictive nature of these lesions, which may encase part of the lung (Singh et al., 1999). These direct measurements of the effect of DPT chest wall and diaphragmatic motion illustrate the role of DPT in reducing lung volume, contributing to restrictive deficits in pulmonary function. Taken together, the epidemiologic evidence and the mechanistic information that support a restrictive effect of fibrotic lesion in the visceral pleura, substantiate the associations between DPT and decreased pulmonary function. As such, the observation of DPT on standard radiographs is representative of pathological changes directly related to reduced lung function and is, therefore, an indication of adversity, and, can serve as an appropriate health endpoint for consideration in RfC derivation.

5.2.2.3. *Health Effects of Localized Pleural Thickening (LPT) Viewed on Standard Radiographs*

Localized pleural thickening (LPT) viewed on a standard radiograph may include both pleural plaques and pleural thickening that does not involve blunting of the costophrenic angle (ILO, 2002). Thus, both parietal plaques and localized thickening of the visceral pleura may be designated as LPT. Thickening of the parietal pleura is due to an acellular collagen plaque (basket weave of collagen fibers) between the parietal pleura and the ribcage (or along the diaphragm) often described as discrete or circumscribed pleural plaques (ATS, 2004; Jones,

2002). Thickening of the visceral pleural is a fibrosis with diffuse borders and may extend into the lung parenchyma (ATS, 2004; Jones, 2002). The pathology and health effects of the different lesions are evaluated here in the characterization of the health significance of LPT.

Costal parietal plaques occur between the thoracic cage and parietal pleura, which is normally adherent to the thoracic cage (ATS, 2004; Jones, 2002). Costal parietal plaques have been described as collagen deposits with ragged irregular edges and up to 1 cm in depth and may be calcified. These parietal plaques have been associated with constricting pain in the thoracic cavity (Mukherjee et al., 2000). The parietal pleura is well innervated by the intercostal and phrenic nerves and is considered very sensitive to painful stimuli (Jones, 2002). With respect to parietal plaques, pain during exertion or exercise could result in restrained chest wall motion during exertion or exercise. Thus, Bourbeau et al. (1990) hypothesized that the dyspnea and changes in pulmonary function noted in individuals with pleural plaques may be due to physical irritation and perhaps a constricting action where parietal plaques are well progressed or numerous and impact a large proportion of the parietal surface.

Kouris et al. (1991) examined the presence of dyspnea, and measures of pulmonary function (i.e., FVC, FEV1, and FEV%[27]) in asbestos-exposed workers ($n = 913$) in relation to radiographic signs of lung and pleural anomalies. Radiographs were contemporary to the study and read in accordance with ILO (1980) guidelines. Pleural plaques were associated with reduced FVC and FEV1.0 (87.6% and 84.1% of predicted, respectively, $p < 0.0005$), although deficits associated with diffuse thickening were greater (76.4% and 73.9%, $p < 0.0005$) (Kouris et al., 1991). Correspondingly odds ratios for decreased FVC and FEV1.0 (80% decrement) were increased by the presence of both plaques and diffuse thickening (1.5 for plaques and 4.2 and 4.7 for diffuse thickening, respectively). Interestingly, when history of lung disease was considered, pleural plaques had a greater effect in individuals without previous lung disease (OR of 2.1 for FVC and 1.7 for FEV1.0).

Pleural thickening in general is associated with decreased pulmonary function (Petrovic et al., 2004; Wang et al., 2001; Miller et al., 1994)and this association is strengthened as the severity of the pleural thickening increases (Lilis et al., 1991). Few available studies have examined the relationship between pleural plaques identified on standard radiographs (ILO,

[27]Forced Vital Capacity (FVC); Forced Expiratory Volume in 1 second (FEV1) and Percent FVC (FEV%) = [(100 × FEV1) ÷ FVC].

1980) and pulmonary function without including DPT in the analysis and adequately controlling for the presence of small opacities (indicative of parenchymal damage)[28].

Lilis et al. (1991) examined pulmonary function in long-term asbestos insulation workers, and found that one measure (FVC) decreased significantly as the severity of pleural fibrosis (all types, as indicated by a pleural index) increased. This decrease was more dramatic when including parenchymal changes (small opacities) or if DPT was viewed separately. A second analysis focusing on participants with pleural plaques found an inverse relationship between severity of the pleural plaques and FVC ($p < 0.0001$), when adjusting for the independent effects of duration, smoking and presence of small opacities (Lilis et al., 1991). This finding supports a view that pleural plaques, when extensive, may contribute to restrictive lung deficits, but the analysis included individuals with known small opacities (e.g., lung fibrosis). The authors do not address the potential that the pleural index may also correspond to increased severity of parenchymal changes, potentially confounding the analysis where accounting for small opacities (profusion scores of 1/0 or greater) may not adequately control for asbestos-related parenchymal damage.

Oliver et al. (1988) studied the relationship between pulmonary function and pleural plaques in asbestos-exposed railway workers ($n = 383$). Case selection included exclusion of workers with DPT (ILO, 1980) and exclusion of any indication of small opacities (only profusion scores of 0/0 were included). Standard spirometry was conducted to evaluate restrictive and obstructive pulmonary deficits. Additionally, single-breath diffusing capacity (DLCO) was measured which would indicate parenchymal defects. The DLCO was similar in subjects with and without circumscribed plaques, suggesting little or no subradiographic parenchymal damage, which corresponded to the presence of pleural plaques. Pleural plaques were associated with both decreased FVC and pulmonary restriction ($p = 0.03$ and 0.04, respectively) where the diagnostic certainty for the plaques was considered 'definite', and there was an association between level of diagnostic certainty and these pulmonary deficits ($p = 0.02$) (Oliver et al., 1988). Quantitative pleural score, based on the number and extent of plaques, was

[28]It is difficult to control for effects subradiographic parenchymal fibrosis on lung function, where it may not have progressed to visible small opacities, and it has been suggested that reduced lung function, which has been associated with circumscribed plaques in some studies, may be reflecting the effects of subradiographic parenchymal changes, rather than a direct effect of DPP (ATS, 2004; Erdinç et al., 2003; Miller and Zurlo, 1996; Broderick et al., 1992).

also associated with decreased FVC and pulmonary restriction ($p = 0.0135$ and 0.0126, respectively) (Oliver et al., 1988). Of the available studies that assess pleural thickening with standard radiographs, this study best controls for the possibility of subradiographic parenchymal damage and is, therefore, strong evidence that circumscribed pleural plaques independently impact pulmonary function. The observed restrictive pulmonary deficit is consistent with the potential for pleural plaques to restrict chest wall motion or the elasticity of the diaphragm.

Three high-resolution computed tomography (HRCT) studies were conducted specifically to assess the potential for parietal plaques to impact lung function. Staples et al. (1989) report no difference in lung function or diffusing capacity between participants ($n = 76$) with and without pleural plaques. Soulat et al. (1999) found no difference in FEV1 or FVC between asbestos-exposed insulators with ($n = 84$) and without ($n = 51$) pleural plaques in the absence of any parenchymal changes. As severity of pleural thickening has been shown to be positively associated with decrease measures of pulmonary function, Van Cleemput et al. (2001) not only examined the effect of HRCT defined pleural plaques on pulmonary function, but also assessed the extent of the pleural plaques. Neither the presence nor extent of pleural plaques were associated with lung function parameters (diffusing capacity or normalized spirometric values) (van Cleemput et al., 2001). Where pleural plaques and diffuse thickening (visceral pleura) were both identified by HRCT and correlated to pulmonary function, diffuse visceral thickening—but not plaques—were associated with decreased lung volume and FVC (Copley et al., 2001). Although CPA involvement was not independently assessed, several scoring systems for severity were compared which included CPA involvement, and as in other studies, increased severity correlated to greater decrements.

The mechanisms for reduced lung volume in individuals with asbestos-related pleural plaques and DPT have been examined by measuring lung function and changes in diaphragm length, rib-cage dimensions and subphrenic volume in 26 patients during breathing (Singh et al., 1999). Pleural plaques alone did not reduce any of the measures of lung function in this study, but there were indications of reduced diaphragm movement (Singh et al., 1999). This may be an indication that diaphragmatic plaques in the parietal pleura have the potential to attenuate the movement of the diaphragm during breathing. Because this study is relatively small ($N = 26$) and a distinction was not made between costal and diaphragmatic plaques by the study authors,

additional work is needed to better understand the direct effects of pleural plaques on lung function.

Although some researchers have questioned that pleural plaques alone directly impact pulmonary function, a critical review of the literature from 1965-1999 concludes: "1) Individuals with asbestos-induced pleural plaques may have alterations in pulmonary function and /or clinical symptoms that are independent of smoking and radiographic parenchymal fibrosis and, 2) the respiratory changes dues to asbestos-induced pleural plaques are generally less severe than those caused by pleural thickening" (Rockoff et al., 2002). Therefore, although the evidence is mixed, pleural plaques may be independently associated with reduced pulmonary function.

No studies correlating pulmonary function to radiographic signs of localized pleural thickening (LPT) using the ILO (ILO, 2002) guidelines could be located. However, several researchers employed similar classification schemes, modifying earlier ILO classification systems, such that DPT was diagnosed only in conjunction with blunting of the CPA. This modification potentially includes cases of diffuse pleural thickening (without CPA blunting) in their analysis of pleural plaques, making their findings somewhat applicable to the current classification of LPT (García-Closas and Christiani, 1995; Broderick et al., 1992). Pleural thickening (without CPA blunting) was associated with mixed respiratory impairment in a study of asbestos-exposed construction carpenters (n = 631) (OR of 3.7 [95% Confidence Interval (CI): 1.4–12.3]) but was only weakly associated when the outcome was restrictive deficit specifically (1.3 [95% CI: 0.4–3.9]) (García-Closas and Christiani, 1995). Broderick et al. (1992) found decreased FVC was not only significantly associated with "diffuse thickening" (with CPA blunting) but also with "pleural plaques" (which included all pleural thickening without CPA blunting). The severity of pleural thickening (both as width or percentage of lateral wall) and calcification was associated with reduced FVC as well (Broderick et al., 1992). Kilburn and Warshaw (1991) assessed pulmonary function in individuals with "plaques only," "diffuse thickening only," and "diffuse thickening with CPA blunting," showing progressive deficits across these categories in FVC, FEV1, and mid-expiratory flow (e.g., FEV1: 90.5, 86.2, and 49.4% [$p < 0.05$], respectively). Again, there is a trend that diffuse thickening has a greater impact on lung function parameters, although an independent effect of plaques cannot be ruled out by these data.

In summary, the radiographic classification of localized pleural thickening (LPT) under current ILO guidelines may include both parietal plaques (in the pleura lining the interior of the ribcage) and diffuse visceral thickening (without CPA obliteration) (ILO, 2002). The two lesions (parietal plaques and localized visceral thickening) are distinct and may contribute independently to observed health effects. Parietal plaques are known to induce chronic constricting chest pain that increases in severity as the extent of the plaques increases. Pleural thickening in general is associated with reduced lung function parameters with increased effect correlating with increased severity of the pleural thickening (Petrovic et al., 2004; Wang et al., 2001; Miller et al., 1994; Lilis et al., 1991). There is clear evidence from HRCT studies that the presence and extent of visceral thickening does impair lung function, although, when evaluated independently, parietal plaques were not statistically correlated with decreased pulmonary function (Copley et al., 2001; Schwartz et al., 1993). Specifically considering the designation of LPT, lung function impairment has been demonstrated in several studies where pleural thickening without CPA involvement has been studied (García-Closas and Christiani, 1995; Broderick et al., 1992; Kilburn and Warshaw, 1991). Thus, the radiographic classification of localized pleural thickening (LPT) (ILO, 2002) includes pleural lesions associated with chronic chest pain, decreased lung volume, and decreased measures of lung function. Therefore, EPA considers LPT an adverse effect and an appropriate endpoint for RfC derivation.

5.2.3. Methods of Analysis

5.2.3.1. *Exposure Data and Choice of Exposure Metric*

EPA collaborated with a research team at the University of Cincinnati to update the exposure reconstruction for use in the job-exposure matrix (JEM) for all workers in the Marysville, OH cohort, taking into account additional industrial hygiene data that were not available for previous studies conducted in this cohort. As discussed in detail in Appendix F, exposure estimates for each worker in the O.M. Scott Marysville, OH plant were developed based on available industrial hygiene data from the plant. Figure 5-1 shows the average exposure concentrations of fibers in air (PCM fibers/cc)[29] of each department from 1957 to 2000,

[29]PCM, where fibers are viewed and counted by light microscopy, does not identify the composition of the fiber. Thus, the mineralogy of fibers identified under PCM cannot be determined.

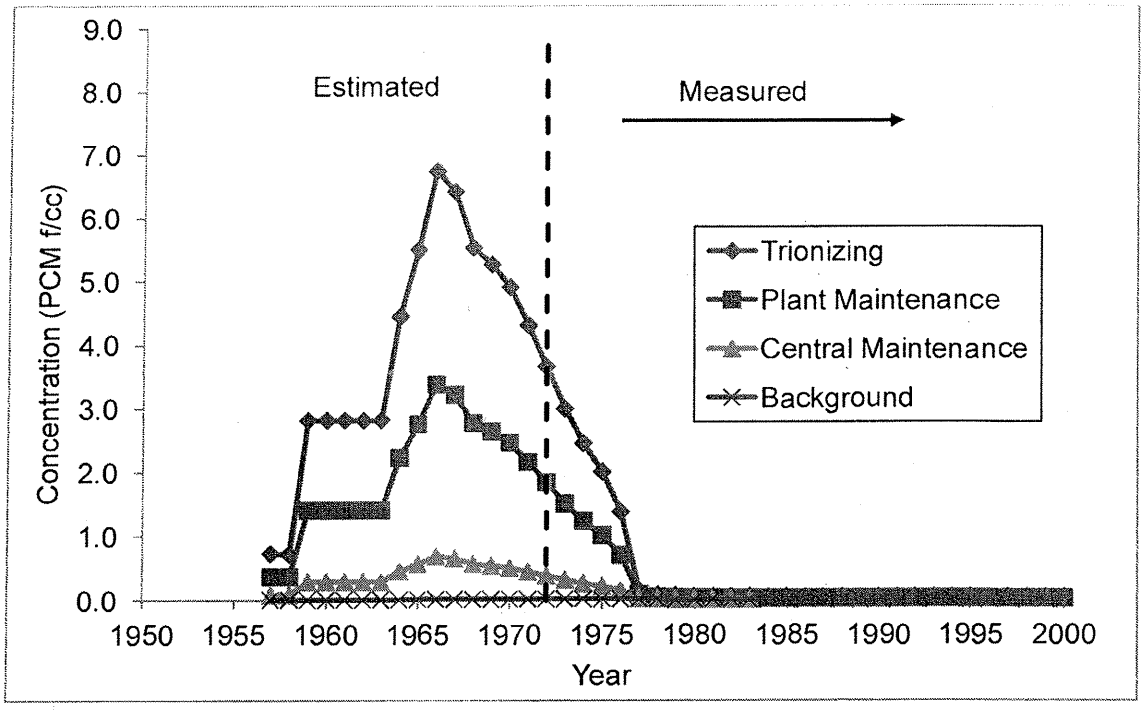


Figure 5-1. Estimated and measured exposure concentrations in Marysville, OH facility[a]

[a]Trionizing is a term used in the Marysville, OH facility and includes unloading of rail cars containing vermiculite ore (track), using conveyers to move the vermiculite ore into the expander furnaces, separation of the expanded vermiculite from sand, blending in of lawn care chemicals, and drying and packaging of the final product. As no unexpanded ore was used in pilot plant, research, polyform, office, packaging, or warehouse, jobs in these categories were assigned as background. Workers assigned to plant maintenance activities spent 50% of their time in trionizing areas and 50% of their time in areas assigned as plant background. Workers assigned to central maintenance spend 10% of their time in trionizing areas and 90% of their time in areas assigned as plant background. Central maintenance jobs were eliminated in 1982 and contracted out (see Appendix F).

indicating the time periods when fiber measurements were not available ('Estimated') and were available ('Measured').

In brief, the starting point for the JEM was the measured or estimated concentration of fibers in air (fibers/cc) of each department from 1957–2000. The distribution of exposure by department is summarized in Figure 5-1. Using available data on the year of hire and the departments in which each person worked, the cumulative exposure (fibers/cc-year) for each worker for each year since the date of hire was estimated. Each worker's cumulative exposure was then adjusted to a cumulative human equivalent exposure for continuous exposure (CHEEC; fibers/cc-year) to represent exposure 24 hours/day and 365 days/year (assuming that any exposure off site was zero) for the full duration of employment. Adjustments for different inhalation rates in working versus nonworking time periods were incorporated in this analysis. The calculated value is similar to what EPA usually refers to as continuous human equivalent exposure (U.S. EPA, 1994b). These calculations are somewhat more complex than the usual conversions to equivalent continuous exposure concentrations that EPA makes in the analysis of occupational studies. Conversions for noncancer effects are usually made using an adjustment factor of 240 days ÷ 365 days × 10 m^3 ÷ 20 m^3 (U.S. EPA, 1994b). However, the adjustment factor in this current assessment takes into account the extensive seasonal overtime for some job codes at the Marysville facility, as well as other annual periods when work hours were reduced (see Appendix F). The estimated CHEEC was used to represent Libby Amphibole asbestos exposure in all subsequent analyses because it combines aspects of both intensity of exposure and duration of exposure.[30] For Libby Amphibole asbestos, the exposure metric is calculated as cumulative exposure (fibers/cc-year). Cumulative exposure is a commonly evaluated exposure metric in occupational studies, especially for mineral fibers, where fiber retention may be relevant to toxicity. It should be noted that discrete parietal plaques have often been associated with other exposure metrics (e.g., mean exposure, TSFE) (i.e., Paris et al., 2008; Jakobsson et al., 1995; Ehrlich et al., 1992; Copes et al., 1985). Paris et al. (2008) show significant exposure-response relationships for both mean and cumulative exposure metrics for pleural plaques (identified by HRCT) among workers with mixed fiber exposures, when accounting for age, smoking, and TSFE. Mean exposure provided a better overall fit (Paris et al., 2009). Thus, EPA has conducted an uncertainty assessment for the RfC derivation from the sub-cohort by also

[30]The University of Cincinnati used the term CHEEC in its report (see Appendix F).

exploring alternative methods to weight the $BMCL_{10}$ in units of cumulative exposure, to represent the average exposure needed for RfC derivation (see Section 5.3.7).

Because localized pleural thickening does not generally occur immediately after exposure and requires some time to develop to the state that it can be detected on a conventional chest X-ray, exposures that occur close to the time of X-ray may not contribute to the occurrence of observable disease and may obscure the exposure-response relationship. Accordingly, a lagged exposure (i.e., cumulative exposure discounting the most recent time period) may be the most appropriate measure to use. Therefore, exposure estimates with various lags were investigated (lags of 0, 5, 10, 15, and 20 years). For example, a CHEEC value based on a lag of 5 years excludes all exposures that occurred within 5 years of the date of X-ray. Looking at the occurrence of the outcome for various categories of time elapsed since first exposure, the first localized pleural thickening was detected ~10 years after the first exposure.

5.2.3.2. *Data Sets for Modeling Analyses*

The individual health outcome data for all workers who participated in the Lockey et al. (1984) study and the follow-up study by Rohs et al. (2008) were used for exposure-response modeling. To avoid any bias from previous occupational exposure to asbestos, only the data from those who did not report any previous occupational exposure to asbestos were used. The data from Lockey et al. (1984) and Rohs et al. (2008) were combined for the full cohort to provide a greater range in time from first exposure (described below). Outcome assessments, i.e., chest X-rays, were performed at two different time points, 1980 and 2002–2005. While the evaluation approaches were generally similar (independent readings by three certified B-readers), it is important to note that X-ray readings were performed by different individuals, under a different reading protocol in 1980 (modified 1971 ILO standards) compared to 2000s [ILO (2002) standards], leading to some uncertainty in statistical analyses that combine these data sets. An additional consideration is human body composition—in some cases, difficulty in distinguishing fat pads from true pleural thickening may lead to misclassification of the outcome. BMI measurements are available for the latter study but not for the 1980 evaluation; the effect of BMI was investigated and is discussed below.

Radiographs were evaluated by two B-readers with a consensus evaluation by a third reader in the case of disagreement in the original study by Lockey et al. (1984). In the follow-up

by Rohs et al. (2008), a radiographic reading was considered positive "when the median classification from the three independent B readings was consistent with pleural and/or interstitial changes" (p. 631). Because the ILO criteria were updated in 2000, the reader forms from Lockey et al. (1984) showing pleural changes were evaluated for consistency with the ILO 2000 criteria. This reevaluation did not result in any change in the diagnosis for any individual from the 1980 reading.[31] In addition, no difference in reported X-ray quality was noted between the Lockey et al. (1984) data and the follow-up by Rohs et al. (2008).

The full data set of the exposure-response relationship for localized pleural thickening was as follows. The radiographic data from Lockey et al. (1984) ($n = 513$) and Rohs et al. (2008) ($n = 280$), were combined for a total of 793 X-ray evaluations (this includes repeated X-rays on the same individual). X-rays obtained from workers who reported exposure to asbestos at other locations were excluded from consideration ($n = 793 - 105 = 688$ X-ray evaluations).

For workers who were X-rayed in both Lockey et al. (1984) and Rohs et al. (2008), one of the observations was excluded so that there were no repeat observations for individual workers in the data set used for modeling. For workers who were negative for localized pleural thickening in Lockey et al., the (1984) study data were excluded, and the Rohs et al. (2008) data were retained. For workers who were positive for localized pleural thickening in Lockey et al. (1984) and also in Rohs et al. (2008), the 1984 study data were retained. One worker was positive in 1984 and negative in 2008 (removing this worker from the analysis did not change results). The 2008 study data were retained for this worker. This procedure resulted in $n = 688$ X-rays − 252 duplicates = 436 X-rays, representing 436 individual workers.

Two workers from Lockey et al. (1984) were excluded because the start day and the X-ray date were the same ($n = 436 - 2 = 434$). For each worker, the estimated cumulative exposure corresponded to the date of the X-ray retained for analysis—if the 1980 X-ray was used, the individual's cumulative exposure estimate covered the period from start of work through the X-ray date in 1980. If the 2002–2005 X-ray was used, cumulative exposure covered the period from start of work through the date of job stop or 2000, whichever occurred earlier.

[31]Personal communication (e-mail) from Dr. James Lockey, University of Cincinnati, to Dr. Robert Benson in March 2011 reports that a review of the 1980 B-reader forms using the ILO 2000 guidelines would not result in changes in individual diagnosis for study participants.

The Marysville cohort data comprise 434 workers who were not previously exposed to asbestos and had at least one X-ray observation. Because the concentration of Libby Amphibole asbestos in workplace air was estimated rather than measured for all years prior to 1972, this data set was stratified into two subsets: (1) workers hired in 1972 or after (for whom all exposure values are measured), and (2) workers hired before 1972 (for whom some of the exposure values are estimated). Distributions of cases and TSFE (T) at each outcome assessment are shown in Table 5-3.

Table 5-3. Distribution of cases and time from first exposure (T) for cohort of Marysville workers

	All participants[a]		First exposed before 1972		First exposed 1972 or later	
	Cases/Total	**Range of T**	**Cases/Total**	**Range of T**	**Cases/Total**	**Range of T**
Examined 1980 (Lockey et al., 1984)	5/434	0.42–23.43	4/236	8.75–23.43	1/198	0.42–8.42
Examined 2002–2005 (Rohs et al., 2008)	57/252	23.14–47.34	45/133	31.07–47.34	12/119	23.14–32.63
Marysville cohort (n = 434, examination in either 1980 or 2002–2005)	61/434	0.42–47.34	48/236	8.75–47.34	13/198	0.42–32.63

[a]The 252 individuals examined in 2002–2005 were also examined in 1980. Note that there were originally 513 individuals in the Lockey et al. (1984) cohort; of these, 77 had previous asbestos exposure and were excluded (n = 436). Two individuals were excluded because their X-ray date was the same as their employment start date (n = 434). These exclusions are also reflected in the Rohs et al. (2008) cohort.

Source: Rohs et al. (2008) and Lockey et al. (1984).

The more accurate exposure data are considered to be those from 1972 and later, as these data were based on analytical measurements. Due to the longer follow-up time and additional covariate information, the most informative outcome data come from the 2002–2005 examination. Based on these considerations, a sub-cohort of the Marysville workers, which includes data from workers in the 2002–2005 examination, and who began work in 1972 or later

(12 cases of localized pleural thickening and 106 unaffected individuals[32]) (Rohs et al., 2008), was chosen as the preferred analysis to develop a point of departure (POD) for localized pleural thickening to serve as the basis for the RfC. Additionally, sample POD estimates based on statistical analyses of results from the full cohort [Lockey et al. (1984) and Rohs et al. (2008) combined, as described above] were included for comparison.

5.2.3.3. *Statistical Modeling of the Sub-cohort*

EPA performed analyses of study results for the sub-cohort whose exposures began on or after 1/1/1972 when workplace PCM measurements were available, reducing uncertainties associated with exposure assessment. Localized pleural thickening (LPT), as diagnosed from a standard radiograph (ILO, 2002), was selected as the critical effect based on the health effects associated with pleural thickening specific to this diagnosis (see Section 5.2.2.3). Alternative critical effects were not considered for the sub-cohort analysis given the limited number of cases (one case of DPT and no cases of small opacities). Epidemiologic methods were used to analyze the exposure-response data, and benchmark concentration (BMC) methodology was used to estimate PODs. In this approach, the available data are fit to a set of mathematical exposure-response models to determine an appropriate empirical representation of the data. General model fit is evaluated to determine whether the model form appropriately represents the data; here, this was done using the Hosmer-Lemeshow test (a form of the Pearson χ^2 goodness-of-fit statistic). Among models with adequate general fit, a recommended model form is then determined; commonly, this is the model with the best fit as measured by Akaike's Information Criterion (AIC) value among these model forms judged to provide an appropriate and statistically adequate representation of the data. For inhalation data, the BMC is defined as the exposure level, calculated from the best-fit model, which results in a specified benchmark response (BMR). The RfC is derived from the lower 95% confidence limit of the BMC, referred to as the BMCL, which accounts for statistical uncertainty in the model fit to the data. All

[32]There was one individual whose radiographic examination indicated diffuse pleural thickening, who was excluded from further analyses of the preferred sub-cohort. Diffuse pleural thickening represents a more severe outcome than the selected critical effect of LPT—including this individual as a case would not be appropriate given that the critical effect is selected to represent a most sensitive endpoint, and the subsequent selection of a benchmark response in modeling efforts. Diffuse pleural thickening is considered separately as an endpoint (with appropriate benchmark response) in sensitivity analyses of alternative outcomes in the larger group of workers examined in 2002–2005 (see Section 5.3.8).

analyses were performed using SAS® statistical software v. 9.1. BMCLs were obtained by the profile likelihood method as recommended by Crump and Howe (1985) using the NLMIXED (nonlinear mixed modeling) procedure in SAS (Wheeler, 2005) (see Appendix E for details).

For models where a background parameter is included, a 1% risk of localized pleural thickening was assumed. Establishing a background rate for LPT prevalence is problematic for several reasons. Little data exist to define background rates for LPT, as this designation is more recent, and the majority of the published data use earlier ILO guidelines, which define discrete pleural plaques (DPP). Secondly, it is difficult to define a population without exposure to asbestos in any setting. As environmental and community exposures can increase pleural thickening (Weill et al., 2011; Luo et al., 2003; Hiraoka et al., 1998; Zitting et al., 1996) the question arises, Is there a true background rate? Also, in general, pleural thickening increases with both age and TSFE in a population. There is a study that reports the LPT in Libby community members with no reported pathways of exposure (Weill et al., 2011). LPT prevalence is reported at 0.4% in participants age 25–40, and 1.4% in participants age 41–50 (based on X-rays taken in 2000). Older study participants (61–90) had a LPT prevalence of 12.7%, likely influenced by high historical exposures, as well as the increased TSFE. In two studies of persons not known to be previously exposed to asbestos, Anderson et al. (1979) and Castellan et al. (1985) report DPP estimated prevalence of 1.2% (4/326) and 0.2% (3/1,422), respectively. In cross-sectional studies, which may include persons with occupational exposure to asbestos, Rogan reported DPP prevalence estimates of 1.2% in the National Health and Nutrition Examination (NHANES) I study (1971–1975) (Rogan et al., 1987) and 3.9% in the NHANES II study (Rogan et al., 2000). Among military populations, two studies have reported an estimated DPP prevalence of 2.3% (Muller et al., 2005; Miller and Zurlo, 1996). Based on these reports, the 1% background rate was chosen as representing the prevalence among persons without occupational exposure to asbestos in the age range of the Rohs et al. (2008) study population. As there is some uncertainty regarding the true background rate for LPT, a sensitivity analysis was performed where the model includes the background rate as an estimated parameter rather than using the set value of 1%. There was little change in the resulting model fits or BMCLs (see Section 5.3.4).

In the absence of agent-specific information to assist in identifying a BMR, a 10% extra risk was judged to be a minimally biologically significant level of change, and is also

recommended for standard reporting purposes (U.S. EPA, 2000a). LPT is an irreversible pathological change and associated with health effects including chronic pain, dyspnea, and deficits in pulmonary function (see Section 5.2.2.3). The likelihood and severity of these health effects increases with increased extent and severity of the pleural thickening. However, as the data from the critical study do not provide information on the severity of the lesions, we cannot assess the relative likelihood of any of these health effects. Thus, the observed LPT prevalence may include a range of lesions from minimally adverse to severe. The biology of more severe lesions (i.e., DPT and small opacities) could justify lower BMRs; however, there are not enough cases to model these endpoints in this sub-cohort. A sensitivity analysis was conducted using the data set included in Rohs et al. (2008) to examine the impact of choice of BMR and critical effect on the POD (see Section 5.3.8).

5.2.3.3.1. *Statistical model evaluation and selection*

Dichotomous statistical models describing the probability of individual response as a function of cumulative exposure (represented by CHEEC in units of fibers/cc-year) were used. In order to investigate the key explanatory variables for analysis, a forward-selection process was used to evaluate the association of each of the potential covariates with the risk of localized pleural thickening, controlling for Libby Amphibole asbestos exposure. Covariates considered for inclusion in the model were TSFE (T), age at X-ray, gender, smoking history, and BMI. This initial modeling was done using a standard logistic regression model, as is commonly applied in analysis of epidemiological data. The base model was a logistic regression model with cumulative Libby Amphibole asbestos exposure (natural log transformed) as the independent variable. This model provided an adequate fit to the data (Hosmer-Lemeshow p-value of 0.64), and the exposure variable was statistically significantly associated with the outcome (beta = 0.5676, standard error, [SE] = 0.2420 increase in log odds for every unit increase in CHEEC, p-value = 0.02). Covariates were evaluated according to whether inclusion of the covariate improved model fit as assessed by the AIC, and statistical significance of the covariate. When controlling for Libby Amphibole asbestos exposure, none of these covariates were associated with odds of localized pleural thickening: T: p-value = 0.89; age at X-ray: p-value = 0.77; gender: p-value = 0.78; smoking history: p-value = 0.17; BMI: p-value = 0.41. The inclusion of each of the covariates with the exception of smoking increased the AIC for the

APPENDIX C – 7

http://www.epa.gov/risk/health-risk.htm

EPA United States Environmental Protection Agency

Risk Assessment

Human Health Risk Assessment

Introduction

A human health risk assessment is the process to estimate the nature and probability of adverse health effects in humans who may be exposed to chemicals in contaminated environmental media, now or in the future.

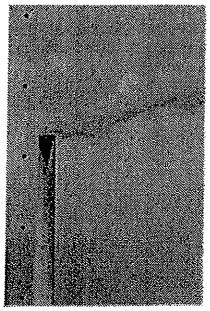
To explain this better, a human health risk assessment addresses questions such as:

- What types of health problems may be caused by environmental stressors such as chemicals and radiation?
- What is the chance that people will experience health problems when exposed to different levels of environmental stressors?
- Is there a level below which some chemicals don't pose a human health risk?
- What environmental stressors are people exposed to and at what levels and for how long?
- Are some people more likely to be susceptible to environmental stressors because of factors such as age, genetics, pre-existing health conditions, ethnic practices, gender, etc.?
- Are some people more likely to be exposed to environmental stressors because of factors such as where they work, where they play, what they like to eat, etc.?

The answers to these types of questions helps decision makers, whether they are parents or public officials, understand the possible human health risks from environmental media.

How does EPA conduct a Human Health Risk Assessment?

Human health risk assessment includes 4 basic steps, and is generally conducted following various EPA guidance documents.



Planning - Planning and Scoping process
EPA begins the process of a human health risk assessment with planning and research.

Step 1 - Hazard Identification
Examines whether a stressor has the potential to cause harm to humans and/or ecological systems, and if so, under what circumstances.

Step 2 - Dose-Response Assessment
Examines the numerical relationship between exposure and effects.

Step 3 - Exposure Assessment
Examines what is known about the frequency, timing, and levels of contact with a stressor.

Step 4 - Risk Characterization
Examines how well the data support conclusions about the nature and extent of the risk from exposure to environmental stressors.

Why does EPA evaluate whether children may be at greater health risks than adults?

Almost 500 years ago Paracelsus (1493-1541) wrote: "Dosis facit venenum" or "the dose makes the poison." The relationship between dose and response (health effect) is still one of the most fundamental concepts of toxicology - or is it? For pollutants that act as developmental toxicants, the same dose that may pose little or no risk to an adult can cause drastic effects in a developing fetus or a child. Methyl mercury is but one example of a chemical that is much more toxic early in life. Scientists have become increasingly aware that children may be more vulnerable to environmental exposures than adults because:

their bodily systems are developing;
they eat more, drink more, and breathe more in proportion to their body size; and
their behavior, such as crawling and hand-to-mouth activity, can expose them more to chemicals and microorganisms.

In light of what is now known about the greater susceptibility early in life to some stressors, Executive Order 13045 -- Protection of Children from Environmental Health Risks and Safety Risks -- was issued in 1997. This Executive Order directs that all federal agencies, including EPA, shall make it a high priority to identify and assess environmental health risks and safety risks that may disproportionately affect children; and shall ensure that their policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks or safety risks.

Note: To assist scientists in assessing risks specifically to children, EPA has developed A Framework for Assessing Health Risk of Environmental Exposures to Children along with specific guidance to risk assessors including Guidance on Selecting Age Groups for Monitoring and Assessing Child-Hood Exposures to Environmental Contaminants and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens.

Last updated on Tuesday, July 31, 2012

EPA United States Environmental Protection Agency

Risk Assessment

Basic Information

Before finding out about risk assessment there are some fundamental principles you need to understand:

What is risk? What is a stressor?

While there are many definitions of the word risk, **EPA considers risk to be the chance of harmful effects to human health or to ecological systems** resulting from exposure to an environmental stressor.

A stressor is any physical, chemical, or biological entity that can induce an adverse response. Stressors may adversely affect specific natural resources or entire ecosystems, including plants and animals, as well as the environment with which they interact.

What is risk assessment?

EPA uses risk assessment to characterize the nature and magnitude of health risks to humans (e.g., residents, workers, recreational visitors) and ecological receptors (e.g., birds, fish, wildlife) from chemical contaminants and other stressors, that may be present in the environment. Risk managers use this information to help them decide how to protect humans and the environment from stressors or contaminants. Note that "risk managers" can be:

- federal or state officials whose job it is to protect the environment,
- business leaders who work at companies that can impact the environment, or
- private citizens who are making decisions regarding risk.

At EPA, environmental risk assessments typically fall into one of two areas:

- Human Health
- Ecological

Risk assessment is, to the highest extent possible, a scientific process. In general terms, risk depends on the following factors:

- How much of a chemical is present in an environmental medium (e.g., soil, water, air),
- How much contact (exposure) a person or ecological receptor has with the contaminated environmental medium, and
- The inherent toxicity of the chemical.

Following a planning and scoping stage where the purpose and scope of a risk assessment is decided, the risk assessment process usually begins by collecting measurements that characterize the nature and extent of chemical contamination in the environment, as well as information needed to predict how the contaminants behave in the future. Here are some useful links to get started:

- EPA's Guidance on Planning and Scoping
- Planning a human health risk assessment
- Planning an ecological risk assessment

Based on this, the risk assessor evaluates the frequency and magnitude of human and ecological exposures that may occur as a consequence of contact with the contaminated medium, both now and in the future.

This evaluation of exposure is then combined with information on the inherent toxicity of the chemical (that is, the expected response to a given level of exposure) to predict the probability, nature, and magnitude of the adverse health effects that may occur. In the ideal world, all risk assessments would be based on a very strong knowledge base (i.e., reliable and complete data on the nature and extent of contamination, fate and transport processes, the magnitude and frequency of human and ecological exposure, and the inherent toxicity of all of the chemicals). However, in real life, information is usually limited on one or more of these key data needed for risk assessment calculations. This means that risk assessors often have to make estimates and use judgment when performing risk calculations, and consequently all risk estimates are uncertain to some degree. For this reason, a key part of all good risk assessments is a fair and open presentation of the uncertainties in the calculations and a characterization of how reliable (or how unreliable) the resulting risk estimates really are.

Developing a risk assessment is often an iterative process, which involves researchers identifying and filling data gaps in order to develop a more refined assessment of the risk. This in turn may influence the need for risk assessors and risk managers to refine the scope of the risk assessment further triggering the need for more data or new assumptions.

What is risk management?

As described in EPA's Risk Characterization Handbook (PDF) (89 pp, 8.9MB, about PDF), "Risk Management" is the process which evaluates how to protect public health. Examples of risk management actions include deciding how much of a substance a company may discharge into a river; deciding which substances may be stored at a hazardous waste disposal facility; deciding to what extent a hazardous waste site must be cleaned up; setting permit levels for discharge, storage, or transport; establishing national ambient air quality standards; and determining allowable levels of contamination in drinking water.

Risk assessment provides "INFORMATION" on potential health or ecological risks, and risk management is the "ACTION" taken based on consideration of that and other information, as follows:

- Scientific factors provide the basis for the risk assessment, including information drawn from toxicology, chemistry, epidemiology, ecology, and statistics - to name a few.
- Economic factors inform the manager on the cost of risks and the benefits of reducing them, the costs of risk mitigation or remediation options and the distributional effects.
- Laws and legal decisions are factors that define the basis for the Agency's risk assessments, management decisions, and, in some instances, the schedule, level or methods for risk reduction.
- Social factors, such as income level, ethnic background, community values, land use, zoning, availability of health care, life style, and psychological condition of the affected populations, may affect the susceptibility of an individual or a definable group to risks from a particular stressor.
- Technological factors include the feasibility, impacts, and range of risk management options.
- Political factors are based on the interactions among branches of the Federal government, with other Federal, state, and local government entities, and even with foreign governments; these may range from practices defined by Agency policy and political administrations through inquiries from members of Congress, special interest groups, or concerned citizens.
- Public values reflect the broad attitudes of society about environmental risks and risk management.

Who evaluates the risks?

The table below outlines which EPA office or other federal agency is responsible for assessing and managing risks associated with particular stressors.

Stressor	EPA Office	Other Federal Agencies
Air Pollution	Office of Air and Radiation	
Hazardous substances, pollutants, and waste	Office of Solid Waste and Emergency Response	
Pharmaceuticals		FDA's Center for Drug Evaluation and Research
Pesticides	Office of Pesticide Programs	U.S. Consumer Product Safety Commission (toys and other consumer products) FDA's Center for Food Safety and Applied Nutrition
Radiation including radon	Radiation Programs	
Toxic substances, human exposure, environmental exposure	Office of Pollution Prevention and Toxics Office of Research and Development	
Vaccines		FDA's Center for Biologics Evaluation and Research
Water pollution	Office of Water	

How does EPA conduct risk assessments?

At EPA, environmental risk assessments typically fall into one of two areas: human health risk assessments or ecological risk assessments. These are described in steps or parts due to the differences in how each of these are conducted at EPA.

Where do I find EPA risk assessments?

Because risk assessments are performed all over EPA (see the EPA Organization Chart for other EPA Offices and Regions), risk assessments are produced by many of EPA's Regions and Program Offices. Here is a list of primary risk assessment sources:

- Integrated Risk Information System (IRIS) Chemical Summaries and Toxicological Reviews
  - What is IRIS?
  - What is the the IRIS Process for chemical assessment?
- National Center for Environmental Assessment (NCEA) Published Assessments
  - Agent-based risk assessments
    - Carbon Monoxide
    - Diesel Exhaust
    - Dioxin
    - Drinking Water and Disinfection By-Products
    - Lead
    - Mercury
    - Nitrogen Oxide (NOx)
    - Ozone
    - Particulate Matter
    - Pesticide Ecological Risk Assessments
    - PCBs
    - Radon in Homes
    - Secondhand Smoke (ETS)

- Sulfur Oxide
- Place-based risk assessments
  - Biological Assessments (Water)
  - National (Water) Assessment Database
  - Watershed and other place based risk assessments

See Tools & Guidance for a list of more resources.

Where can I find additional information on risk assessment for the public?

EPA has posted a few citizen guides that may be of help for those new to risk assessment. Here is a list of available publications:

- U.S. EPA. A Citizen's Guide to Radon: The Guide to Protecting Yourself and Your Family from Radon. EPA 402-K-07-009. May 2007.
- U.S. EPA. Air Pollution and Health Risk. EPA 450/3-90-022. March 1991
- U.S. EPA. Evaluating Exposures to Toxic Air Pollutants: A Citizen's Guide. EPA 450/3-90-023. March 1991.
- U.S. EPA. RCRA: Reducing Risk from Waste. EPA 530-K-97-004. Sept 1997.
- U.S. EPA. Risk Assessment for Toxic Air Pollutants: A Citizen's Guide . EPA 450/3-90-024. March 1991.

What can I do? Participating in risk assessments

- A Community Guide To Superfund Risk Assessment--What It's All About And How You Can Help
  In Spanish: De qué se trata la evaluación de los riesgos y cómo nos puede ayudar
- Superfund Today: Focus on Revisions to Superfund's Risk Assessment Guidance (1999) (PDF) (2 pp., 50K)
- Regional Vulnerability Assessment (ReVA) Decision Toolkit
- Risk-Screening Environmental Indicators (RSEI) Screening Tool

What does EPA mean by "variability","uncertainty", and "probabilistic modeling"?

Consideration must be given to two important factors throughout the development of a risk assessment: variability and uncertainty.

Variability - Refers to the range of toxic response or exposure. For example, the dose that might cause a toxic response can vary from one person to the next depending on factors such as genetic differences, preexisting medical conditions, etc. Exposure may vary from one person to the next depending on factors such as where one works, time spent indoors or out, where one lives, how much people eat or drink, etc.

Uncertainty - Refers to our inability to know for sure - it is often due to incomplete data. For example, when assessing the potential for risks to people, toxicology studies generally involve dosing of sexually mature test animals such as rats as a surrogate for humans. Since we don't really know how differently humans and rats respond, EPA often employs the use of an uncertainty factor to account for possible differences. Additional consideration may also be made if there is some reason to believe that the very young are more susceptible than adults, or if key toxicology studies are not available. [Learn more about determining uncertainty]

Probabilistic Modeling, a related term, is a technique that utilizes the entire range of input data to develop a probability distribution of exposure or risk rather than a single point value. The input data can be measured values and/or estimated distributions. Values for these input parameters are sampled thousands of times through a modeling or simulation process to develop a distibution of likely exposure or risk. Probabilistic models can be used to evaluate the impact of variability and uncertainty in the various input parameters, such as environmental exposure levels, fate and transport processes, etc.

What is peer review?

Peer review is a documented critical review of a scientific/technical work product which is conducted by scientific experts who are independent of those who performed the work. Peer review can provide an independent evaluation of the assumptions, calculations, extrapolations, alternate interpretations, methodology, acceptance criteria, and conclusions pertaining to the scientific/technical work product.

When evaluating the scientific rigor of our risk assessments, EPA utilizes both standing federal advisory groups of experts such as the Science Advisory Board (SAB) and the FIFRA Scientific Advisory Panel, as well as ad hoc panels to provide peer review. EPA will occasionally seek peer review from outside expert groups such as the National Academy of Science (NAS) for highly complex and/or critical scientific topics.

Last updated on Tuesday, July 31, 2012

APPENDIX C – 8

Tracy B. Horch

From:	Schmitt, Addy (USADC) <Addy.Schmitt@usdoj.gov>
Sent:	Monday, December 16, 2013 11:06 AM
To:	Jayni Lanham
Subject:	Beveridge and Diamond v. HHS, 13-1155-JEB
Attachments:	B-Reader Form.pdf; CADELAY.doc; CAPILAY.doc; PFTLAY.doc; Questionnaires.doc

Dear Jayni,

I write in response to your email of Thursday evening, December 12, 2013. First, to be clear, my client has already provided all of the information agreed upon by the parties in order to resolve this litigation. We have no obligation to provide additional information, nor do we have any obligation to explain the data you requested and my client provided. Nevertheless, my client is providing the additional information included in and attached to this email as a courtesy - and we trust that you recognize this goes far beyond the terms of the agreement or any obligation to do so. We also trust that you will abide by your agreement to dismiss this case with prejudice by no later than December 20, 2013. Again, my client has gone above and beyond and we do not anticipate any further inquiries or requests before you dismiss the case.

With respect to the occupational categories, my client conducted a search for all instances in which a participant said they did NOT work in a particular job, but for which there were nevertheless start and end dates entered for that job. There were 1,958 records (about 27%) that met this criterion. In other words, that is the data as my client has it.

Regarding the year-of-birth variable, the following code was used:

if 1900<=pbyr<1905 then yrbirth=1;
if 1905<=pbyr<1910 then yrbirth=2;
if 1910<=pbyr<1915 then yrbirth=3;
if 1915<=pbyr<1920 then yrbirth=4;
if 1920<=pbyr<1925 then yrbirth=5;
if 1925<=pbyr<1930 then yrbirth=6;
if 1930<=pbyr<1935 then yrbirth=7;
if 1935<=pbyr<1940 then yrbirth=8;
if 1940<=pbyr<1945 then yrbirth=9;
if 1945<=pbyr<1950 then yrbirth=10;
if 1950<=pbyr<1955 then yrbirth=11;
if 1955<=pbyr<1960 then yrbirth=12;
if 1960<=pbyr<1965 then yrbirth=13;
if 1965<=pbyr<1970 then yrbirth=14;
if 1970<=pbyr<1975 then yrbirth=15;
if 1975<=pbyr<1980 then yrbirth=16;
if 1980<=pbyr<1985 then yrbirth=17;
if 1985<=pbyr<1990 then yrbirth=18;
if 1990<=pbyr<1995 then yrbirth=19;

Finally, in response to your questions regarding the variables - again, as a courtesy and without any obligation to do so - we are providing copies of the B-Reader Form, a version of the paper questionnaire (the questionnaire was administered by computer in the field), and the data layouts provided by NORC.

Again, I trust this more than answers your questions.

All the best,

Addy R. Schmitt
Assistant United States Attorney
Civil Division
U.S. Attorney's Office for the District of Columbia
501 3rd Street, NW | 4th Floor | Washington, D.C. 20530
202-252-2530 | 202-252-2599 | addy.schmitt@usdoj.gov

Please note the new phone and fax numbers.

APPENDIX C – 9

Treasury and General Government Appropriations Act for Fiscal Year 2001 (Public Law 106-554)

Sec. 515. (a) In General.--The Director of the Office of Management and Budget shall, by not later than September 30,2001, and with public and Federal agency involvement, issue guidelines under sections 3504(d)(1) and 3516 of title 44, United States Code, that provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies in fulfillment of the purposes and provisions of chapter 35 of title 44, United States Code, commonly referred to as the Paperwork Reduction Act.

(b) Content of Guidelines.--The guidelines under subsection (a) shall--

(1) apply to the sharing by Federal agencies of, and access to, information disseminated by Federal agencies; and

(2) require that each Federal agency to which the guidelines apply--

(A) issue guidelines ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by the agency, by not later than 1 year after the date of issuance of the guidelines under subsection (a);

(B) establish administrative mechanisms allowing affected persons to seek and obtain correction of information maintained and disseminated by the agency that does not comply with the guidelines issued under subsection (a); and

(C) report periodically to the Director--

(i) the number and nature of complaints received by the agency regarding the accuracy of information disseminated by the agency; and

(ii) how such complaints were handled by the agency.

The full text of Public Law 106-554 is available through the Government Printing Office website.

APPENDIX C – 10

EPA United States Environmental Protection Agency

Newsroom
News Releases By Date

EPA Administrator Gina McCarthy Testimony Before House Committee on Science, Space and Technology

Release Date: 11/14/2013
Contact Information: press@epa.gov

WASHINGTON – As prepared for delivery.

Good morning Chairman Smith, Ranking Member Johnson, and other distinguished members of the Committee. I am pleased to be here to talk about the central role science plays at the U.S. Environmental Protection Agency.

Let me begin by stating that science is and has always been the backbone of the EPA's decision-making. The Agency's ability to pursue its mission to protect human health and the environment depends upon the integrity of the science upon which it relies. I firmly believe that environmental policies, decisions, guidance, and regulations that impact the lives of all Americans must be grounded, at a most fundamental level, in sound, high quality, transparent, science.

Because we rely so heavily on science to meet our mission on behalf of the American people, it must be conducted in ways that are transparent, free from bias and conflicts of interest, and of the highest quality, integrity, and credibility. These qualities are important not just within our own organization and the federal government, but across the scientific community, with its long established and highly honorable commitment to maintaining strict adherence to ethical investigation and research. That's why the agency has established—and embraced—a Scientific Integrity Policy that builds upon existing Agency and government-wide policies and guidance documents, explicitly outlining the EPA's commitment to the highest standards of scientific integrity. And that commitment extends to any scientist or organization who wishes to contribute to our efforts. All EPA-funded research projects, whether conducted by EPA scientists or outside grantees and collaborators, must comply with the agency's rigorous quality assurance requirements.

To ensure that we have the best possible science, we are committed to rigorous, independent peer review of the scientific data, models and analyses that support our decisions. Peer review can take a number of forms, ranging from external reviews by the National Academy of Sciences or the EPA's federal advisory committees to contractor-coordinated reviews. Consistent with OMB guidance, we require peer review for all EPA research products and for all influential scientific information and highly influential scientific assessments.

Among the external advisory committees is the EPA Science Advisory Board (SAB). SAB reviews are conducted by groups of independent non-EPA scientists with the range of expertise required for the particular advisory topic. We invite the public to nominate experts for SAB panels and to comment on candidates being considered by the EPA for SAB panels. The EPA evaluates public comments and information submitted about SAB nominees. The EPA reviews experts' confidential financial information to ensure that there are no conflicts of interest.

SAB peer reviews are conducted in public sessions in compliance with the open-government requirements of the Federal Advisory Committee Act. The public is invited to attend and to provide oral and written comments for consideration by the SAB. Public comments help to ensure that all relevant scientific and technical issues are available to the SAB as it reviews the science that will support our environmental decisions.

Another example is the Clean Air Scientific Advisory Committee (CASAC) which provides independent advice to the EPA Administrator on the science that supports the EPA's National Ambient Air Quality Standards. The CASAC reviews the EPA's Integrated Science Assessments which deliver science in support of the Clean Air Act.

Thanks to the science behind the implementation of the Clean Air Act, we have made significant and far-reaching improvements in the health and well-being of the American public. In 2010 alone, EPA estimates that programs implemented pursuant to the Clean Air Act Amendments of 1990 avoided 160,000 premature deaths millions of cases of respiratory problems such as acute bronchitis and asthma attacks; 45,000 cardiovascular hospitalizations; and 41,000 hospital admissions. These improvements have all occurred during a period of economic growth; between1970 and 2012 the Gross Domestic Product increased by 219 percent.

Through a transparent and open process, we have also committed to enhancing the Agency's Integrated Risk Information System (IRIS) assessment program. A strong, scientifically rigorous IRIS Program is of critical importance, and the EPA is in the process of: 1) enhancing the scientific integrity of assessments; 2) enhancing the productivity of the Program; and 3) increasing transparency so that issues are identified and debated early in the process. In 2009, the EPA made significant enhancements to IRIS by announcing a new 7-step assessment development process. Since that time, the National Research Council (NRC) has made recommendations related to enhancing the development of IRIS assessments. The EPA is making changes to the IRIS Program to implement the NRC recommendations. These changes will help the EPA produce more high quality IRIS assessments each year in a timely and transparent manner to meet the needs of the Agency and the public. A newly released NRC report is largely supportive of the enhanced approach the EPA is taking to develop the IRIS assessment for inorganic arsenic.

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12/11/2013 EPA Announces Dec. 17 Public Availability Session in York, Neb., to Discuss Groundwater Contamination Issues
12/11/2013 EPA Proposes Pair of Groundwater Contamination Sites in York, Neb., for Addition to Superfund's National Priorities List

As I mentioned in my opening statement, science is the backbone of our decision-making and our work is based on the principles of scientific integrity and transparency that are both expected and deserved by the American people. I am proud of the EPA's research efforts and the sound use of science and technology to fulfill the EPA's mission to protect human health and safeguard the natural environment.

Thank you for the opportunity to testify before you today. I am happy to answer any questions you may have at this time.

R183

APPENDIX C – 11

United States Environmental Protection Agency

Office of Research and Development Washington DC 20460

EPA/600/8-90/066F October 1994

EPA

Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry

GLOSSARY

Activity Median Diameter (AMD)
Refers to the median of the distribution of radioactivity, toxicological, or biological activity with respect to particle size.

Acute Exposure
A one-time or short-term exposure with a duration of less than or equal to 24 h.

Aerodynamic Diameter
Term used to describe particles with common inertial properties to avoid the complications associated with the effects of particle size, shape, and physical density.

Aerodynamic Equivalent Diameter (d_{ae})
"Aerodynamic diameter" generally used. The diameter of a unit density sphere ($\rho_p = 1$ g/cm^3) having the same settling velocity (due to gravity) as the particle of interest of whatever shape and density. Refer to Raabe (1976) and Appendix H for discussion.

Aerodynamic (Viscous) Resistance Diameter (d_{ar})
The "Lovelace" definition for aerodynamic diameter. Characteristic expression based on terms describing a particle in the Stokes' regime. Refer to Raabe (1976) for equation.

Aerosol
All-inclusive term. A suspension of liquid or solid particles in air.

ATPS
Ambient temperature and pressure, saturated (a condition under which a gas volume is measured).

BTPS
Body temperature and pressure, saturated (a condition under which a gas volume is measured).

Critical Effect
The first adverse effect, or its known precursor, that occurs as the dose rate increases. Designation is based on evaluation of overall data base.

Chronic Exposure
Multiple exposures occurring over an extended period of time, or a significant fraction of the animal's or the individual's lifetime.

Dosimetric Adjustment Factor (DAF)
A multiplicative factor used to adjust observed experimental or epidemiological data to human equivalent concentration for assumed ambient scenario. See regional gas dose ratio (RGDR) and regional deposited dose ratio (RDDR).

1. INTRODUCTION AND OVERVIEW

This document describes the U.S. Environmental Protection Agency (EPA) methodology for estimation of inhalation reference concentrations (RfCs) (earlier terminology was "inhalation reference dose" or "RfD_i") as benchmark estimates of the quantitative dose-response assessment of chronic noncancer toxicity for individual inhaled chemicals. Noncancer toxicity refers to adverse health effects other than cancer and gene mutations. This overview chapter discusses general principles of dose-response assessment for noncancer toxicity, the development of the RfC methodology, and its role within the context of the risk assessment process. Subsequent chapters of the document discuss criteria and information to be considered in selecting key studies for RfC derivation, provide an overview of the respiratory system and its intra- and interspecies variables, and discuss areas of uncertainty and data gaps in relation to the proposed methodology.

1.1 INHALATION REFERENCE CONCENTRATION: DEVELOPMENT, DEFINITION, AND DERIVATION

The EPA has a history of advocating the evaluation of scientific data and calculation of Acceptable Daily Intake (ADI) values for noncarcinogens as benchmark values for deriving regulatory levels to protect exposed populations from adverse effects. For example, the Office of Pesticide Programs has long used the concept of ADI for tolerance estimates of pesticides in foodstuffs, the Office of Health and Environmental Assessment (OHEA) has used ADI values for characterizing levels of pollutants in ambient waters (Federal Register, 1980), and the National Research Council (1977, 1980) has recommended the ADI approach to characterize levels of pollutants in drinking water with respect to human health.

In 1983, the National Academy of Sciences (NAS) published a report entitled "Risk Assessment in the Federal Government: Managing the Process" (National Research Council, 1983). The NAS had been charged with evaluating the process of risk assessment as performed at the federal level in order to determine the "mechanisms to ensure that government regulation rests on the best available scientific knowledge and to preserve the integrity of scientific data and

judgements" so that controversial decisions regulating chronic health hazards could be avoided. The NAS recommended that the scientific aspects of risk assessment should be explicitly separated from the policy aspects of risk management. Risk assessment, as shown in Figure 1-1, was defined as the characterization of the potential adverse human health effects of exposures to environmental hazards and consists of the following four steps: (1) hazard identification: the determination of whether a chemical is or is not causally linked to a particular health effect; (2) dose-response assessment: the estimation of the relation between the magnitude of exposure and the occurrence of the health effects in question; (3) exposure assessment: the determination of the extent of human exposure; and (4) risk characterization: the description of the nature and often the magnitude of human risk, including attendant uncertainty.

Following the NAS report, the EPA developed a methodology for evaluating available data pertaining to xenobiotics for purposes of developing oral reference doses (RfDs) (Barnes and Dourson, 1988). Although similar to ADIs in intent, RfDs were based upon a more rigorously defined methodology that adhered to the principles proposed by the NAS and included guidance on the consistent application of uncertainty factors for prescribed areas of extrapolation required in the operational derivation. The RfD methodology represents a quantitative approach to assess toxicity data in order to derive a dose-response estimate. According to the NAS paradigm, the final step of the risk assessment process, risk characterization, would involve the comparison of the RfD as a dose-response estimate with an exposure estimate.

The RfC methodology to estimate benchmark values for noncancer toxicity of inhaled chemicals significantly departed from the RfD approach. The same general principles were used, but the RfC methodology was expanded to account for the dynamics of the respiratory system as the portal of entry. The major difference between the two approaches, therefore, is that the RfC methodology includes dosimetric adjustments to account for the species-specific relationships of exposure concentrations to deposited/delivered doses. The physicochemical characteristics of the inhaled agent are considered as key determinants to its interaction with the respiratory tract and ultimate disposition. Particles and gases are treated separately, and the type of toxicity observed (respiratory tract or toxicity remote to the portal-of-entry) influences the dosimetric adjustment applied.

An inhalation reference concentration (RfC) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human

exposure-dose-response continuum and will therefore be revised accordingly, it must be recognized that the definition of HEC is iterative and dynamic as well. That is, the HEC is a concentration back-extrapolated from an appropriate surrogate internal dose to the extent that this has been defined.

Although it is preferable to use human studies as the basis for the dose-response derivation, adequate human data are not always available, often forcing reliance on laboratory animal data. Presented with data from several animal studies, the risk assessor first seeks to identify the animal model that is most relevant to humans, based on comparability of biological effects using the most defensible biological rationale; for instance, by using comparative metabolic, pharmacokinetic, and pharmacodynamic data. In the absence of a clearly most relevant species, however, the most sensitive species is used as a matter of science policy at the EPA. For RfCs, the most sensitive species is designated as the species that shows the critical adverse effect at an exposure level that, when dosimetrically adjusted, results in the lowest HEC.

The critical toxic effect used in the dose-response assessment is generally characterized by the lowest $NOAEL_{[HEC]}$ that is also representative of the threshold region (the region where toxicity is apparent from the available data) for the data array. The objective is to select a prominent toxic effect that is pertinent to the chemical's key mechanism of action. This approach is based, in part, on the assumption that if the critical toxic effect is prevented, then all toxic effects are prevented (see Section 1.2, general principles of dose-response assessment for noncancer toxicity). The determination of the critical toxic effect from all effects in the data array requires toxicologic judgment because a chemical may elicit more than one toxic effect (endpoint) in tests of the same or different exposure duration, even in one test species. Further, as discussed in Appendix A, the NOAEL and LOAEL obtained from studies depend on the number of animals or subjects examined and on the spacing of the exposure levels. The $NOAEL_{[HEC]}$ from an individual study (or studies) that is also representative of the threshold region for the overall data array is the key datum synthesized from an evaluation of the dose-response data. Determination of this critical effect represents the first scientific evaluation required by the RfC dose-response assessment.

The RfC is an estimate that is derived from the $NOAEL_{[HEC]}$ for the critical effect by consistent application of uncertainty factors (UFs). The UFs are applied to account for

2. QUALITATIVE EVALUATION OF THE DATA BASE

This chapter outlines considerations for the collection and qualitative evaluation of diverse data into a cohesive toxicity profile that then can be evaluated by means of the quantitative procedures for dose-response analysis provided in Chapter 4. The conceptual basis for the dosimetry adjustments applied to inhaled agents and other considerations specific to this administration route are addressed in Chapter 3.

The aim of the inhalation reference concentration (RfC) methodology is to establish a relationship between a particular agent in the air and a specific health effect (or effects). To define such a relationship, evidence must be collected from diverse sources and synthesized into an overall judgment of health hazard (Hackney and Linn, 1979). One of the major challenges to performing dose-response assessment for noncancer endpoints is that it requires the evaluation of effects measured in a number of different tissues. Often different endpoints are investigated in different studies, in different species, and at various concentrations. The effects measured may represent different degrees of severity (adversity) within disease continuums. Qualitative evaluation of the data base, also known as the hazard identification component of risk assessment, involves integrating a diverse array of data into a cohesive, biologically plausible toxicity "picture" or weight-of-the-evidence relationship to establish that the agent causes an effect (or effects) and is of potential human hazard. Questions addressed by this process include whether the agent associated with an effect is responsible for the effect, if the effect is biologically significant, and what the potential public health implications might be. Answering such questions requires ascertaining the validity and meaning of the toxicity data, determining whether the experimental results as a whole suggest or show causality between the agent and the effect, and evaluating whether or not the causal relationship is applicable under other sets of circumstances (e.g., in extrapolating from test animals to humans). This entails consideration of all relevant human and laboratory animal data of various study types, studies with differing results (e.g., positive and negative), pharmacokinetic disposition data (deposition, absorption, distribution, metabolism, elimination) mechanistic information, and structure-activity relationships. This process integrates information needed for the dose-response assessment, which is discussed in

TABLE 2-3. COMPARISON OF THE QUALITIES OF FIELD AND EXPERIMENTAL APPROACHES IN THE STUDY OF THRESHOLD LIMIT VALUE/BIOLOGIC EXPOSURE INDICES RELATIONSHIPS

	Approach	
Factor	Field	Experimental
Exposure (dose) measurement	+ +	+ + +
Physical workload characterization	+	+ + +
Timing of biological sampling	+	+ + +
Effects of exposure repetition	+ + +	+ +
Environmental variability	+ +	+ +
Representativity of the subjects	+ + +	+

+++ = Good; ++ = Medium; + = Poor.

Source: Droz (1985).

Application of Physiologically Based Pharmacokinetic Models

Physiologically based pharmacokinetic models are simulation models described by simultaneous differential equations, the number of which is dictated by the number of compartments needed to describe the physiological and metabolic processes involved. In the context of characterizing the exposure-dose-disease continuum, simulation models can be considered as complementary, providing critical insight on key processes related to the fate of chemicals in the body and for depicting the contribution of various exposure and biological factors to the variability of response. That is, these models can provide the following information on which biological monitoring (e.g., BEIs) is designed and data are interpreted: (1) concentration-effect relationships, (2) time-effect relationships, (3) matching exposure in the workplace with integrated exposure, (4) depicting effects of external and internal factors that alter the relationship between intensity of exposure and biological concentration and body burden of the biologic marker, (5) extrapolation and prediction of biological concentrations resulting from exposure to new compounds or new exposure conditions, and (6) verification of data (Leung, 1992; Fiserova-Bergerova, 1990; Leung and Paustenbach, 1988; Droz, 1985). Simulation models, because of their ability to match the extent of exposures associated with the predetermined dose or biological markers of exposure, are a valuable tool

in extrapolation of reference values for workers with unusual workshifts (Andersen et al., 1987b; Saltzman, 1988).

2.1.1.2 Epidemiologic Data

There are essentially three areas of concern in assessing the quality of an epidemiologic study. These involve the design and methodological approaches used for: (1) exposure measures, (2) effect measures, and (3) the control of covariables and confounding variables (Lebowitz, 1983). The study population and study design must adequately address the health effect in question in order to support a risk assessment (Lebowitz, 1983). In order to accomplish this goal, the exposure measures must be appropriate and of sufficient quality; the statistical analysis methods must be suitable to the study design and goals; the health effect measures must be reliable and valid; and the covariables and confounding variables need to be controlled or eliminated. Additional guidance on evaluation of the quality of individual epidemiologic studies is provided in Appendix B. Criteria for causal significance are provided in Appendix C.

Assessment of Exposure Measures

The problem of the accuracy and relevance of exposure measurements is not unique to epidemiologic investigations, but it can be exacerbated due to the long-term nature of these studies. For example, the nature of aerometric data may change over time because of different air sampling techniques. Exposures also change over time because of different industrial hygiene practices and because individuals change jobs and residences. Accurate documentation of air toxicant levels, therefore, is critical in determining the usefulness of an investigation as well as documentation that the analysis of the air toxicant is appropriate and of sufficient sensitivity. It also is advisable to have the concentrations of other pollutants reported and considered in the statistical analyses to help rule out confounding or interactive effects. The number, location, and timing of monitors should be suitable to allow an appropriate determination of exposure of the subjects to the pollutant being studied and to the pollutants that could confound the results. When appropriate, the exposure measure or estimate should take into account indoor/outdoor exposures and activity and subject location data. Unfortunately, exposure measures often are the weakest component of an

Other considerations include the adequacy of study duration and quality of the follow-up. A disease with a long latency before clinical presentation requires a longer study duration than one with an acute onset. Valid ascertainment (such as verification according to the International Classification of Diseases IX) of the causes of morbidity and death also is necessary.

Evaluation of epidemiologic studies may require interpretation of a variety of subjective health effects data. Questionnaire responses may be biased by the way questions are worded, the training of an interviewer, or the setting. However, a study based on a high-quality questionnaire can provide useful results. For example, a committee of the American Thoracic Society (ATS) charged with defining an adverse respiratory health effect, has come to a consensus that "in general, increased prevalence of chronic respiratory symptoms as determined from questionnaire surveys should be considered to be an adverse health effect" (American Thoracic Society, 1985). Questionnaires should be validated as part of the investigation protocol, unless a standard questionnaire that has previously been validated is used (Medical Research Council, 1960; Ferris, 1978; National Institute for Occupational Safety and Health, 1986).

It is very important to consider differences between statistical significance and medical or biological significance. Both the variability of an outcome measure and the magnitude of an exposure's effect determine the level of statistical significance. For example, data from a large study population analyzed with sophisticated techniques may yield statistically significant effects of small magnitude that cannot readily be interpreted biologically. Conversely, apparently large changes of clinical importance may not be statistically significant if the study population is too small. In addition, some studies present false negative or no-effect results due to the lack of power. Judgments concerning medical or biological significance should be based on the magnitude and class of a particular effect. For example, cough or phlegm production can be considered less important than effects resulting in hospital admissions, but daily productive cough can be more important than infrequent cough. Underlying assumptions and nuances of the statistical procedures applied to the data also need to be considered. This will probably best be accomplished on a case-by-case basis.

Because the RfC considers both portal-of-entry and remote (systemic) effects, it would be helpful to define an "adverse respiratory health effect." An ATS committee published

guidelines that defined such an effect as medically significant physiologic or pathologic changes generally evidenced by one or more of the following (American Thoracic Society, 1985):

- Interference with the normal activity of the affected person or persons
- Episodic respiratory illness
- Incapacitating illness
- Permanent respiratory injury or
- Progressive respiratory dysfunction

Appendix D provides detailed descriptions of adverse respiratory effects in humans.

Assessing the Control of Confounding and Covariables

Epidemiologic investigations attempt to relate an exposure to a given health effect, but this includes accounting for the "background" health effect (pathologic condition) that exists in individuals due to predisposing factors and preexisting health conditions, or from other variables, such as occupational exposures.

Various host factors contribute as risk factors for disease and can influence the health indices assessed. For example, asthmatics may be particularly susceptible to effects from exposure to irritant gases. Epidemiologic evaluation of these factors often not only accounts for such interactions but also can help to characterize susceptible or sensitive groups. Covariables can be as important as the major aerometric variables themselves in affecting human health. Other exposures, such as concomitant occupational exposures and smoking, in particular, can affect the disease outcome. Meteorologic variables such as air velocity, temperature, and humidity also are very important factors when considering respiratory health effects. These covariables should be controlled by both the study design and analysis, as appropriate.

The final step in the inferential process from an epidemiologic investigation is the extension of the study results to persons, populations, or settings not specifically included in the experimental design, that is, to demonstrate consistency of results within replicates in

2.1.2.4 Study Validity and Relevance to Extrapolation

The validity of the study and its relevance to human extrapolation is another major area to consider when assessing individual animal studies. It involves the evaluation of a number of factors, including all elements of exposure definition (concentration, duration, frequency, administration route, and physicochemical characterization of the chemical used), reliability of and limits to the procedures used for both exposure and effects measurements, relevance of the exposure level tested to the anticipated human exposure level, nature of the effect (consistency with the area of toxicology assessed and the suspected mechanism of action), and the similarities and differences between the test species and humans (e.g., in absorption and metabolism).

Animal studies are conducted using a variety of exposure scenarios in which the concentration, frequency, and duration of exposure may vary considerably. Studies may use different durations (acute, subchronic, and chronic) as well as schedules (single, intermittent, and continuous). All of these studies contribute to the hazard identification of the risk assessment. Special consideration should be addressed to those studies of appropriate duration for the reference level to be determined (i.e., chronic investigations for the RfC).

These exposure concerns (concentration and duration) are compounded when the risk assessor is presented with data from several animal studies. An attempt to identify the animal model most relevant to humans should be made on the most defensible biological rationale (e.g., comparable metabolism and pharmacokinetic profiles). In the absence of such a model, the most sensitive species (i.e., the species showing a toxic effect at the lowest administered dose) is adopted for use as a matter of science policy at the EPA (Barnes and Dourson, 1988). This selection process is more difficult if the laboratory animal data are for various exposure routes, especially if the routes are different from that in the human situation of concern.

Because the data base may be deficient for the route of exposure of interest, it is the EPA's view that the toxicity potential manifested by one route can be indicative of potential toxicity via any other exposure route unless convincing contrary evidence exists (Barnes and Dourson, 1988). Quantitative extrapolation, however, requires consideration of the differences in the dosimetry for the chemical resulting from the different exposure routes. Detailed consideration is given to route-to-route extrapolation in Section 4.1.2.

design, or is a function of designating a specified health effect measure (e.g., 10% incidence of a lesion) as the outcome of interest in the case of some alternative approaches presented in Appendix A[3], and therefore, does not necessarily reflect the "true" biological threshold.

Table 4-2 presents the four types of effect levels that may be applicable when evaluating an individual study. Historically, the distinction between adverse effects and nonadverse effects has been and remains problematic. For example, although disease is a dynamic process (injury, adaptation, or healing), a pathologist records a morphologic change at a single point in time and these "freeze-frame" data are used to determine the probable cause and pathogenesis (past) and probable progression or outcome (future). Designation of an effect level (i.e., the designation of adversity) requires interpretation of the data based on an ability to deduce the preceding events that have led to the observed change and to predict the outcome or progression. The relationship between structural alterations to altered function is not always simple, however.

Determining whether altered morphology is an adaptive response or truly an expression of toxicity (functional impairment) can be extremely difficult and even controversial (Burger et al., 1989; Ruben and Rousseaux, 1991). In some cases, structural alteration can occur, but normal function can continue in target tissues with functional reserve such as the lung, liver, and kidney. Not all tissues demonstrate this high reserve. The central nervous system can compensate to only a limited degree and where the damage occurs is vitally important for the function of the system. Therefore, "focal" damage may be adverse in some but not all target tissues. Also, the lack of observed functional change may be due to failure to detect subtle or unknown functional changes rather than to their absence.

A similar morphologic alteration may have both functional and physiologic significance, but often it is difficult to differentiate toxicity from physiologic response by morphologic means alone. Not all functional abnormalities manifest themselves morphologically. Temporal-spatial patterns are particularly challenging when evaluating toxicologic pathology. Problems concerning time include reversibility, adaptation versus toxicity, progression versus

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[3]There are alternative approaches under development (presented and discussed in Appendix A) aimed at deriving estimates of exposures that are analogous in intent to the establishment of a NOAEL. The NOAEL/LOAEL approach outlined is not intended to discourage alternative or more sophisticated dose-response procedures when sufficient data are available, but rather to present key issues necessarily involved (e.g., dosimetric adjustment and data array analysis) in any approach for the assessment of noncancer toxicity.

TABLE 4-2. FOUR TYPES OF EFFECT LEVELS[a] (RANKED IN ORDER OF INCREASING SEVERITY OF TOXIC EFFECT) CONSIDERED IN DERIVING INHALATION REFERENCE CONCENTRATIONS FOR NONCANCER TOXICITY

NOEL:	No-Observed-Effect Level. That exposure level at which there are no statistically and biologically significant increases in frequency or severity of effects between the exposed population and its appropriate control.
NOAEL:	No-Observed-Adverse-Effect Level. That exposure level at which there are no statistically and biologically significant increases in frequency or severity of adverse effects[b] between the exposed population and its appropriate control. Effects are produced at this level, but they are not considered to be adverse.
LOAEL:	Lowest-Observed-Adverse-Effect Level. The lowest exposure level in a study or group of studies that produces statistically and biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.
FEL:	Frank Effect Level[c]. That exposure level that produces frankly apparent and unmistakable adverse effects, such as irreversible functional impairment or mortality, at a statistically and biologically significant increase in frequency or severity between an exposed population and its appropriate control.

[a]Note that these levels represent points on a continuum and are not discrete.
[b]Adverse effects are defined as any effects resulting in functional impairment and/or pathological lesions that may affect the performance of the whole organism, or that reduce an organism's ability to cope with an additional challenge.
[c]Frank effects are defined as overt or gross adverse effects (e.g., severe convulsions, lethality, etc.).

regression, and peracute lethal toxicity. Problems concerning space are limited to missing the lesion completely or missing a relevant area because of sampling method. For example, histologic examination of the nasal cavity should select four tissue sections, not one, to achieve a thorough examination (Young, 1981). Further, due to the proximal to distal inspiratory airstream, some examination of the upper respiratory tract is indicated when respiratory toxicity from an inhaled irritant is evident in the lower respiratory tract.

Due to the structural-functional and temporal-spatial problems discussed above, an approach that integrates pathological studies (ultrastructural, histochemical, cellular, and molecular) with functional methods is recommended (Ruben and Rousseaux, 1991). Morgan (1991) has provided guidance on the identification and interpretation of URT lesions in toxicologic studies. A systematic but flexible approach to evaluation of lesions in the URT is

recommended, one that considers selection of section level in context with the physicochemical characteristics of the inhaled gas (e.g., water solubility and reactivity), the role of factors that may account for lesion distribution (e.g., dosimetry and tissue susceptibility), and development of a pathogenesis profile or a chronological order of events (e.g., degenerative, adaptive, and adaptive/regenerative changes versus time). The nasal diagrams proposed by Mery et al. (in press) offer an approach to recording data and mapping lesions that aids this type of interpretation strategy. This approach is also likely the best to compile the data and precludes the restraint to interpretation and mathematical modeling presented by data scored categorically for severity (e.g., + = mild, ++ = moderate; and +++ = severe) and/or without sufficient section detail with respect to lesion location (Jarabek, 1994).

In the early stages of respiratory disease, there is considerable uncertainty concerning how to differentiate between acute reversible effects, which are the immediate consequence of an exposure episode, and potential progression to chronic, nonreversible respiratory pathology. The boundary between adaptive and toxic responses also remains controversial for some respiratory tract lesions (Burger et al., 1989). These are important issues both in terms of evaluation of respiratory tract effects per se, as well as for decisions concerning the critical effect in inhalation studies. Inhalation-specific issues such as evaluation of pulmonary function, sensory irritation, and allergic sensitization data are discussed in Section 2.2.

Designation of effect levels usually contains an element of scientific judgment in addition to objective criteria. Considerable experience and precedent for such decisions have accrued over the last several years in the process of developing oral reference doses, RfCs, and other health-related benchmark estimates. Table 4-3 presents guidance as to how general effects would usually be designated as different (adverse) effect levels. In general, effects that may be considered marginal are designated as adverse only to the extent that they are consistent with other structural and functional data suggesting the same toxicity. For example, altered liver enzymes (statistically out of normal range) would only be considered adverse in context with altered structure (pathology) and liver weight changes.

APPENDIX C – 12

EXCERPTS

EPA-540-R-070-002
OSWER 9285.7-82
January 2009

Risk Assessment Guidance for Superfund
Volume I: Human Health Evaluation Manual
(Part F, Supplemental Guidance for Inhalation Risk Assessment)

Final

Office of Superfund Remediation and Technology Innovation
Environmental Protection Agency
Washington, D.C.

Category 3 gases are relatively water-insoluble and are unreactive in the respiratory tract (e.g., benzene, styrene). Their toxicity is generally at sites remote to the respiratory tract (USEPA, 1994). The DAF for Category 3 gases is based on the ratio of the animal blood:gas partition coefficient ($H_{b/g\text{-}animal}$) and the human blood:gas partition coefficient ($H_{b/g\text{-}human}$). See Appendix A, Section 4 of this guidance for an example of a Category 3 DAF equation.

Category 2 gases are moderately water-soluble and may be rapidly reversibly reactive or moderately to slowly irreversibly reactive in respiratory tract tissue (e.g., acetonitrile, xylene, propanol, isoamyl alcohol). These gases have potential for significant accumulation in the blood, so they can exhibit both respiratory and remote toxicity (USEPA, 1994). The DAF for respiratory effects of Category 2 gases consists of an RGDR and is based on the animal to human ratio of the V_e and the SA of the region of the respiratory tract where the effect occurs, as for Category 1 gases. The DAF for extra-respiratory (ER) effects of a Category 2 gas is based on the ratio of the $H_{b/g\text{-}animal}$ and the $H_{b/g\text{-}human}$, as for Category 3 gases.

Particles also vary by solubility and reactivity. However, the default equations used to estimate the predicted regional deposition fractions for particles are based on non-soluble, non-hygroscopic particles (USEPA, 1994, Section 4.3.5.3). The DAF for a particle causing an effect in the respiratory tract is the $RDDR_r$. The $RDDR_r$ is based on the animal to human ratio of the V_e and the fractional deposition of the particle in that region (F_r), divided by the SA_r of the region where the effect occurs. This derivation, from the *Inhalation Dosimetry Methodology,* conservatively assumes that 100 percent of the deposited dose remains in the respiratory tract; clearance mechanisms are not considered. The DAF for a particle causing an ER effect, the $RDDR_{ER}$, is based on the animal to human ratio of the V_e and the total deposition of the particle in the entire respiratory tract (F_{total}), divided by BW (USEPA, 1994). The $RDDR_{ER}$ assumes that 100 percent of the deposited dose in the entire respiratory tract is available for uptake into the systemic circulation. See Appendix A, Section 5 for examples of specific particle DAF equations.

2.1.2 Default Approach - Extrapolation from Human Occupational Data

When human data are available to derive an RfC, duration adjustments are often required to account for differences in exposure scenarios (e.g., extrapolation from an 8 hour/day occupational exposure to a continuous chronic exposure). The default approach recommended by the *Inhalation Dosimetry Methodology* for adjusting the POD concentration (e.g., the no observable adverse effect level (NOAEL)) obtained from human study data is provided below in Equation 3 (USEPA, 1994, Equation 4-49).[17,18]

[17] If sufficient data are available, a PBPK model or intermediate approach using chemical-specific information may be employed in preference to the default method for extrapolating human occupational data to an HEC.

[18] EPA's IRIS glossary defines an adverse effect as the following: "A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge" (USEPA, 2008b).

$NOAEL_{[HEC]}$ = NOAEL x (VEho/VEh) x 5 days/7 days	(Equation 3)
Where:	$NOAEL_{[HEC]}$ (mg/m^3) = the NOAEL or analogous exposure level obtained with an alternate approach, dosimetrically adjusted to an ambient HEC; NOAEL (mg/m^3) = occupational exposure level (time-weighted average over an 8-hour exposure period); VEho = human occupational default minute volume over 8 hours (10 m^3); and VEh = human ambient default minute volume over 24 hours (20 m^3).

2.2 Derivation of the Inhalation Unit Risk

The default approach for determining predictive cancer risk recommended by EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005a; hereafter, *Cancer Guidelines*) is a linear extrapolation from exposures observed in the animal or human occupational study.[19] This approach involves drawing a straight line from the POD to the origin. The default linear extrapolation approach is generally considered to be conservatively protective of public health, including sensitive sub-populations (USEPA, 2005a). The slope of this line is commonly called the slope factor, and when the units are risk per $\mu g/m^3$, it is also called the IUR. EPA defines an IUR in the IRIS glossary as "the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air" (USEPA, 2008b). Equation 4 below presents a linear extrapolation from a POD of 10 percent response (LEC_{10}).[20]

$IUR = 0.1/LEC_{10[HEC]}$	(Equation 4)
Where:	IUR $(\mu g/m^3)^{-1}$ = Inhalation Unit Risk; and $LEC_{10[HEC]}$ ($\mu g/m^3$) = the lowest effective concentration using a 10 percent response level, dosimetrically adjusted to an HEC.

2.3 Derivation of the Reference Concentration

EPA defines an RfC in the IRIS glossary as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime" (USEPA, 2008b). The RfC is derived after a review of the health effects database for a chemical and identification of the most sensitive and relevant endpoint along with the principal study or studies demonstrating that endpoint. EPA Chemical Managers use UFs to account for recognized

[19] According to the *Cancer Guidelines*, "[a] nonlinear approach should be selected when there are sufficient data to ascertain the mode of action [MOA] and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses" (USEPA, 2005a, page 3-22). In addition, [l]inear extrapolation should be used when there are MOA data to indicate that the dose-response curve is expected to have a linear component below the POD" (USEPA, 2005a, page 3-21). This information will appear on the IRIS profile or other toxicological information source for a chemical. Chemicals with a mutagenic MOA are thought to pose a higher risk during early life. Procedures for assessing cancer risk from these chemicals are outlined in Section 5.1.

[20] The POD used in Equation 4 is an LEC_{10}, which is the lower 95 percent confidence limit on the concentration corresponding to a 10 percent response rate (i.e., the EC_{10}). Other PODs may be substituted for this value, which could be associated with alternative response levels (e.g., 1 percent, 5 percent).

uncertainties in the extrapolations from the experimental data conditions to an estimate appropriate to the assumed human scenario (USEPA, 1994). See Table 3 for a description of the standard UFs. The formula used for deriving the RfC from the HEC is provided below.

$$RfC = NOAEL_{[HEC]}/(UF)^{1} \qquad \text{(Equation 5)}$$

Where:

RfC (mg/m^3) = Reference Concentration

$NOAEL_{[HEC]}$ (mg/m^3) = The NOAEL or analogous exposure level obtained with an alternate approach, dosimetrically adjusted to an HEC; and

UF = Uncertainty factor(s) applied to account for the extrapolations required from the characteristics of the experimental regimen.

[1] Some toxicological information sources for RfCs will incorporate an additional factor to account for deficiencies in the available data set, called a modifying factor (MF). In 2002, however, EPA published the *RfD/RfC Review*, which recommended that the use of MFs be discontinued because their purpose is "sufficiently subsumed in the general database UF" (USEPA, 2002c, page xviii). Therefore, RfCs published subsequent to this document will not include MFs.

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EXCERPTS

EPA/630/P-02/002F
December 2002
Final Report

A REVIEW OF THE REFERENCE DOSE AND REFERENCE CONCENTRATION PROCESSES

Prepared for the
Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC

Reference Dose/Reference Concentration (RfD/RfC) Technical Panel

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Professional judgment is required to decide, on the basis of a thorough review of all available data and studies, whether any observed effect is adverse and how the results fit with what is known about the underlying mode of action. These judgments require the input of experts trained in toxicology, statistics, and epidemiology and, often, of specialists in the structure and function of the target organ systems. Both the biological and the statistical significance of the effects are considered when making these judgments. Biological significance is the determination that the observed effect (a biochemical change, a functional impairment, or a pathological lesion) is likely to impair the performance or reduce the ability of an individual to function or to respond to additional challenge from the agent. Biological significance is also attributed to effects that are consistent with steps in a known mode of action. Statistical significance quantifies the likelihood that the observed effect is not due to chance alone. Precedence is given to biological significance, and a statistically significant change that lacks biological significance is not considered an adverse response.

For many discrete or quantal endpoints (e.g., birth defects, tumors, or some discrete pathological changes), this judgment is more straightforward because criteria have been established for deciding what type and incidence of effects are to be considered to be adverse, and an increase above the background rate can be judged using statistical tools. In the case of continuous measures (e.g., body weight, enzyme changes, physiological measures), this tends to be more difficult, because the amount of change to be considered adverse has not been defined by toxicologists or health scientists. Consequently, the endpoint is often decided in the context of the endpoint itself, the study, and the relationship of changes in that endpoint to other effects of the agent.

Decisions about the amount of change to consider adverse must always be made using professional judgment and must be viewed in light of all the data available on the endpoint of concern. All toxicological data on a chemical must be reviewed before deciding whether an effect is biologically significant and adverse. Using a default cutoff value to define adversity for continuous measures may result in an inappropriate interpretation of data and less than optimum evaluation of a chemical's effects.

4.3.2. Issues to be Considered in Characterizing the Database for Risk Assessment

4.3.2.1. *The Weight-of-Evidence Approach*

A weight-of-evidence approach such as that provided in EPA's RfC Methodology (U.S. EPA, 1994) or in EPA's proposed guidelines for carcinogen risk assessment (U.S. EPA, 1999a) should be used in assessing the database for an agent. This approach requires a critical

evaluation of the entire body of available data for consistency and biological plausibility. Potentially relevant studies should be judged for quality and studies of high quality given much more weight than those of lower quality. When both epidemiological and experimental data are available, similarity of effects between humans and animals is given more weight. If the mechanism or mode of action is well characterized, this information is used in the interpretation of observed effects in either human or animal studies. Weight of evidence is not to be interpreted as simply tallying the number of positive and negative studies, nor does it imply an averaging of the doses or exposures identified in individual studies that may be suitable as PODs for risk assessment. The study or studies used for the POD are identified by an informed and expert evaluation of all the available evidence.

4.3.2.2. *Use of Human and Animal Data in Risk Assessment*

Adequate human data are the most relevant for assessing risks to humans. When sufficient human data are available to describe the exposure-response relationship for an adverse outcome(s) that is judged to be the most sensitive effect(s), reference values should be based on human data. Much more data on a wide range of endpoints typically are required to establish confidence that there are no effects of exposure. If sufficient human data are not available to provide the basis for reference values, data from animal studies must be employed. It is advantageous if some human data are available to compare with effects observed in animals, even if the human data are not adequate for quantitative analysis. Availability of data on effects in humans at least allows qualitative comparison with effects observed in animals for determining whether toxicity occurs in the same organ systems and whether the nature of the effects is similar or different. If no human data are available, reliance must be exclusively on animal data. In that case, attention should be paid to whether data are available in more than one species and, if so, whether the same or similar effects occur in different species and possible sources of any observed differences.

One of the major default assumptions in EPA's risk assessment guidelines is that animal data are relevant for humans (e.g., U.S. EPA, 1991, 1996, 1998c). Such defaults are intended to be used in the absence of experimental data that can provide direct information on the relevance of animal data.

Several types of information should be considered when determining the relevance or nonrelevance of effects observed in animal models for humans. This information is used in a variety of ways, from determining the role of metabolism in toxicity (Is the parent chemical or a metabolite responsible for toxicity?), to assessing whether homologous activity would be

APPENDIX C – 14

EXCERPTS

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

January 30, 2013

EPA-SAB-13-001

The Honorable Lisa P. Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Subject: Review of EPA's Draft Assessment entitled *Toxicological Review of Libby Amphibole Asbestos* (August 2011)

Dear Administrator Jackson:

EPA's Office of Research and Development (ORD) requested the Science Advisory Board (SAB) to conduct a peer review of EPA's draft Integrated Risk Information System (IRIS) assessment, entitled *Toxicological Review of Libby Amphibole Asbestos (August 2011).* The draft document is the first IRIS assessment specific to Libby Amphibole asbestos (LAA), a term used to refer to the mixture of amphibole mineral fibers identified in the Rainy Creek complex near Libby, Montana. The SAB was asked to comment on the scientific soundness of the hazard and dose-response assessment of LAA-induced cancer and non-cancer health effects.

The SAB finds the EPA's draft assessment to be comprehensive and generally clear, logical and well-written. There are several areas that need more consideration, and we provide recommendations to further enhance the clarity and strengthen the scientific basis for the conclusions presented. The SAB responses to the EPA's charge questions are detailed in the enclosed report. The SAB's major comments and recommendations are provided below:

- Localized pleural thickening is an appropriate health endpoint for the derivation of the inhalation reference concentration (RfC). It is an irreversible structural, pathological alteration of the pleura and is generally associated with reduced lung function. The SAB has identified additional references and recommends that the agency include a more detailed review of the literature to further support this conclusion.

- The SAB supports the derivation of an RfC for LAA based on radiographic evidence of localized pleural thickening in an occupationally exposed Marysville, Ohio, cohort. However, the SAB recommends that the EPA conduct additional analyses to substantiate the RfC (to the extent data permit) of pleural abnormalities using the recently published studies on two other cohorts.

- The SAB recommends that more justification be provided for the selection of the "best" model for non-cancer exposure-response analysis. The SAB also recommends examining other exposure metrics besides the simple cumulative exposure, such as time-weighting of exposures. In addition, more justification is needed for the selection of 10 percent extra risk as the benchmark response since it is not consistent with the guideline for epidemiological data in EPA's *Benchmark Dose Technical Guidance*.

- A composite uncertainty factor of 100 was applied to the point of departure to obtain the RfC. EPA applied an uncertainty factor of 10 to account for human variability and sensitive subpopulations, and a database uncertainty factor of 10 to account for database deficiencies in the available literature for the health effects of LAA. The SAB recommends that the EPA re-evaluate the use of a default database uncertainty factor of 10 as part of the consideration of additional studies; additional data (e.g., Minnesota cohort and data on other amphiboles) might support a lower value, such as 3, for the database uncertainty factor. In addition, the SAB recommends EPA re-visit its judgement of a subchronic-to-chronic uncertainty factor and a LOAEL-to-NOAEL uncertainty factor of 1-fold.

- The SAB agrees that the weight of evidence for LAA supports the descriptor "Carcinogenic to Humans by the Inhalation Route" in accordance with EPA's *Guidelines for Carcinogen Risk Assessment*. The SAB views the mode of carcinogenic action of LAA as complex, and recommends that the agency conduct a formal mode of action analysis in accordance with EPA's *Guidelines for Carcinogen Risk Assessment*. Based on this formal analysis, the agency may still conclude that the default linear extrapolation at low doses is appropriate.

- The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation unit risk (IUR) and agrees that the use of the subcohort post-1959 for quantification may be reasonable due to the lack of exposure information for many of the workers in earlier years. The SAB has suggested sensitivity analyses that would explore the implications of the selection of the subcohort. The SAB finds it appropriate to use lung cancer and mesothelioma as endpoints for the derivation of the IUR. The SAB recommends a more detailed discussion and justification of how the use of mortality data rather than incidence data may have resulted in an undercount of cases of lung cancer and mesothelioma and what implications, if any, it may have for the derivation of the IUR.

- The draft assessment clearly described the methods selected to conduct the exposure-response modeling for lung cancer and mesothelioma. However, the SAB recommends that the agency provide more support for its choice of statistical models for the exposure-response analysis. The SAB also recommends consideration of several models in addition to the Poisson and Cox models used in the draft assessment.

- The agency has been overly constrained by reliance on model fit statistics as the primary criterion for model selection. The SAB recommends graphical display of the fit to the data for both the main models and for a broader range of models in the draft document to provide a more complete and transparent view of model fit. The SAB also recommends that the EPA consider literature on epidemiological studies of other amphiboles for model selection for dose-response assessment, since the size of the Libby subcohort used in the exposure-response modeling is small.

- The EPA has summarized many sources of uncertainty, sometimes quantitatively, as well as the direction and magnitude of the likely impact of each source of uncertainty. The SAB recommends that model uncertainty be evaluated by estimating risks using a more complete set of plausible models for the exposure-response relationship. This sensitivity analysis, while not a full uncertainty analysis, would make explicit the implications of these key model choices.
- Finally, the SAB has identified critical research needs for epidemiological studies, mode of action, and measurement methods for LAA to strengthen future LAA assessment.

The SAB appreciates the opportunity to provide the EPA with advice on this important subject. We look forward to receiving the agency's response.

Sincerely,

/signed/

Dr. David T. Allen, Chair
Science Advisory Board

/signed/

Dr. Deborah L. Swackhamer, Immediate Past Chair
Science Advisory Board

/signed/

Dr. Agnes Kane, Chair
SAB Libby Amphibole Asbestos Review Panel

Enclosure

1. EXECUTIVE SUMMARY

EPA's Office of Research and Development (ORD) requested the Science Advisory Board (SAB) to conduct a peer review of EPA's draft Integrated Risk Information System (IRIS) assessment, entitled *Toxicological Review of Libby Amphibole Asbestos (August 2011)*. The draft document is the first IRIS assessment specific to Libby Amphibole asbestos (LAA), a term used to refer to the mixture of amphibole mineral fibers identified in the Rainy Creek complex near Libby, Montana. The SAB was asked to comment on the scientific soundness of the hazard and dose-response assessment of LAA-induced cancer and non-cancer health effects (see Appendix A).

The SAB finds the EPA's draft assessment to be comprehensive and generally clear, logical and well-written. There are several areas that need more consideration, and we provide recommendations to further enhance the clarity and strengthen the scientific basis of the analyses. The SAB's major findings and recommendations are summarized below.

Mineralogy

The SAB notes that the section on mineralogy provides an important foundation for understanding the properties of Libby Amphibole asbestos (LAA) as related to the evaluation of its potential toxicity and carcinogenicity. The SAB recognizes that physical-chemical characteristics of asbestos (e.g., mineral composition, fiber dimensions) have not typically been available in toxicity studies of LAA. The SAB encourages a more rigorous and accurate description of LAA in the document, while acknowledging the potential ambiguities in the use of mineral-species names in toxicity studies.

Fiber Toxicokinetics

The SAB finds the section on fiber toxicokinetics does not distinguish between chrysotile and amphibole fibers. Since the focus of the draft document is on LAA fibers, it would be better to limit most of the literature reviews and discussion to those dealing with the family of amphibole asbestos fibers. The authors of this section should draw on more authoritative and comprehensive reviews in the literature to correctly specify and clarify issues on deposition and dosimetry.

Noncancer Health Effect

Selection of Critical Studies and Effects

The SAB supports the EPA's selection of the Marysville, Ohio, cohort for development of the RfC. The SAB finds it reasonable to select the subcohort for the main analysis (118 workers who began work in 1972 or later when exposure data were available and who had X-rays from the 2002-2005 exam), with the full cohort of 434 workers used for additional substantiating analysis. However, the SAB recommends additional analyses/cohorts to strengthen and support the RfC since the size of the Marysville subcohort is small. In addition to localized pleural thickening (LPT), the SAB suggests that the EPA consider any X-ray abnormalities as the outcome: LPT, diffuse pleural thickening (DPT), or asbestosis. The SAB also suggests that the EPA conduct analogous analyses (to the extent the data permit) of pleural abnormalities among the Libby workers cohort and the Minneapolis Exfoliation Community cohort.

The SAB agrees that the radiographic evidence of LPT in humans is the appropriate adverse critical effect for the derivation of the RfC. LPT has the appropriate specificity and is not confounded by cigarette smoking. It is a permanent structural, pathological alteration of the pleura and is generally associated with reduced lung function. The reported findings are compatible with the animal data showing tissue injury and inflammation. The SAB has identified additional relevant publications and recommends that the agency include a more detailed review of the literature to further support this conclusion.

Use of Animal and Mechanistic Studies

In general, the SAB finds the laboratory animal studies identified in Tables 4-15 and 4-16 and summarized in Appendix D of the EPA draft report to be appropriate and complete. Laboratory animal studies using a variety of non-inhalation routes of exposure have been used to ascertain the potential fibrogenic and carcinogenic potential of LAA. While inhalation is regarded as the most physiologically relevant means of fiber exposure in animals, there is no published study using this route of exposure for delivery of LAA to experimental animals. Therefore, the deposition and clearance of LAA has not been adequately assessed in experimental animals. However, inhalation studies have been conducted with tremolite, an asbestiform amphibole that is a component of LAA. The potency of inhaled LAA from epidemiology studies should be compared with that of tremolite fibers in rodents to add new information for refining the RfC for LAA.

Carcinogenicity

Weight of Evidence Characterization

The SAB supports the EPA's conclusion that the weight of evidence for LAA is "Carcinogenic to Humans by the Inhalation Route," in accordance with EPA's *Guidelines for Carcinogen Risk Assessment.* The occupational studies showed dose-related increased risks of lung cancer and mesothelioma among workers exposed by inhalation. Effects from short-term intra-tracheal instillation studies in mice and rats include altered gene expression, collagen induction, and inflammatory responses, and are consistent with the early-stage pathological change induced by other amphibole fibers. The EPA also has provided supporting evidence of the carcinogenic potential of LAA from studies with tremolite fibers, in light of LAA being about 6 percent tremolite by composition.

Mode of Action

The SAB finds the weight of evidence for the mode of action (MOA) of LAA based on laboratory studies to be weak. However, there are abundant MOA data for other amphiboles such as crocidolite and tremolite that are likely similar to the MOA for LAA. The SAB views the mode of action of LAA as complex, and recommends that a formal mode of action analysis of LAA be conducted in accordance with EPA's *Guidelines for Carcinogen Risk Assessment.* Based on this formal analysis, the agency may still conclude that the use of the default linear extrapolation at low doses is appropriate.

Selection of Critical Study and Endpoint

The SAB concludes that the EPA's selection of the Libby cohort for the derivation of the inhalation unit risk (IUR) is scientifically supported and clearly described. This cohort has been studied thoroughly,

with detailed work histories and a job exposure matrix. This cohort had elevated asbestos exposure, a wide range of measurements of asbestos exposure, and available cancer mortality data.

The SAB finds the use of the subcohort post-1959 may be reasonable due to the lack of exposure information in many of the workers in earlier years; out of 991 workers hired before 1960, 706 had all department and job assignments listed as unknown.

The SAB supports the use of lung cancer and mesothelioma as endpoints for derivation of the IUR. Since determining the cancer outcome from mortality rather than incidence data may have resulted in an undercount of both cancer outcomes, the SAB recommends more detailed discussion on how the use of mortality data could impact the derived IUR. It also would have been useful to know other major categories of mortality in this cohort.

Use of Laboratory Animal and Mechanistic Studies

The SAB agrees that the database of laboratory animal and mechanistic studies pertaining to LAA is appropriately presented in the report and its Appendices for support of its analysis of the human effects observed. However, the SAB finds the body of the document deficient in not utilizing what is known about the dimensions of the administered fibers from Appendix D. It is generally accepted that differences in biological potency among the various amphibole fiber types are due primarily to differences in dimensions, especially in fiber length distributions. The SAB also recommends that Section 4.6.2.2 be modified to reflect that there are insufficient data to determine the mode of action for LAA.

Inhalation Reference Concentration (RfC)

Estimates of Human Exposure Concentration

The approach described (in Appendix F of the EPA document) for exposure reconstruction is detailed and specific. Due to large uncertainties associated with the unmeasured pre-1972 exposures, the SAB agrees that the draft document appropriately eliminates this set of estimates and adheres only to exposure estimates based on measured concentrations for the derivation of the RfC.

With regard to the exposure metric, the SAB recommends that the EPA re-evaluate the raw exposure data and review pertinent sampling documentation to bolster its use of the geometric mean to represent the job group exposures, rather than an estimate of the arithmetic mean. The agency should consider whether a sensitivity analysis using the minimum variance unbiased estimator (MVUE) of the mean is warranted in the development of the cumulative exposure metric.

Exposure-Response Modeling

EPA's approach to the primary exposure-response modeling was generally appropriate, but the SAB recommends that the procedure be refined and the document should provide a clearer description of how the "best" model was chosen, in accordance with EPA's 2012 *Benchmark Dose Technical Guidance.* Since the Marysville cohort does not support precise estimation of the plateau, the EPA should consider fixing the plateau level based on a study of highly exposed asbestos insulation workers.

The SAB suggests examining other exposure metrics besides the simple cumulative exposure, such as time-weighting of exposures. In addition, the document uses a 10% Extra Risk (ER) as the benchmark response level (BMR) which is not typically used for human quantal response data. The SAB recommends that EPA explain what features of the dataset or outcome variable led the agency to choose a BMR that is considerably greater than the norm for epidemiological data.

Alternative Modeling Approach

The SAB agrees that the rationale for performing additional analyses of the full Marysville cohort is scientifically justified; the analysis of the entire cohort increases the number of cases of LPT available for analysis and substantiates the RfC estimated using the subcohort. However, the SAB recommends that the EPA revise its modeling approach and remove "time since first exposure" (TSFE) from the model of the plateau. EPA should determine whether it is appropriate to use TSFE in the linear predictor alongside cumulative exposure and/or use an alternative exposure metric that incorporates TSFE. The SAB also recommends the revised procedures for the subcohort analysis be followed, such as fixing the plateau using literature values.

Evaluation of Potential Confounders and Covariates

The SAB recommends a revised strategy for evaluation of confounders and covariates. Since the quantity of interest in the analyses of the Marysville cohort is the point of departure (POD), the evaluation of the various covariates should be made with respect to this quantity. The SAB suggests that the covariates fall into two classes: *exposure-related covariates* (various exposure metrics and TSFE) and *non-exposure-related covariates* [age, body mass index (BMI), gender, and smoking status]. For non-exposure related covariates, no additional primary analyses are needed. For exposure-related covariates, the SAB recommends that additional work be done to refine the models to consider alternative exposure metrics, as well as the inclusion of TSFE or other time-related variables in the analyses of the full cohort.

Conversion from Cumulative Occupational Exposure to Lifetime Exposure

The modeled POD is based on cumulative exposure estimates for the worker cohort examined. The SAB recommends using the full 70-year lifetime when converting cumulative to continuous exposure rather than 60 (70 minus the lag of 10 used for exposure in the POD derivation); i.e., do not correct for the lag of 10 for a 10-year lagged exposure, since the time of disease onset is not known in prevalence data.

Selection of Uncertainty Factors

The uncertainty factors deserve additional consideration and analysis. A composite uncertainty factor of 100 (an intraspecies uncertainty factor of 10 to account for human variability and sensitive subpopulations; and a database uncertainty factor of 10 to account for database deficiencies) was applied to the POD for derivation of the RfC. Although it may be difficult to identify specific data on LAA to support departure from the default value of 10 for human variability, concern for the impact on susceptible subpopulations, especially women and children, remains an issue. Consideration of additional data (Minnesota cohort and data on other amphiboles) might support a lower value, such as 3, for UF_D. In addition, a subchronic-to-chronic uncertainty factor higher than 1 may be used, given that the mean and maximum exposure duration in the study are well below the lifetime exposure of interest.

There also is concern that the BMR of 10% for a severe endpoint is not reflected by the choice of a LOAEL- to-NOAEL uncertainty factor (UF_L) of 1.

Characterization of Uncertainties

Overall, the SAB found that while the discussion on uncertainties in the methodology and approach on the derivation of the RfC was thorough, detailed, and logical, the uncertainty assessment can be strengthened. The SAB recommends that additional work be done to substantiate the RfC estimate through additional sensitivity analyses and discussion of results and insights from other datasets and studies.

Inhalation Unit Risk (IUR)

Exposure-Response Modeling

The SAB supports the agency's reliance on the Libby worker subcohort for derivation of the IUR because of its focus on good quality exposure data that are specific for LAA. However, it is important to acknowledge that this small subcohort may have its own limitations as a basis for modeling exposure-response relationship that might be expected in a larger population exposed over a lifetime. The SAB had particular concern about adequate characterization of early life exposures and the potential time dependence for development of disease.

The SAB agrees that the agency clearly described the methods used to conduct the exposure-response modeling for lung cancer and mesothelioma. However, given limitations in the subcohort and other statistical considerations, the SAB made a number of recommendations for providing greater support for this choice of modeling approach and for characterizing model uncertainty.

Having made these points, the SAB recognizes that the agency did conduct extensive sensitivity analyses of their chosen models in various ways to characterize exposure in the Libby cohort. However, the analyses rely on essentially the same underlying models. They do not address the fundamental question of model uncertainty – that is, whether any one model can or should be assumed to represent the exposure-response relationship for LAA. This issue is of particular concern for the estimation of risks from partial lifetime exposure where risk is essentially assumed to be independent of when in the course of a lifetime exposure occurs. Recommendations for addressing model uncertainty are discussed under response to charge question 5 in Section 3.2.6.5.

Approach for Quantification of Inhalation Unit Risk

In order to derive an IUR that represents the combined risk of mortality from lung cancer and mesothelioma, a cancer-specific unit risk for each tumor type was calculated according to the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005) by linear extrapolation from the corresponding POD. The IUR was then determined as a combined upper bound risk estimate for mortality considering both cancers. The SAB considers the approach to be consistent with the agency's own guidance, and found the description of the procedure used to be clear. However, the SAB recommends that EPA acknowledge that the assumption of independence is a theoretical limitation of the analysis and should provide a fuller justification for this assumption.

Potential Confounding by Smoking

The SAB agrees that the agency's use of the Richardson (2010) method for exploring possible confounding for smoking was appropriate. However, the SAB finds the statement that there is no evidence of confounding by smoking is too strong, and suggests modifications to the discussion that would be more compelling.

Adjustment for Mesothelioma Mortality Under-ascertainment

The number of mesothelioma deaths was adjusted for under-ascertainment stemming from inadequate coding in death certificates. The procedure is not described in any detail, but can be found in Kopylev et al. (2011). The EPA method appears to be scientifically supported, but is not clearly described. The SAB recommends that this section be expanded to provide a more detailed statement of how the numbers were calculated.

Characterization of Uncertainties

The SAB commented that the EPA has summarized the many sources of uncertainty and has evaluated qualitatively, and sometimes quantitatively, the direction and likely magnitude of their impact on uncertainty in the IUR. However, the SAB notes that an important source of uncertainty, that of model uncertainty, might not be accounted for either in the sensitivity analyses conducted to date or in the use of the 95% upper confidence limit (UCL). The SAB recommends that a more straightforward and transparent treatment of model uncertainty would be to estimate risks using a more complete set of plausible models for the exposure-response relationship. This sensitivity analysis would make more explicit the implications of these key model choices for uncertainty in the IUR.

Long-Term Research Needs

The SAB identifies long-term research needs for epidemiological studies, mode of action, and measurement methods for LAA.

- The National Institute for Occupational Safety and Health (NIOSH) and Agency for Toxic Substances and Disease Registry (ATSDR) should continue to monitor mortality among Libby workers and residents of Libby and Troy.
- The SAB recommends future research on mode of action on LAA to focus on biomarkers that are more clearly and specifically related to non-cancer endpoints (i.e., asbestosis) or cancer endpoints (e.g., mesothelioma). Inhalation studies in animal models that can provide both quantitative as well as mechanistic insight should be included.
- EPA should develop a TEM method that provides equivalent data to PCM for LAA.

3.2.3. Noncancer Health Effects of Libby Amphibole Asbestos

3.2.3.1. Selection of Critical Studies and Effects

Question 1. An occupational cohort of workers in a Marysville, OH facility exposed to Libby Amphibole asbestos (Lockey et al., 1984; Rohs et al., 2008) was selected as the basis for the derivation of the reference concentration (RfC). Please comment on whether the selection of this study population is scientifically supported and clearly described. If a different study population is recommended as the basis for the RfC, please identify this study and provide scientific support for this choice.

The rationale for the use of the Marysville, Ohio, cohort for development of the RfC was well described and scientifically supported. However, there are clear drawbacks to this cohort due to the lack of exposure sampling prior to 1972 when most of the cohort began work, the use of self-reported work histories, the end of Libby vermiculite use in 1980 and the mixture of vermiculite sources used throughout the life of the plant. These drawbacks are offset by the solely occupational exposure of this cohort, the use of better quality radiographs taken for research purposes, the use of 2000 ILO standards for reading radiographs, and a cohort with exposures closer to environmental levels. The selection of the subcohort for the main analysis has a clear and strong rationale. (There were 118 workers who began work in 1972 or later when exposure data were available, and who had X-rays from the 2002-2005 exam.) The full cohort of 434 workers was used for analyses to substantiate the subcohort findings.

Although the SAB agrees that the Marysville subcohort represents the best population upon which to base the RfC, there was discussion about the need for additional analyses/cohorts to strengthen and support the RfC since the size of the Marysville subcohort was small. One suggestion is to use the Marysville cohort but include any X-ray abnormalities as the outcome [LPT, diffuse pleural thickening (DPT), or asbestosis]. In addition, cause of death might be assessed for those who died between the two exams. Another suggestion for providing support and perspective to the Marysville findings is to conduct analogous analyses (to the extent the data permit) of pleural abnormalities among the Libby workers cohort (Larson et al., 2012) and among the Minneapolis exfoliation community cohort (Adgate et al., 2011; Alexander et al., 2012). The Libby workers have higher, well characterized occupational exposures compared to the Marysville cohort. The Minneapolis cohort of non-workers generally had estimated exposures at the lower end of the Marysville cohort but included women and children, thus providing a cohort more representative of the general population. However, because the Minneapolis cohort had estimated, not measured exposures, it would not be suitable for the primary RfC analysis. Similarly, because the Libby workers have both environmental and occupational exposures, this cohort should not be used for primary RfC analysis.

Question 2. Radiographic evidence of localized pleural thickening in humans was concluded by EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural thickening is associated with restrictive lung function, breathlessness during exercise and, for some individuals, chronic chest pain. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described. If a different health endpoint is recommended as the critical effect for deriving the RfC, please identify this effect and provide scientific support for this choice.

Radiographic evidence of localized pleural thickening (LPT) in humans is the appropriate adverse and critical effect for the derivation of the RfC. This is clearly described and well supported by the lines of evidence presented in section 4.1.1.4.2. However, the SAB believes additional evidence is available to further support this view and should be reported.

While other health endpoints (such as diffuse pleural thickening and small opacity profusion) might have been considered candidates for the critical effect for deriving the RfC, the use of LPT is appropriate and well supported. LPT is a permanent, structural, pathological alteration of the pleura. LPT is found at a significantly elevated prevalence in exposed individuals, has the appropriate specificity and is not confounded by cigarette smoking. LPT also is associated with reduced lung function. Furthermore, the findings reported in this section are compatible with the animal data showing tissue injury and inflammation.

It is important to provide a more detailed review of the literature to support the use of LPT as the appropriate endpoint, including studies addressing the relationship between LPT and both pathologic and physiologic abnormalities. Published studies that address the relationship between LPT and lung function suggested by the SAB include Lilis et al., 1991b; Paris et al., 2009; Clin et al., 2011; Sichletidis et al., 2006; Whitehouse, 2004; and Wilken et al., 2011, along with those referenced in the American Thoracic Society (ATS) Statement entitled, *Diagnosis and Initial Management of Nonmalignant Diseases Related to Asbestos: Official Statement of the American Thoracic Society* (ATS, 2004) (Ohlson et al., 1984; 1985; Jarvolm and Sanden, 1986; Hjortsberg et al., 1988; Oliver et al., 1988; Bourbeau et al., 1990; Schwartz et al., 1990; Miller et al., 1992; Van Cleemput et al., 2001; Miller, 2002;). Consistent with that ATS Statement, the SAB concludes that cohort studies have shown significant reduction in lung function, including diminished diffusing capacity and vital capacity associated with LPT. To help clarify the difference between "clinically significant" effects of plaques in a given patient vs. epidemiological studies evaluating the effects of asbestos exposure in an exposed population, the SAB suggests that the EPA clarify in the assessment the range of endpoints that generally can be used to derive an RfC.

In addition to localized pleural thickening, the SAB also suggests that the EPA consider looking at LPT, DPT and small opacity profusion score together as an outcome. There is evidence that LPT is not always the first adverse effect that is detected on chest radiographs, and some individuals with LAA exposure can develop either DPT or increased profusion of small opacities without developing evidence of LPT. Combining outcomes is appropriate, since DPT and small opacity profusion also are effects of asbestos exposure and the goal is to define an exposure level below which LAA is unlikely to have adverse health effects.

Recommendations:

- The SAB suggests the EPA assessment clarify the range of endpoints that generally can be used to derive an RfC.
- The agency should include a more detailed review of the literature to support the selection of LPT through detailing the studies that show the relationship between LPT and both pathologic and physiologic abnormalities, and also risk of other non-cancer asbestos-related diseases.
- In addition to LPT, the document should include an analysis that uses all radiographic outcomes (LPT, DPT and small opacities), recognizing this change may have little impact on the current analysis.

3.2.5.3. Alternative Modeling Approaches

Question 3. EPA's assessment also provides the results of alternative modeling approaches to derive a POD for localized pleural thickening. This modeling used the full Marysville worker data set with exposures from 1957 and later and a Cumulative Normal Michaelis-Menten model that incorporates both cumulative exposure and time from first exposure as explanatory variables. Please comment on whether EPA's rationale for presenting these alternative approaches is scientifically justified and clearly described. Please identify and provide the rationale if a different approach for identifying the most appropriate population within the cohort of Marysville workers is recommended as the basis for estimating a POD.

The SAB notes that this question applies to the full Marysville cohort. The SAB agrees that the rationale for performing additional analyses of the full Marysville cohort is scientifically justified and that the analysis of the entire cohort increases the number of cases of LPT available for analysis and substantiates the primary RfC estimate derived from the subcohort.

However, the SAB does not find the rationale for the analysis approach to be well justified and it recommends that the full cohort analysis be redone. With respect to the approach:

- It is not clear that the scientific basis of using time since first exposure (TSFE) is well founded. EPA should consider what TSFE is supposed to be measuring and how it is related to other variables in the dataset (specifically age and exposure). There is some suggestion in the draft document that in this dataset it is a surrogate measure of intensity since people with larger TSFEs would be more likely to have been exposed to higher levels of LAA present during the early time periods. This perspective should help identify modeling options.

- The SAB also finds that the method for incorporating TSFE into the full cohort analysis is not well justified. Currently, the EPA uses TSFE as a predictor for the plateau in the Cumulative Normal Michaelis-Menten model. No biological justification is given for why this maximum proportion would vary with TSFE.

Regarding revisions to the analysis, the SAB recommends that in this dataset a more natural way to incorporate TSFE into the model would be to allow TSFE to affect the rate of change in the probability of LPT by: (1) including it directly in the linear predictor portion of the model alongside cumulative exposure; and/or (2) using an alternative exposure metric such as residence time weighting (RTW) that more heavily weights exposure in the distant past. The functional form of TSFE could then be selected using standard approaches (e.g., comparing AICs). Since adding TSFE to the model should affect the coefficient of cumulative exposure, the EPA should consider a dichotomous Hill model which allows an exposure parameter (b in Table 5-4) to be estimated, as an alternative to the Michaelis-Menten model. Finally, the SAB recommends that other changes to the analysis follow the approaches used for the subcohort analysis, such as fixing the plateau using literature values as recommended in the response to charge question 2 in Section 3.2.5.2 of this report.

The SAB notes that in principle it may be preferable to base the RfC on an analysis of incidence rather than prevalence data. Because of the nature of the dataset, the Marysville cohort does not support a direct analysis of incidence. While it may be possible to fit an alternative model derived from integration of a plausible incidence model (e.g., see Berry et al., 1979; Berry and Lewinsohn, 1979; Paris et al., 2008), this approach will require a number of untestable assumptions, particularly given the small size

of the Marysville cohort. In lieu of conducting such an analysis, the SAB recommends that an explicit acknowledgement be added to the report regarding the implications of various model alternatives.

Recommendations:

- Improve the scientific justification for using TSFE in the full cohort analysis; this justification will include an explanation of its meaning in the context of this dataset.
- Revise the full cohort analysis to change the approach to incorporating TSFE, removing it from the model of the plateau. As part of the revision, the SAB suggests assessments be made to determine whether it is appropriate to use (a) the dichotomous Hill model, (b) TSFE in the linear predictor alongside cumulative exposure and/or use an alternative exposure metric that explicitly incorporates TSFE, and (c) the approaches recommended for the subcohort such as a fixed plateau. As appropriate, such analyses should include assessment of the functional form of TSFE.
- The SAB recommends that the EPA present the lower 95% confidence limit of the benchmark concentration (BMCL) estimates from a set of reasonable and plausible models, and selections of data, which will both inform selection of a preferred model and illustrate the range of model uncertainty.

3.2.5.4. Potential Confounders and Covariates

Question 4. EPA has evaluated potential confounders and covariates where data are available. Specifically, EPA has explored the influence of age, body mass index, smoking status, time since first exposure, gender, and alternative exposure metrics on model fit and evaluated their association with the modeled health outcomes (see Section 5.3). Are these analyses clearly described and appropriately conducted? Are the results of these analyses appropriately considered in the RfC derivation? Additionally, there is a possibility of exposure-dependent censoring in participant selection for the update of the Marysville cohort (Rohs et al., 2008) but no evidence of selection bias. Does the SAB have any specific recommendations for evaluating and, if appropriate, quantitatively addressing exposure-dependent censoring in these analyses?

The SAB recommends a revised strategy for evaluation of covariates. The target of inference for the analyses of the Marysville cohort is the POD, which in this case is the BMCL. The evaluation of the various covariates should be made with respect to this target of inference. The SAB suggests the covariates fall into two classes: *exposure-related covariates* (various exposure metrics and TSFE) and *non-exposure-related covariates* [age, body mass index (BMI), gender, and smoking status]. We provide recommended revised strategies for considering these two classes of covariates that follow directly from consideration of the target of inference.

Non-exposure-related covariates: A decision on whether to control for the non-exposure-related covariates should account for how the EPA wishes to determine and apply the RfC. The SAB suggests a BMCL most directly applicable to all members of the general population is most appropriate. This implies that the BMCL should be estimated from a model that includes exposure covariate(s), but that is otherwise unadjusted. This is the same approach used in the current draft document; only the rationale for the approach is different. The SAB suggests it would be informative to conduct sensitivity analyses to examine how the BMCL varies across subgroups defined by covariate values (e.g., older males or smokers). Because the Marysville subcohort is a small dataset, it is difficult to conduct this evaluation exclusively in the subcohort. Therefore the SAB suggests that the EPA use the *full* cohort for the model selection and parameter estimation components of sensitivity analyses incorporating these covariates.

For this activity the EPA would use its selected final model after excluding all exposure variables (e.g., the dichotomous Hill model with fixed background, fixed plateau, and after dropping exposure variables). After fitting a model with a specific set of non-exposure-related covariates in the full cohort, one can estimate a "risk score" (i.e., the linear predictor for the non-exposure-related covariates). This risk score would be included as a single term (as either an unscaled offset or scaled by its estimated coefficient) in the subcohort analysis. Similar to the approach presented in Table E-5, these analyses can be used to produce a new table of subgroup-specific conditional BMCLs; these values will give some evidence of how the target of inference varies by subgroup. In addition, weighted averages of the conditional BMCLs can be computed to reflect population average BMCLs for specific covariate distributions in target populations. For instance, Gaylor et al. (1998) gives a formula for the upper tail of a 95% confidence interval and this formula can be extended to obtain BMCLs for weighted averages.

Exposure-related covariates: The inclusion of exposure-related covariates in the model is fundamental to the inference. The EPA has done excellent preliminary work, and the SAB has provided recommendations in Sections 3.2.5.2 and 3.2.5.3 of this report about how to revise the approach. In addition the SAB recommends that the EPA consider taking several further steps. First, alternative exposure metrics should be assessed directly in the subcohort dataset to determine whether they fit the data better. In particular, alternative metrics (such as residence time weighted exposure) that more heavily weight more distant exposure may be more biologically plausible because individuals exposed at an earlier age might be more susceptible to the damaging effects of asbestos. Second, TSFE should be considered for addition to the model. Since TSFE is complete and equally well estimated across all members of the cohort, the full cohort can be used to determine how to model this variable. Similar to the approach recommended for the sensitivity analyses discussed above, this would be done using the model intended for the subcohort, but omitting exposure variables other than TSFE. Then, the functional form of TSFE selected using the full cohort can be added to the subcohort analysis, either as an unscaled offset term or as a scaled covariate. Given biological understanding of the disease process, for models with both estimated exposure and TSFE included, it would be appropriate to report the BMCL conditional on a large TSFE.

Additional comments on covariates:

- BMI: In section 5.2.3.3.1., it would be helpful if the justification for considering BMI as a covariate were briefly explained. It is included elsewhere, but readers may have missed it.
- TSFE:
    - TSFE deserves careful consideration for both biological and dataset-specific reasons. It is an important determinant of LPT both because individuals' lung tissues exposed at an earlier age might be more susceptible to the damaging effects of asbestos and because asbestos' effect over time is increasingly damaging. It is correlated with exposure in this dataset since subjects with the longest TSFE were exposed in the early years of the cohort when exposures were higher. It is also more accurately estimated than exposure.
    - The SAB does not agree with the use of the Cumulative Normal Michaelis–Menten model to adjust for TSFE because it makes the assumption that the TSFE only affects the plateau. This has not been justified biologically or in the context of features of this particular dataset. Instead, the SAB recommends that EPA consider alternative approaches to account for TSFE.

- Smoking:
  - Smoking is included in the follow-up by Rohs et al. (2008). However, the ever/never categorization of smoking is much less informative than the pack-year analysis of smoking used in the earlier study by Lockey et al. (1984).
  - There is an important discussion of the evidence linking pleural changes and smoking in footnote 34 on page 5-46. This information could be moved into the body of the report, and amplified somewhat. A table summarizing the relevant studies (irrespective of type of amphibole asbestos) summarizing the evidence regarding the role of smoking would be useful.
- Gender: There is little discussion of gender, except in places where the number of females is listed as too few to analyze in any detail. The SAB did not regard this as a serious concern because it is reasonable to assume that females and males have similar probabilities of developing LPT.

The SAB recommends that a table be included summarizing the results of the various sensitivity analyses and how they change the POD.

Exposure-dependent censoring: The exposure-dependent censoring discussion is based on results from Rohs et al. (2008) that inappropriately separated deceased non-participants from the remaining non-participants. Once all non-participants are combined there is no evidence of exposure-dependent censoring. Furthermore, exposure-dependent sampling by itself does not lead to bias in risk estimates. The important issue for bias is whether two individuals with the same exposure, one diseased and the other not, are equally likely to participate in screening. There has been no strong rationale presented that would indicate that such differential selection has occurred in this cohort.

Recommendations:

- Revise consideration of covariates to focus on their impact on the target of inference.
  - For non-exposure-related covariates, this only alters the presentation; no additional primary analyses are needed. Sensitivity analyses conditional on subgroups defined by covariates can be added.
  - For exposure-related covariates, additional work is needed to refine the models to consider alternative exposure metrics, as well as the inclusion of TSFE or other time-related variables in analyses of the full cohort. The SAB encourages the EPA to either fully justify analyses based on the Cumulative Normal Michaelis-Menten model in the context of this particular dataset, or replace them.
- Revise this discussion of Rohs et al. (2008) to make note (perhaps in a revised table) that the dose distribution in participants is similar to the overall dose distribution of the original full cohort. Furthermore, revise the discussion of exposure dependent sampling to distinguish this from bias differential sampling in the sense above.

With respect to exposure assessment, analytical methods and environmental conditions are substantial contributors to uncertainty because of differences between the 1970s and today. As discussed throughout the report, PCM was the only generally accepted method for measuring airborne fiber concentrations used until the 1980's. PCM's limitations are well-detailed in the report: an inability to detect fibers smaller than 0.25 μm, an inability to differentiate asbestos fibers from other fibers, and a limitation to counting only fibers longer than 5 μm. Today, TEM can easily detect and positively identify airborne asbestos of all sizes. But, because the RfC is based on 1970's PCM analyses, the RfC must be implemented in a way that most closely replicates analysis in the 1970's. At the 1970's study site, the vast majority of measured fibers were almost certainly LAA, so PCM's inability to identify asbestos did not create much uncertainty. Today, even ambient air will yield fiber concentrations that exceed the RfC. The culprit fibers will likely be cellulose fibers from cotton, wood, paper or synthetic fibers, rather than asbestos. Hence, today's PCM counts will be from fibers that are unrelated to the RfC. Thus it is important that TEM be used to identify and count asbestos fibers in air samples for RfC purposes. Finally, Page 5-118, Lines 22-33 of the EPA's draft document discuss the two-fold under-reporting of fibers because of PCM's poorer resolution in the 1970's, 0.44 μm versus 0.25 μm today. Because today's PCM analysts have no capability for discriminating fibers > 0.44 μm, the need for TEM analysis of samples collected for implementation of the RfC is even more important. A TEM protocol for PCM equivalent fibers wider than 0.44 μm could be easily developed.

Recommendations:

- Harmonize the uncertainty discussions across the document.
- Substantiate the RfC estimate through
    - Additional sensitivity analyses of the subcohort;
    - Discussion of results from other studies;
    - Additional sensitivity analysis of the full cohort; and
    - Summarizing in tabular form the results of the various sensitivity analyses and model alternatives, to show how they affect the POD.
- Use TEM to identify and count asbestos fibers longer than 5, 10, and 20 μm in air monitoring samples for implementation of the RfC.

3.2.6. Inhalation Unit Risk (IUR)

3.2.6.1. Exposure-Response Modeling

Question 1. Exposure-response modeling was conducted separately for lung cancer and mesothelioma mortality. The POD estimates for these endpoints are based upon analysis of the subcohort of workers first exposed after 1959 when the exposure data were judged to be better characterized. The exposure-response modeling included consideration of a variety of exposure metrics that varied with time and incorporated different lag and decay parameters. Based on the results of the exposure-response modeling, a life table analysis was used to determine the PODs for each type of cancer for the various exposure metrics. Have the exposure-response modeling and determination of the PODs from life table analysis been appropriately conducted and clearly described? If a different approach to exposure-response analysis is recommended as the basis for estimating the IUR, please identify the recommended methods and provide a rationale for this choice.

In general, the EPA clearly described the methods it had selected to conduct the exposure-response modeling for lung cancer and mesothelioma. The risk calculations in the life tables appeared correct but would benefit from clearer explanations. Some suggestions for clarifications are noted below.

The agency was overly constrained by reliance on model fit as the primary criterion for model selection and the SAB recommends a broader discussion of biological and epidemiological criteria as well. For the mesothelioma data, for example, the Peto model was disregarded due to a poorer fit than the Poisson model. The results for this analysis are not shown and, given the particular interest in this model, should have been. A parametric survival model (e.g., Weibull) could have also been used to obtain estimates of absolute risk. It would also be appropriate to compare the results of the final model against those from fitting a two-stage clonal expansion (TSCE) model. Use of the TSCE model would allow for a more direct evaluation of, and possibly justification for, age-dependency of the IUR. The Richardson (2008) paper provides a publicly available and transparent approach to application of the TSCE. Ultimately, there are many competing models that could have been used instead of the Poisson and Cox models (e.g., parametric survival models, accelerated failure time models, additive models) that could have provided very different estimates of risk, but they were not discussed.

Data exist that suggest that the lifetime risk of developing the mesothelioma increases the earlier in life that exposure is first received. The Peto model (Peto, 1979; Peto et al., 1982) was developed to explain such observations in the empirical data. While the Peto model has been more widely used for risk assessment, most notably in the previous IRIS summary for asbestos, it has also only been formally fitted to data in a limited number of cohorts (HEI-AR, 1991). Ongoing analysis of incidence of mesothelioma appears to be consistent with the exposure-response relationship described in the Peto model. The draft report needs to do a more complete job of justifying why this and other epidemiologic evidence should be excluded as a basis for selection of a plausible model for predicting mesothelioma risk. Chapters 2 and 3, for example, consider toxicological and other evidence developed with exposures to asbestos that are not strictly LAA. The cohorts used in the development of the Nicholson/Peto model and the exposures they experienced should provide information about the time course of the development of disease.

The SAB recognizes that the agency's effort to focus on good quality exposures specific to LAA has led to reliance solely on the Libby worker subcohort. This rationale is understandable, but at the same time, it is important to acknowledge that this small subcohort may have its own limitations as a basis for modeling exposure-response relationships for a larger population over a lifetime. As a sensitivity analysis to evaluate the potential impact of omitting the Libby workers hired before 1959, the SAB recommends analyzing the entire Libby cohort using interval statistics (Nguyen et al., 2012; Manski 2003; *inter alia*) or other traditional approaches for data censoring in predictors (cf. Küchenhoff et al., 2007). It can be misleading to use midpoint substitution (as described in Section 5.4.6.1.2) that assumes poorly measured or missing predictors have some constant value. Interval statistics and traditional censoring approaches to measurement uncertainty would, in essence, replace point values with interval ranges. When the intervals are narrow, as they might be for 21% of the early hires for which jobs titles are available, there might be a good deal of recoverable information present. When the intervals are much wider, there would be accordingly less information. Whatever empirical information may be present, it is worth evaluating whether its inclusion is better than leaving out the data entirely, which in principle amounts to replacing them with intervals that are completely vacuous, from zero to infinity. This approach can produce an interval range for the final outputs, which would provide the explicit quantitative uncertainty statement as recommended by previous National Academy of Sciences reviews.

The SAB recognizes that the agency did conduct sensitivity analyses with several analyses of the Libby cohort data, including those that used different models (Tables 5-20 for lung cancer and 5-21 for mesothelioma). A limitation of these analyses is that they all rely on the assumption that the effect of exposure can be modeled as a function of cumulative dose. This assumption is consistent with the agency's *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005), which state that "unless there is evidence to the contrary in a particular case, the cumulative dose received over a lifetime, expressed as an average daily exposure prorated over a lifetime, is recommended as the appropriate measure of exposure to a carcinogen." EPA therefore did not address the fundamental question about whether any one model can or should be assumed to represent the exposure-response relationship for LAA. Therefore, one cannot be confident that the "true" exposure-response relationship for LAA is really "accounted for" by use of the upper confidence limit (UCL) on the slope (per fiber/cc) or, ultimately, the combined IUR from mesothelioma and lung-cancer mortality (see related discussion in response to question 3 and 5 in Section 3.2.5).

This issue is of particular concern for the estimation of mesothelioma risks from partial lifetime exposures, where risk is essentially assumed to be independent of when in the course of a lifetime exposure occurs. For example, one year of exposure to a given concentration in childhood yields the same lifetime average daily dose as one year of the same exposure in adulthood. This assumption is not consistent with the relevant body of evidence on the development of asbestos-related disease. Therefore, there is some probability — not well characterized — that this approach underestimates the relative effect of early exposure, but exaggerates the effect of exposure later in life.

Recommendations:

Two types of recommendations have been made. The first set is asking for simple explanations in the text that the SAB thinks will clarify the rationale for analytic choices made by the EPA. The next set includes requests for additional presentations of data or analyses, roughly in order of priority, that the SAB concludes are important to provide some quantitative perspective on the analytic choices made.

Clarifications:

- Poisson regression analyses: the mathematical form of the regression function should be given, and discussion of whether the potential for over-dispersion was assessed.
- Cox proportional hazards modeling: the reasons should be given for not conducting a Bayesian analysis as was done for the Poisson regression model for mesothelioma.
- Life-table analysis: the method used to estimate the hazard function for the exposed population should be clearly spelled out in the text. Was it based on a nonparametric estimate of the baseline hazard from the sub-cohort? Given that the SEER data were used to calculate the background incidence of lung cancer, it would seem more appropriate to use those data to estimate the baseline hazard and then to use the regression coefficient obtained from the Cox model applied to the sub-cohort data to obtain the hazard of the exposed group. Thus, the reasons for not using the SEER data to estimate the baseline hazard should be explained.
- Expand the discussion of model selection to explain the reliance on model fit criteria for model selection. In particular, why should the broader epidemiologic evidence on the time course of disease not argue at least for the presentation of more than one statistical model?

Provision of additional data or analysis:

- In a tabular form, summarize the fit results, POD estimates, and IUR estimates from the full range of models considered in order to show the dependence of the IUR estimate on model selection.
- Present the fit to data graphically for both the main models and for a broader range of models, including the Peto model. This step would provide a more thorough and transparent view of fit, particularly in the region of the BMR, than is allowed by examining summary statistical values alone.
- Provide in an appendix the details of the Nicholson/Peto model fit for which the text currently states "data not shown".
- Allow evaluation of the time dependence of disease by providing tabulations of mesothelioma mortality rates and lung cancer SMRs by time since first exposure, duration of exposure and period of first exposure (for both the full and sub-cohorts of Libby workers).
- Evaluate the feasibility of conducting an ancillary analysis of the full Libby data set, including hires before 1959, using interval statistics or other traditional censoring methods (not simple midpoint substitution). At a minimum, discuss the possible quantitative uncertainties associated with using the smaller subcohort.

3.2.6.2. Potential Confounding by Smoking

Question 2. Smoking is a strong independent risk factor for lung cancer and may be an important confounder of the lung cancer mortality analysis. Data on individual smoking habits and history were largely missing and could not be used to control for potential confounding in regression analyses. However, EPA used three approaches to evaluate the confounding issue, including restriction of the cohort and two analytic evaluations of the potential for confounding by smoking (see Section 5.4.3.6.5). Please comment on whether the methods and analyses are clearly presented and scientifically justified. If additional analyses are recommended, please identify the methods and scientific rationale.

The SAB recognizes the challenges in controlling for smoking given the lack of data on smoking histories for the cohort. The agency has taken reasonable steps to identify the potential for confounding using independent approaches. However, statements in the document (on p. 5-96 and again on p. 5-127) that— because the proportional hazards assumption is satisfied in the subcohort— there is no evidence of confounding by smoking, are too strong. Reaching this conclusion requires some strong assumptions, including one that the decline in smoking prevalence observed in the general U.S. population also occurred in the Libby cohort.

The agency's use of the Richardson (2010) method for exploring possible confounding for smoking was appropriate. However, the conclusion that there is no evidence for confounding by smoking relies more heavily on the *p*-values, which are marginally non-significant, than it needs to. More compelling is the observation of a negative association with COPD in their analyses. The fact that the coefficients for exposure in the COPD Cox models were negative is strong evidence against positive confounding; smoking is positively related to COPD risk and thus if positive confounding is occurring, then one would also expect the relationship between asbestos exposure and COPD risk to be positive.

Recommendations:

- The numbers of COPD deaths (n) in the sub-cohort that were the basis for the analysis should be presented in the text.

- The statements about the evidence against confounding by smoking given by restriction of the cohort should be qualified by the assumptions required to justify them, or deleted.
- The SAB had no recommendations for further analyses.
- The reference to three methods is confusing. There are actually only two, the restricted cohort and the Richardson analysis for which two exposure metrics are explored.

3.2.6.3. Quantification of Inhalation Unit Risk

Question 3. In order to derive an IUR which represents the combined risk of mortality from lung cancer or mesothelioma, a cancer-specific unit risk for each tumor type was calculated according to the Guidelines for Carcinogen Risk Assessment (U.S., EPA, 2005; Sections 3.2 and 3.3) by linear extrapolation from the corresponding POD (i.e., the lower 95% confidence limit on the exposure associated with 1% extra risk of lung cancer or 1% absolute risk of mesothelioma mortality). The IUR was then determined as a combined upper bound risk estimate for mortality considering both cancers. Has this approach been appropriately conducted and clearly described?

The SAB found the description of the procedure used to be clear but considered the justification for the independence assumption to be lacking in depth. The EPA should provide a discussion of the potential consequences of assuming that the estimated IURs for mesothelioma and lung cancer mortality are independent, noting the possibility that the upper bound on the IUR may be understated if the risks are positively correlated. The document may refer to the 1994 NRC report, which suggested that treating different tumor occurrences as independent is "not likely to introduce substantial error in assessing carcinogenic potency". However, the document should acknowledge that this statement was made in the context of animal bioassays and that human populations are more heterogeneous in risk factors related to mesothelioma and lung cancer mortality. If any risk factors are shared across outcomes and not accounted for in the modeling, the risk estimates generated by the different models are likely correlated. Given the small size of the data set, and lack of an appropriate statistical method, this correlation cannot be estimated reliably. One approach might be to undertake bounding analysis on the lifetime risk estimates using, for example, the Fréchet inequality for disjunctions (Fréchet, 1935) that makes no assumption about the nature of the dependence. This analysis could reveal how large the impact of dependence might be. At the very least, the restrictive assumption of independence must be mentioned and the potential consequences of a violation of this assumption must be discussed.

Recommendations:

- The EPA should acknowledge that the assumption of independence is a theoretical limitation of the analysis, and should provide a fuller justification for this assumption. EPA has cited the NRC (1994) analysis as suggesting the impact of this issue is likely to be relatively small. This view is also echoed in the EPA's (2005) *Guidelines for Carcinogen Risk Assessment*. These provide the basis for a default assumption. However, it would be preferable if this assessment discussed the evidence base and rationale for lung cancer and mesothelioma specifically.
- As a sensitivity analysis, the EPA should consider quantitatively accounting for dependence in the risks of mesothelioma and lung cancer mortality either using a method that models the dependence explicitly, or a bounding study that evaluates the numerical consequences of the assumption of independence.

3.2.6.4. Adjustment for Mesothelioma Mortality Under-ascertainment

Question 4. Please comment on the adjustment for mesothelioma mortality under-ascertainment. Is this adjustment scientifically supported and clearly described? If another adjustment approach is recommended as the basis for the IUR, please identify that approach and provide the scientific rationale.

The number of mesothelioma deaths was adjusted for under-ascertainment stemming from inadequate coding used in death certificates. The procedure used is not described in any detail, but can be found in the Kopylev et al. (2011) reference. A total of 18 mesotheliomas were observed in the Libby cohort from 1980 to 2006. The estimated number of 24 mesotheliomas was obtained after using a Monte Carlo analysis. The ratio of 24 to 18 yields the median of 1.33. The Kopylev manuscript also provides a figure of 1.39 in Table 3, which is the mean later reported in the EPA report. The EPA method appears to be scientifically supported, but is not clearly described. This section should be expanded and a much more detailed statement of how the numbers were arrived at should be provided.

No additional adjustment approach is described in the EPA report. The authors should provide an additional estimate using the 37% figure mentioned on page 46 of the Kopylev et al. (2011) reference. This is the percentage of mesothelioma cases that would be missed using previous histopathological analyses of cancer registry data. Using 37% would yield an estimate of about 29 mesothelioma cases instead of 24. The median ratio would then be 1.61 instead of 1.33. This number, and its related mean, should be utilized to provide a separate analysis of unit risk for comparison purposes.

3.2.6.5. Characterization of Uncertainties

Question 5. Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the IUR and whether this information is presented in a transparent manner.

The SAB commends the EPA for summarizing (in Section 5.4.6.1 of the draft document) the many sources of uncertainty considered in the course of this document and evaluating, at least qualitatively, and sometimes quantitatively, the direction and magnitude of the likely impact of each source of uncertainty.

However, the SAB noted that most of what the document has accomplished is through targeted sensitivity analyses that examine one assumption at a time, while holding all others more or less constant. For example, the agency has indeed done a thorough job of exploring sensitivity of the IURs to a range of investigator analyses of lung cancer (Table 5-20) and mesothelioma (Table 5-21) for the Libby worker subcohort, and to a wide range of assumptions about the exposure metrics to be used in the basic models (e.g., Table 5-9). The basic underlying models chosen for lung cancer and for mesothelioma are the same.

The sensitivity analyses in the document are individually well described, appear well-done and provide reassurance, under the assumptions of the basic models and approaches chosen to estimate the IUR, that the particular exposure metric and lag, for example, do not appear to make a big difference in the value of the IUR. However, they are currently presented somewhat in isolation, and thus do not take into account the magnitude and likelihood of multiple sources of uncertainty in the same analysis or address the overall distribution of uncertainty in the IUR. Consequently, the SAB did not think that the following statement had been fully justified:

> ...the EPA's selected combined IUR of mesothelioma and lung-cancer mortality accounts for both the demonstrated cross-metric uncertainty as well as several additional uncertainties, which could have resulted in underestimates of the mesothelioma and lung-cancer mortality risks (p 5-105, lines 1-5).

As noted in response to question 1 in Section 3.2.6.1 above, the SAB identified that model uncertainty is an important source of uncertainty that might well not be accounted for by using the 95% UCL on the IUR and the combined IUR [redacted] or at least that had not been represented by the sensitivity analyses provided.

Recommendations:

- The SAB recommends that a more straightforward and transparent treatment of model uncertainty would be to estimate risks using a more complete set of plausible models for the exposure-response relationship (discussed in response to question 1 in Section 3.2.6.1), including the Poisson models. This sensitivity analysis would make the implications of these key model choices explicit.

- The SAB recommends that, as an initial step in conducting an integrated and comprehensive uncertainty analysis, the agency provide a tabular presentation and narrative evaluation of the IUR estimates based on a reasonable range of data selections (e.g., all or part of the earlier hires as well as the "preferred" subcohort), model forms and input assumptions (as discussed, in the response to question 1 in Section 3.2.5). These input assumptions should include *inter alia* exposure metrics and externally defined parameters, as discussed in the response to question 1 in Section 3.2.5. As noted in the current cancer risk assessment guidelines (EPA, 2005, page 3-29):

  > The full extent of model uncertainty usually cannot be quantified; a partial characterization can be obtained by comparing the results of alternative models. Model uncertainty is expressed through comparison of separate analyses from each model, coupled with a subjective probability statement, where feasible and appropriate, of the likelihood that each model might be correct (NRC, 1994).

The SAB notes that ideally, the agency would develop a quantitative characterization of the overall uncertainty in its IUR estimates by incorporating the major sources of uncertainty the agency has identified in its evaluation. However, the SAB recognizes the challenge of conducting such an analysis, and is not recommending that it be undertaken at this time.

4. LONG-TERM RESEARCH NEEDS

4.1. Epidemiology

It would be informative and very important for NIOSH and ATSDR to continue monitoring mortality among Libby workers (including those residing in Libby and nearby towns such as Troy, Montana) and residents of Libby and nearby towns, respectively, to determine the number of new lung cancers, mesotheliomas, and non-malignant pulmonary diseases (i.e., asbestosis) in these two populations.

The last occupational ascertainment was through 2006; an additional five years of data should now be available. In addition to a dose-response evaluation, an overall SMR should be calculated for lung cancer in this population by comparison to both the Montana and U.S. populations.

The previous ATSDR community SMR mortality survey was from 1979-1998. It should now be extended through 2011 and should include an analysis specific for community, non-occupationally exposed, individuals. Early-life exposure to LAA could possibly be obtained from surrogate interview information from the community population. Smoking, occupational, and residential histories should be obtained for the lung cancer, mesothelioma, and non-malignant respiratory disease (i.e., asbestosis) categories. Data concerning previous Libby residents who had moved away (and died in other states) would need to be obtained by means of a special effort of ATSDR.

A community cross-sectional respiratory health screening was conducted in Libby by ATSDR in 2000 and 2001. A non-malignant respiratory health update since then would be useful. The appropriate smoking, occupational, and residential histories should be included.

4.2. Mode of Action

It would be valuable for future research on LAA mode of action to focus on biomarkers that are more clearly and specifically related to non-cancer endpoints (i.e., asbestosis) or cancer endpoints (e.g., mesothelioma). Critical genotoxicity studies including mutagenesis and chromosomal aberration studies have not been investigated with LAA. Inhalation studies in animal models that can provide mechanistic and dose-response relationship should be conducted.

4.3. Future Development of a TEM Method for PCM Equivalency

EPA needs to develop a transmission electron microscopy (TEM) method that provides equivalent data to phase contrast microscopy (PCM). This TEM method development must first recognize fundamental differences between TEM and PCM analysis. Areas that need better definition include differences in analyzable areas, changes in PCM resolution over time, measuring complex fibrous structures, measuring obscured fibers, defining TEM analysis parameters more succinctly, recognition of several other measurement characteristics of importance (such as surface area), defining inter-laboratory variations and their causes, as well as other areas related to analysis.

Other areas of analysis may include but not limited to: differences between PCM reticule areas and TEM grid opening areas that create biases; TEM rules with regard to fibers obscured by grid bars which create positive bias in TEM results; measurement of obscured, complex arrangements of fibers by TEM that differ from PCM counts; TEM measurement errors associated with fibers of various widths; differences between laboratories with interpretation of TEM counting rules; differences in magnification and orientations used for analysis; and other issues which create variation between analyses.

APPENDIX C – 15

EXCERPTS

In the Matter of:

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY SCIENCE ADVISORY BOARD

LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL MEETING
May 1, 2012

MERRILL LAD
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SCIENCE ADVISORY BOARD

LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL MEETING

Meeting Via Teleconference

Tuesday, May 1, 2012

(Transcript Revised July 2012 Following Review by Counsel)

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DR. KANE: Do other members of the panel have any comments on this?

MALE SPEAKER: Well, I understand Lianne's point, and I don't have any problem trying to add a sentence or two in that regard. I will say that it's not put in for the current report because I think that it's probably too late to include anything new, but I work on a regular basis on a different project altogether with Jim Lockey who's the senior author of the work -- senior deputy on the Marysville cohort.

And they have a paper, I believe it's actually been accepted already, but I'm not entirely sure about that where they've done HRTC scanning of members of the Marysville cohort. And they are going to have data about some clinical interstitial fibrosis or asbestos that's related to the exposure. And that's down the line, but it's coming.

So while it may not be pertinent to this report, it's I think Lianne's point that we should establish that all radiographic abnormalities should be considered in the future is one worth adding to the section.

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DR. KANE: Other panel members agree with that?

UNIDINTIFIED SPEAKER: MMO?

FEMALE SPEAKER: And I think the particular point that the panel was making is whether, if you actually look at the papers that were included the diffuse pleural thickening, the fact the numbers that she said changed very little.

MALE SPEAKER: Right.

DR. KANE: But the general recommendation that these should be considered in future I think that was pretty clear when stated.

DR. SHEPPARD: Yeah. Yeah. It's maybe not relevant for this particular response but I think I felt like it wasn't completely clear throughout the entire document, but I haven't identified where I might recommend changes, but I think we'd want to be -- we want to be clear about looking forward versus specific changes to this document.

DR. KANE: Okay. We will definitely flag that one to look at very carefully.

Any other issues related to the

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radiographic changes and LPT and the derivation for the RfC?

DR. SALMON: This is Andy Salmon here. I think it's probably worth just putting in a very small side comment to the effect that we are looking at these radiographic changes as an adverse effect in their own right. We are not necessarily arguing whether or not they progress to some other disease entity. And that it needs to be considered as an adverse in its own right.

DR. KANE: I think that is clearly stated but I will make sure that that is clear.

DR. SALMON: I say that mainly because some comments have attempted to obfuscate that point.

DR. KANE: I don't think the members of the panel meant to do that.

DR. SALMON: No, I don't mean comments from members of the panel. Members of the panel have been absolutely clear on that, in my opinion. I mean the public comments.

DR. KANE: Absolutely. All right. We will check. I will carefully read that part of the report

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and make sure that our statement is clear.

DR. SALMON: Thank you.

DR. KANE: Thank you. All right. With respect to charge 3 refers to the database laboratory study, what kinds of mechanisms may be responsible for the noncancer endpoint this is begins on page 19 of the draft summary.

Does anyone have any substantive comments to make here? I'll particularly ask the people who considered this. Are you here now. Jeff? David Bonner?

DR. BONNER: Yes, I'm here.

DR. KANE: Do you have any comments or questions on this section?

DR. BONNER: No.

DR. HEI: I am here. I thought that the section is pretty straightforward in terms of the mechanisms that promote the inflammatory response and the many of the noncancerous lesions that was observed. So based on what is a lesion, I have no further addition.

DR. KANE: Excellent. Okay. At this point

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when we consider our full discussion on localized pleural thickening and the derivation of the RfC and the discussions that we will make sure we have made it very clear about what we consider in terms of the radiographic changes and the fact that these are an adverse effect, not adverse effect nevertheless. Any other comments or anything we should clarify at this point?

DR. SHEPPARD: This is Lianne Sheppard. I was -- I wrote some notes to myself about whether the last paragraph of this response on page 20, lines 18 through 22 needed a little bit more elaboration. And I don't have any suggestions. I just guess I wanted to revisit that.

DR. KANE: Do other members of the panel have comments?

DR. BONNER: This is Jamie Bonner. I think I lost you guys. I pressed the wrong button trying to mute back in. I had no further comments on the non-cancer study for animals.

DR. KANE: Thank you, Jamie.

DR. BONNER: You are welcome.

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DR. KANE: I'm glad you are back.

DR. BONNER: Thank you. Sorry about that.

DR. KANE: All right. Lianne Sheppard raises some questions on lines 18 through 22 on page 20. Lianne, you did specifically comment about clarifying who SAB is agreeing with. We've changed that to considers a more conservative approach and deriving the RfC is therefore appropriate policy choice. I will clarify that. But do you think we need further discussion in this paragraph?

DR. SHEPPARD: Well, I guess I'm just making sure that nobody else does. I am okay if -- because I didn't write this section, I'm okay with it. I just wanted to raise it and make sure that everybody was okay with it.

DR. KANE: Are the members of the panel, you satisfied with this that it is clear? Okay. Again, I thank you.

DR. BALMES: Yes, this is John Balmes. Do you think there might be misinterpretation possibilities with a more conservative approach? I mean do you mean health conservative or I think that's

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what we mean, right?

DR. KANE: Could the members of the panel who wrote this clarify that? What is meant by that?

DR. BALMES: I think that could be interpreted possibly different ways. That's my only -- I don't know who wrote it.

DR. KANE: Does anyone wish to comment?

DR. BALMES: If we mean public health conservative, we should say that, I think.

DR. KANE: A more conservative approach.

MALE SPEAKER: Does that mean less aggressive on the part of EPA picking an RfC because there's a limited and complex database, or does it mean because we have a limited, complex database we should be public health conservative? I think --

DR. SHEPPARD: You mean more protective of public health?

MALE SPEAKER: Yes.

DR. SHEPPARD: Yeah. I think we should add that language.

DR. KANE: I like that, a more conservative approach that is more protective of public health.

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MALE SPEAKER: Yeah.

DR. KANE: Does everyone agree with that?

DR. HEI: That's fine.

FEMALE SPEAKER: Yes.

MALE SPEAKER: Yeah, I would agree.

DR. KANE: Okay.

MALE SPEAKER: Dr. Hei, you and I are protesting.

MR. BUSSARD: This is David Bussard again. I guess I'm not sure more conservative than what? I am not sure about the more in that sentence, what you mean by it?

DR. HEI: Yes.

MALE SPEAKER: Why don't we just say a conservative approach, i.e. protective of public health; leave out the more.

DR. KANE: Yes. I think that's appropriate. Do the members of the panel agree? A conservative approach that is more protective of public health?

MALE SPEAKER: Yes.

DR. KANE: Okay.

APPENDIX C – 16

From: Kane, Agnes
To: Diana-M Wong/DC/USEPA/US@EPA
Subject: Re: Fw: Edited Response to Question 2 on Noncancer Health Effects
Date: 07/09/2012 11:17 AM

Dear Diana,
I agree with Carrie's changes.
Sincerely,
Agnes

Agnes B. Kane, MD, PhD, Chair
Department of Pathology and Laboratory Medicine
Brown University
Email: Agnes_Kane@Brown.Edu
Phone: 401-863-1110

On Mon, Jul 9, 2012 at 10:11 AM, Diana-M Wong <Wong.Diana-M@epamail.epa.gov> wrote:

> Dear Agnes,
>
> Welcome back!
>
> Attached please find Dr. Redlich's edits on response to Question 2. Thanks.
>
> Diana
>
> Diana Wong, Ph. D., DABT
> Toxicologist and Designated Federal Officer
> USEPA
> Science Advisory Board Staff Office
> MC: 1400R
> 1200 Pennsylvania Ave, N.W.
> Washington, DC 20460
>
> Phone:(202) 564-2049
>
> ----- Forwarded by Diana-M Wong/DC/USEPA/US on 07/09/2012 10:07 AM -----
>
> From: "Redlich, Carrie" <carrie.redlich@yale.edu>
> To: Diana-M Wong/DC/USEPA/US@EPA, John Balmes <jbalmes@medsfgh.ucsf.edu>, "Newman, Lee" <Lee.Newman@ucdenver.edu>
> Cc: "Salmon, Andy@OEHHA" <Andy.Salmon@oehha.ca.gov>, Agnes Kane <agnes_kane@brown.edu>, "Morton.Lippmann@nyumc.org" <Morton.Lippmann@nyumc.org>, Susan Woskie <Susan_Woskie@uml.edu>, "David Kriebel" <David_Kriebel@uml.edu>
> Date: 07/08/2012 05:30 PM
> Subject: Re: Edited Response to Question 2 on Noncancer Health Effects
>
> ---
>
> Diana
> I agree that it IS OK to leave in that plaques are indicators of increased risk for the future development of lung cancer, in agreement with ATS Asb reference.
> I have made some additional minor edits (see attached) mainly deleting a few phrases per the "less is more" principle, wanting to avoid statements that critics may attack.
> Carrie
> John and Lee – Are you OK with?
>
> On 7/5/12 7:02 PM, "Diana Wong" <Wong.Diana-M@epamail.epa.gov> wrote:
>
> Dear All,

I checked the ATS, (2004) reference, which is available in the reference section of the HEROized Libby assessment.

On page 705, it did state: "The presence of plaques is associated with a greater risk of mesothelioma and of lung cancer compared with subjects with comparable histories of asbestos exposure who do not have plaques".

On page 707, it stated: "Plaques are indicators of increased risk for the future development of asbestosis".

However, we are still waiting for the input of our pulmonologists experts to let me know if "lung cancer" should be deleted. Thank you very much.

Diana

Diana Wong, Ph. D., DABT
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MC: 1400R
1200 Pennsylvania Ave, N.W.
Washington, DC 20460

Phone:(202) 564-2049

----- Forwarded by Diana-M Wong/DC/USEPA/US on 07/05/2012 06:45 PM -----

From: Diana-M Wong/DC/USEPA/US
To: jbalmes@medsfgh.ucsf.edu, Lee.Newman@ucdenver.edu, carrie.redlich@yale.edu, Susan_Woskie@uml.edu, David_Kriebel@uml.edu
Cc: "Salmon, Andy@OEHHA" <Andy.Salmon@oehha.ca.gov>, agnes_kane@brown.edu, Morton.Lippmann@nyumc.org
Date: 07/03/2012 11:49 AM
Subject: Fw: Edited Response to Question 2 on Noncancer Health Effects

---

Dear All,

Dr. Lippmann commented on p. ii, line 6,7 of the cover letter that "lung cancer" should be deleted. To be consistent, lung cancer is also deleted in the response to question 2. Please review and let me know if you have other suggestions. Thanks.

(See attached file: dw Response to Question 2 on Noncancer Health Effects.docx)

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----- Forwarded by Diana-M Wong/DC/USEPA/US on 07/03/2012 11:41 AM -----

From: Diana-M Wong/DC/USEPA/US
To: jbalmes@medsfgh.ucsf.edu, Lee.Newman@ucdenver.edu, carrie.redlich@yale.edu, Susan_Woskie@uml.edu, David_Kriebel@uml.edu
Cc: "Salmon, Andy@OEHHA" <Andy.Salmon@oehha.ca.gov>, agnes_kane@brown.edu
Date: 07/02/2012 05:50 PM
Subject: Fw: RE: Public Comments Posted on Our Website

Dear All,

Attached please find Karl Bourdeau's comments on June 25, Dr. Salmon's response to these comments on LPT, and the subgroup response to question 2 on the selection of critical effect for the derivation of RfC.

(See attached file: Bourdeau June 25 no sig.pdf) (See attached file: Response to Question 2 on Noncancer Health Effects.docx)

Please let me know ASAP if any changes to the response to question 2 is needed, based on the comments, and Dr. Salmon's response to comments.

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----- Forwarded by Diana-M Wong/DC/USEPA/US on 07/02/2012 05:30 PM -----

From: "Salmon, Andy@OEHHA" <Andy.Salmon@oehha.ca.gov>
To: Diana-M Wong/DC/USEPA/US@EPA
Date: 06/27/2012 05:13 PM
Subject: RE: Public Comments Posted on Our Website

Having taken a look at these comments, I do need to respond to their mischaracterization of my earlier remarks about LPT as a toxicity endpoint. They appear to think that I was discounting the possibility that LPT was associated with changes in lung function. I never said anything of the sort. In the first place, the discussion about where LPT stands on the overall mechanistic pathway started in the context of mesothelioma rather than lung function changes. The general conclusion of the panel (with which I agree) is that there certainly are common elements to the causative pathways for mesothelioma and LPT, but it is not correct to see LPT as an obligatory precursor to mesothelioma, i.e. not all LPT lesions will progress to mesotheliomas and not all mesotheliomas arise by progression of LPT lesions. But both types of lesion arise as the result of the cellular damage induced by the persistent fibers and other associated effects. With regard to lung function changes, the point of my remarks is that regardless of whether or not LPT is associated with observable lung function changes, it is in and of itself an irreversible pathological change in tissue structure. Risk assessment guidelines identify that endpoint as a suitable (and indeed, fairly severe) endpoint for use in risk assessment, regardless of whether functional changes are observed as a result of or associated with that finding. The panel subsequently discussed the question of whether, in addition to LPT, the amphibole exposures were also associated with observable lung function changes in the dose range of interest, and it was concluded that they were. It appears that LPT findings are not invariably associated with observable lung function changes, or vice versa: how much of this is due to relative insensitivity and imprecision of these clinical evaluations, or merely to the fact that they are seldom done simultaneously on the same subject, is unclear. However, the risk assessment conclusions are simpler: both LPT and lung function changes are separately demonstrable effects of exposure to amphiboles, which may be considered independently in determining dose response relationships for adverse effects.

From: Diana-M Wong [mailto:Wong.Diana-M@epamail.epa.gov]
Sent: Monday, June 25, 2012 11:32 AM
To: Diana-M Wong
Subject: Public Comments Posted on Our Website

Dear Panel Members,

A set of public comments submitted by Karl Bourdeau of Beveridge & Diamonds is posted on our website for your consideration. The link is provided below:

http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/DE16F40DF2BE9271852579FB0054C2BF?OpenDocument
<http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/DE16F40DF2BE9271852579FB0054C2BF?OpenDocument>

The pdf file is also attached.

(See attached file: Bourdeau June 25 no sig.pdf)

Sincerely,

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(See attached file: cr edits.Response to Question 2 on Noncancer Health Effects.docx)

APPENDIX C – 17

From:	Redlich, Carrie
To:	Diana-M Wong/DC/USEPA/US@EPA; Agnes Kane
Subject:	Word of explanation re LPT associated with increased risk meso, lung ca
Date:	07/28/2012 09:04 PM
Attachments:	asb pleural meso[3].pdf asb plaques lung cancer.pdf Reid Addit risk meso wittenoom OEM 2005.pdf

Agnes/ Diana
I found this in my outbox – not sure if sent earlier in the week- may be duplicate email
carrie

Agnes / Diana
I thought I should add a word of explanation for deleting a sentence that generated so much attention (below - I didn't write it) and my other more minor edits.
While the ATS asbestos document does say LPT associated with increased risk asbestosis, ca, meso, it cites only 2 references to support LPT associated with increased risk of mesoth and lung cancer (beyond exposure history). Most clear, and what we discussed at our meeting and prior calls, was that LPT associated with reduced lung function, which a number of well done studies document. We suggested EPA further highlight this literature and added a few additional references. Not a big deal / change.
I had been uncomfortable with LPT being predictive / associated with increased risk of meso, lung cancer, so I had done some searches of the epi literature (see attached). The question is complicated by 1) confusion if referring to plaques as a marker of asbestos exposure vs increased risk beyond estimated exposure (the real Q), and 2) studies have mostly used occupational history for exposure assessment.
One of the better articles (Reid) and brief lit search attached. (Reid already cited by EPA somewhere. Don't think EPA needs to add any refs).
Bottom line – while ATS statement likely correct, **there's not much evidence to support LPT and increased risk meso, lung ca (beyond exposure),** and as mentioned, no need to go there. It's confusing and nonmalignant changes sufficient justification as endpoint, and it's just opening up EPA for criticism. This is referring to LPT and risk of meso, lung cancer. There is good data that supports LPT and reduced lung function. (my edits tried to clarify this).
Sorry didn't bring this up on the call – I was hesitant to start a whole discussion about. I looked over articles etc more carefully when doing edits and realized that while "associated" better than "predictive", even better to omit.

As you know, asbestos differs somewhat from pollutants such as ozone, as there are well known clinical entities caused by asbestos. It may be helpful for the EPA to more fully explain Rfc version of health effect vs clinical disease. ATS document focused on clinical asbestos-related disease. Clinicians / others are so used to reassuring patients that plaques are no big deal, don't affect lung function (esp as typically past exposure can't do anything about), that they may need an extra reminder as far as Rfc / the public health perspective.

It took me a while to remember this after "minimizing" plaques with individual patients for so long.
Hope this helps.
Carrie

On 7/25/12 6:52 PM, "Carrie Redlich" <carrie.redlich@yale.edu> wrote:
"Additionally, the presence of LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer, a point that the EPA should include."

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APPENDIX C – 18

EXCERPTS

In The Matter Of :

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD

LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL
MEETING - DAY 1
February 6, 2012

MERRILL LAD
1325 G Street NW, Suite 200, Washington, DC
Phone: 800.292.4789 Fax:202.861.3425

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SCIENCE ADVISORY BOARD

LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL MEETING

DAY 1

Monday, February 6, 2012

(Transcript with Revised Corrections After Review of Counsel, July 2012)

Page 206

DR. WOSKIE: I have to remind you that my training is as an industrial hygienist, not a respiratory physician. So I have to defer to my colleagues' knowledge about the physiology. But the argument I thought was well made in the document and made sense to me and also was supported by the reported latency results that the localized pleural thickening occurs in, you know, 8, 10 years compared to the diffuse as far as follow-up, you know, having a cohort with sufficient follow-up to actually see disease.

So that was the other piece of the argument that made sense to me.

DR. KANE: Dr. Sheppard?

DR. SHEPPARD: Yeah, I generally also agreed. I brought up a question this morning and I want to revisit it and engage our physician colleagues on the panel with a little bit more discussion.

I think I've been convinced, but the basis in this data set is x-ray findings. And there are other changes on x-rays besides localized pleural thickening which are also caused by asbestos. And so

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as a statistician why not just look at all of them, any change on x-ray that might be caused -- that's considered caused by x-ray, I mean, by asbestos, particularly since these are prevalent x-rays.

And the changes most likely happened way back in time. So we are not looking at any time to event in this analysis at all. So I just wanted to revisit that question one more time before we put it to bed. Why -- and in fact in the primary analysis cohort it makes almost no difference because there's one case that's excluded that has another outcome. But in the bigger cohort there are more cases.

So why not help me understand a little bit better why wouldn't we look at more -- more changes on x-rays than just that one?

DR. KANE: Can anyone answer that question? Dr. Newman.

DR. NEWMAN: Well, I may not answer it, but I'll try. And I'll welcome input from some of my colleague pulmonologists. I think that's a really interesting idea.

As a general observation, the pleural

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findings will appear before the other findings. And so I think that's why the thinking has tended to focus on the pleural abnormalities.

DR. SHEPPARD: But my understanding is that sometimes you see the one outcome and not the other, right?

DR. NEWMAN: That's true. One can see, for example, asbestosis, the fibrotic lung disease, you can that on x-ray and in an individual who never develops any pleural abnormalities. So that definitely does occur.

DR. BALMES: I guess I'll just chime in as another pulmonary physician that again I think it's an interesting idea. I agree with Lee that usually you'll see localized pleural thickening before you would see asbestosis or diffuse pleural thickening.

The advantage of diffuse pleural thickening or asbestos is those are clearly linked to decreased lung function where localized or pleural thickening has been brought up isn't necessarily associated with decreased lung function. I don't know how much difference it would make with the Marysville cohort,

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but it's certainly a reasonable suggestion.

DR. KANE: Dr. Redlich, I would like to ask another pulmonologist.

DR. REDLICH: I think we would all sort of feel more comfortable because of this question of how significant our pleural plaques is if there was enough data to do a risk estimate on other outcomes, but in that same paper there were only 12 participants, I believe, or 8 with interstitial changes.

So it ends unbeing a much smaller number. And of the 80 with pleural changes, only 12 had diffuse pleural thickening. So -- what number was it? Did I have it wrong?

I am sorry. Even less. So I think the problem is there haven't been enough of those other endpoints.

DR. SHEPPARD: Yeah, but I'm talking about adding them all together, not looking at one outcome versus another.

DR. WOSKIE: So you are saying any --

DR. SHEPPARD: Yeah, any change.

DR. KANE: Yes, Dr. Salmon.

APPENDIX C – 19

EXCERPTS

In The Matter Of:

U.S. EPA - SCIENCE ADVISORY BOARD - LIBBY ASBESTOS REVIEW PANEL MEETING

July 25, 2012

MEETING (U.S. EPA - SCIENCE ADVISORY BOARD LIBBY ASBESTOS) - Vol. 1

MERRILL LAD
1325 G Street NW, Suite 200, Washington, DC
Phone: 800.292.4789 Fax:202.861.3425

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SCIENCE ADVISORY BOARD

LIBBY AMPHIBOLE ASBESTOS REVIEW PANEL MEETING

Meeting Via Teleconference

Wednesday, July 25, 2012

1:00 p.m.

(Includes Revisions Amended By Counsel as of September 17, 2012)

The U.S. Environmental Protection Agency, Science Advisory Board, Libby Asbestos Meeting held via teleconference on Wednesday, July 25, 2012, commencing at 1:00 p.m., reported stenographically by Elizabeth Mingione, Registered Professional Reporter and Notary Public for the State of Maryland, Commonwealth of Virginia, and the District of Columbia.

Job No.: 1-218474
Reported By: Elizabeth Mingione, RPR
Pages 1 - 127

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* * *

PROCEEDINGS

DR. WONG: I think we can start right now. According to my records, the panel members present for this conference call include Dr. James Bonner, Mr. John Harris, Dr. Hei, Dr. Kriebel, Dr. Lippmann, Dr. Neuberger, Dr. Newman, Dr. Pennell, Dr. Rutledge, Dr. Salmon, Dr. Sheppard, Dr. Southard and Dr. Walker. Did I miss anyone?

And of course we have our Chair also, Dr. Agnes Kane. Did I miss anyone?

DR. GUTHRIE: George Guthrie just joined in.

DR. WONG: Thank you. Who else?

DR. WEBBER: Jim Webber.

DR. WONG: Thank you. And who else?

DR. WOSKIE: Susan Woskie.

DR. WONG: Oh, great. Okay. Okay. We can start.

INTRODUCTORY REMARKS

DR. WONG: Good afternoon. I am Diana Wong, the Designated Federal Officer or DFO for the Science Advisory Board, Libby Amphibole Asbestos

Review Panel. I would like to convene this public teleconference of the panel.

Before we start today's discussion, I would like to provide a short statement concerning the Federal Advisory Committee Act. The SAB Libby Amphibole Asbestos Review Panel is a Federal Advisory Committee. And by EPA policy it's meetings and deliberations are held as public meetings that meet the requirements of the Federal Advisory Committee Act also known as FACA.

Through the charter, Science Advisory Board the panel is empowered by law to provide advice to the administrator. Consistent with the requirements of FACA and with EPA policy, the deliberations of the panel are conducted in public at meetings for if and when public notice is given. The discussions and substantive deliberations of the panel, its interactions with the public and the agency are conducted in sections where I as the DFO am present to ensure that the requirements of FACA are met.

And this includes the requirements for open meetings, for maintaining records of deliberation of

Page 6

the panel, making available to the public summaries of meetings, and provide opportunities for public comment. I would like to note that four members of the public have asked to make their own statements. And there is time on the agenda of this teleconference to hear public comments.

I have received three sets of written comments from the public for the panel's consideration. These comments and other meeting materials have been posted on the SAB web site. And I also want to note that the status of this panel's compliance of the federal ethics law, the SAB staff office have determined that there are no conflict of interest or appearance of a lack of impartiality issues for any of the advisory committee members.

After this teleconference, minutes will be prepared to summarize discussions and action items, an accordance requirement of FACA. And these minutes will be certified by the panel chair once completed.

I have already noted the names of the SAB panel members participating. We will not ask representatives of EPA or members of the public to

Page 7

identify themselves. I will include in the minutes a list of those who directly request the call-in number for this teleconference. If there are others who would like to have the name included in the minutes, please send me an e-mail.

And i would also like to mention one other point. This is a large conference call, so please put your phone on mute by pressing star 6 when you are speaking. To unmute, press pound 6.

And now I would like to turn the call over to Dr. Agnes Kane, Chair of the SAB Libby Amphibole Asbestos Review Panel to review the agenda and begin the teleconference. Dr. Kane. Dr. Kane?

DR. KANE: Can you hear me?

DR. WONG: Yes, I can hear you.

MEETING COMMENCES, CHAIRED BY DR. AGNES KANE

DR. KANE: Okay. Good. Thank you very much, Diana, for organizing this. And I would like to thank in advance the members of the panel and also acknowledge their hard work in revising this draft document that we are going to be discussing today.

We have a lot to cover this afternoon. And

Page 8

we will first hear remarks from the EPA followed by the public comments which are limited to three minutes for each presenter, followed by any questions that the panel will have for each speaker.

Then we will turn to the discussion of our draft report beginning with Section 3.2.5, inhalation reference concentration. The major changes that were involved in this draft are focused on the section. And many of the outside comments as well as questions from EPA deal with this section.

And this will probably occupy our discussion for most of the afternoon. Then we will review the Executive Summary, the letter to the Administrator, followed by a review of other sections.

Are there any questions? Okay. At this point I would like to ask Mr. David Bussard from EPA to summarize their remarks.

PRESENTATION BY DAVID BUSSARD

DR. BUSSARD: Thank you, Dr. Kane. First of all, again, our appreciation of the time and attention. We can see the drafts converging and appreciate clarifications that have already been made.

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The whole team looked at the draft report and we have a couple things to raise, some of which are kind of nuances of wording and consistency. So you may pick them up as you go through making sure all the parts are consistent. And a few which I'll flag were really -- in some cases not quite sure how to implement a recommendation as we read it.

I'll try to go through these quickly. I do think the first topic on your agenda is one of the areas where we have the most interest in hearing the discussions and clarifications, so I would not want to divert you from the agenda that you have got.

The first issue is probably one of in part consistency of wording across pieces. We got music for a minute there. Okay. And I think it's explanatory, but it has to do with just being clear whether the panel has a view on whether LPT is adverse on its own, whether it's adverse as a predictor --

- - -

(Music is playing on the phone call)

- - -

DR. BUSSARD: -- is a predictor, is it a

Page 10

predictor controlling for exposure or without --
DR. WONG: Excuse me. I need to interrupt. Please put your line on mute by pressing star 6 if you are not speaking because we can hear music.
We can still hear the music. Okay. Sorry for the interruption, Dave. Just go on.
DR. BUSSARD: No. That's fine. It was distracting. I appreciate that.
So the first issue is just wanting to be clear from the committee if you have got a view as to whether LPT is adverse on its own, whether it impairs lung function, whether it's predictive, controlling for exposure, or predictive but not controlling for exposure. And if you think it's predictive controlling for exposure, it would be really helpful to highlight particular references that you would cite that would support that.
Issue 3, and I appreciate there's already been some response to that, we think we captured the information that's available on fiber characteristics study by study in Appendix D. If that's not the case, we'd love to know that and get additional information.

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From there I think we can have discussion about how much to put in the body of the text and how much to put in the appendix. We'd particularly like to know if we've missed some information that would be available study by study.
Issue 4, I think we understand what the panel is recommending in terms of allowing for TSFE to affect the slope and fixing the plateau instead. What we would ask for is some thought or clarity about if even after we do all of that Michaelis-Menten is a better fit, a better relative fit.
Is there a reason that you would really tell us we just cannot use that? And we raise this because at least with some of the past modeling that we didn't fix the plateau, my recollection is the Michaelis-Menten was a much better fit for something like 50 AFC points. We don't know what will happen when we rewrite that.
And we get the idea of a broader set and keeping some things flexible, but it would be useful to clarify if at the end of the day that still was the best fit. Is there a reason it really should just be

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off the table towards the point that we should look at a broader set of models.
Issue 5 is one that we would particularly love to hear some discussion today. And I think it tracks with your agenda item. We, as I understand it, and I'm really representing the team here, I think we kind of understand the principle of what's being suggested here but are not totally sure how to implement it.
If there get to be issues of a few (inaudible) model on the full set do you carry over the MRE estimate for things that affect that. Do you capture the -- the uncertainty in them. So we'd love some discussion about really practical advice or references or citations, examples is this -- how to implement this and deal with the things that come up. And we have folks that would be happy to answer questions earlier, more the kinds of questions we've got.
From the ones we labeled six and seven, I think we are -- we understand what the panel is getting at. We looked at the references that were

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available and while there -- they help explain some things, we don't think it quite gets us to the point of understanding how to practically do this. The data that sometimes is missing lots of -- lots of data points are missing, unfortunately.
So we might want some acknowledgment that there may be difficulties doing this, and it may not be cut and dry how to do this with this kind of a data set. And, similarly, for using the forshay (sp) inequality approach, at least at this point we understand that as way to deal with probability information, but we are not sure how it folds into the process of actually -- (inaudible) -- possible statistical analysis coming up with confidence. So, again, some either recognition that that may be difficult or -- (audible).
So that's a fast walk through. We'd be happy at the appropriate time to resharpen the question or help in any way, but that's a quick walk through. But, again, great appreciation for what you have done really -- (inaudible) -- forward to getting the final report.

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DR. KANE: All right. Thank you, Mr. Bussard. We will be addressing your questions after we hear from our public commenters, specifically when we talk about the draft report. And if we omit anything, please do not hesitate to remind us.

At this point I would like to invite those members of the public who have signed up to present public comments. And the first speaker will be Dr. Elizabeth Anderson.

DR. ANDERSON: Thank you, Dr. Kane. Today I would like to refer to prior comments that I have made in my Comment Number 1, and coauthored with Dr. David Hoal in my Comment Number 2, and also point to comments made by Dr. John Desesso and Dr. Larry Moore who address specific issues that I have noted in the current draft.

The first of those issues is the choice of the critical endpoint. And the particular language is that localized pleural thickening is predictive of diffuse pleural thickening, asbestosis and lung cancer and is a risk factor for all three. The second language I noticed is that the structural alteration

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of the pleura is associated with reduced lung function.

I think the scientific content in the prior comments present some challenges to support scientific foundations for each statement. One question is whether these statements are necessary to support the choice available to a critical endpoint, that is if LPT is not a risk factor for a known predictor.

(Phone noises making speaker inaudible)

DR. ANDERSON: -- EBT, asbestosis and lung cancer are associated with lung function, would it still be selected as a critical endpoint.

EPA's comments address the issue that LPT is primarily a marker of exposure and can occur at various levels of exposure and is not associated with the levels of exposure necessary to induce diffuse pleural thickening, asbestosis and lung cancer. And it is not on a biological pathway to these endpoints. And by definition they found the parietal pleura and not the visceral pleura and, therefore, because of this anatomical location unlikely to impair lung function.

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The second point I noted in the current draft is the reference to the lung function deficit relationship to LPT. I think we have challenges here. I noted in my earlier report that the Marysville cohort when it was first published by Lockey in 1984 showed no association between lung function deficit and LPT.

The current database on Marysville data is currently lacking lung function data. These data are expected later this year. So I think it's compelling that we get these data in order to look at the association critically. As best I can tell, we have no single study that combines the ability to evaluate exposure, the occurrence of LPT and lung function deficit.

I note also with only ten cases of LPT and one subcohort of one study we have a very limited basis to support the derivation of the RfC. I point to the particular issue from a current draft because of the profound applications of the current level. And, as I noted, the current level is within background.

Page 17

In fact, it's at the lower end of background as described in the ATSDR document that places urban background at .00001 and rural at .00001. Also this level is -- it will become the risk driver. It's going to be the risk driver in all cases that the de minimus risk brings for 20 years of exposure or less at the 10-to-the-minus-6 level.

I also note that the sensitivity cancer end the large-scale measurements, when large volumes of air have been pulled through filters in Libby that this level is two times higher and had not been detected by the data. And I noted in this draft document the language that says that -- one second -- the specific language, "In considering other studies, the appropriate assumption is that LAA fibers have the same mechanisms of toxicity and quantitative risk relations as that of other asbestos fibers," which goes to the point that the draft RfC if adopted is likely to be applied broadly to all asbestos types.

I feel that there are many challenges for this RfC and particularly important in light of the current focus on EPA and the IRIS database. Thank

Page 18

you, Dr. Kane.

DR. KANE: Thank you, Dr. Anderson. Do members of the panel have any questions? Okay.

Our next public speaker will be Dr. Moolgavkar.

DR. MOOLGAVKAR: Thank you very much, Dr. Kane, for giving me this opportunity to speak today. And forgive me for being blunt, but I think the midnight hour is upon us; and this panel's report is still replete with loose and inaccurate statements. And I feel that it could come back to embarrass the panel at a later date.

So the first point that I want to touch on is related to the RfC. And it's the same point that Dr. Anderson has raised and Mr. Bussard talked about this morning. I don't perceive any evidence that pleural plaques are predictive of more serious lung disease or of pulmonary function deficits because there is no evidence that conditional on asbestos exposure that there's any association between pleural plaques and these more serious conditions.

And if the panel knows of good literature

Page 19

supporting this position, they should let the agency know what this literature is. And I would like to know whether the panel has critically evaluated the papers that they are recommending to the agency on this particular topic.

The panel continues to make the ill-advised recommendation that all x-ray abnormalities be thrown together in a single analysis. This is analogous to saying that lung cancer and mesothelioma should be analyzed together for the cancer end. And I don't think that anyone should advocate that -- so this is a poor recommendation as I've been saying for quite some time.

The panel recommends also that the Dichotomous Hill model be used instead of Michaelis-Menten model. And I don't think there's any more biological justification for the Dichotomous Hill model and for the Michaelis-Menten model. In fact, it requires the estimation of four parameter -- one more than the number of parameters estimated for the Michaelis-Menten model.

And what the panel appears to be

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recommending is that two of these parameters, the background rate and the plateau we get fixed at really what are highly uncertain values derived in populations that may not even remotely resemble the Marysville cohort. I cannot see any justification for doing so.

Then I want to talk just briefly about some issues arising in the derivation of the inhalation unit risk for cancer. With respect to lung cancer, the principal issue I think is the clear indication of effect modification by age, or in other words departures from proportionality of hazards in the Cox Proportional Hazards Model.

Instead of addressing the issue, the agency has swept it under the rug by choosing a small subcohort. And instead of talking about this issue which is really quite central to lung cancer risk assessment, the panel has actually wasted quite a bit of time talking about secondary or tertiary issues like whether mesothelioma and lung cancer endpoints are independent or not. That is really a non issue, a total non issue.

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And, finally, in terms of inaccuracies, in several locations in the revised draft the panel refers to linearity of exposure response relationships for amphibole associated carcinogenesis and even suggesting that there is limited evidence to support said linearity. Well, this is really a loose statement; linearity of what?

What is the response they are talking about? What is the measure of exposure? If it's cumulative exposure, then there is no evidence of linearity. There are two mesothelioma models that we have: The Hodgson-Darnton model, which can be expressed in terms of cumulative exposure -- (inaudible) -- and that is nonlinear.

We have the Peto-Nicholson model, which cannot even be expressed in terms of cumulative exposure, that's linear in concentration but nonlinear in duration of exposure. So there's no linearity here.

The Cox model for lung cancer is log linear. It's not linear. Sometimes the excess relative risk model is used. The relative risk is

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modeled linearly in that case. However, that is an exception for lung cancer, and I do not believe that it will fit the data as well as the biologically based models such as the two-stage clonal expansion model.

Therefore, these loose statements should either be clarified in the draft or they should be removed. Thank you very much.

DR. KANE: Thank you, Dr. Moolgavkar. So far the public commenters have focused their discussion on LPT, localized pleural thickening, and the derivation of the RfC. And I believe that the last public commenter also will address this issue.

And so I would like the members of the panel to be considering specific responses about the LPT and perhaps an additional question for the public commenters after we hear from Dr. Hoal.

Are there any other questions for Dr. Moolgavkar? All right. I would like to ask the next speaker, Dr. Hoal to talk.

DR. HOAL: Thank you, Dr. Kane. First thing I have to say has pretty much been said, but I would like to get back to the RfC and the use of the

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LPT as a predictor of supposedly adverse effects. That I don't think has been established, and as such is purely a marker, I don't know how good it is, of exposure.

And that's how I thought about the good markers we have for ionize (ph) and radiation with dicentrics and rings on circulating lymphocytes. These are markers of exposure, but biologically cannot progress to the (inaudible) cells will divide. Hear?

DR. KANE: Yes.

DR. HOAL: Okay. Now, when it comes to the models, we keep talking about the Hill model and the Michaelis-Menten model which are specific biological models. And I think they are -- they do not -- or I do not see how they apply to LPT. I am used to in modeling to have things like two-stage clonal expansion model in cancer or a multistage model in cancer and working off those models. Having a background and a plateau doesn't really make sense with the definitions of the Michaelis-Menten or the Hill model.

Now, if in fact we want some nonlinear

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function, and we could just as well come up with any old nonlinear function or simple palm (ph) linear regression why there would be a plateau at a particular level. To me that implies then certain individuals are immune no matter what the duration or propensity of the exposure is. And, therefore, this is not clear at all how one should be using a plateau less than 100 percent.

I didn't see much in the way of discussion of BMIs and subpleural fat which can be misdiagnosed as pleural plaques, at least using radiographic film as opposed to CT scans. And of course BMI is also a risk factor for reduced pulmonary function. So you may have some problems there.

And, finally, I am surprised that we have a single small data set is being used to develop a RfC or an RFD or whatever you want. These are usually -- if you look at a number of animal studies or a number of epidemiological studies, you go through your calculation of NOAELs and come up with your RfCs and compare them and may end up selecting the value coming from this, but particular data set as the best but at

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least see the dependency of the various data sets and the various models that can be used.

And I say I agree with the comments that Dr. Moolgavkar made in his statement about the cancer risk modeling and also Dr. Anderson's general comments. Thank you.

DR. KANE: Thank you. Do members of the panel have a question? Is Dr. Jay Flynn available?

DR. FLYNN: Yes.

DR. KANE: You may present now.

DR. FLYNN: Thank you. I'm Jay Flynn, medical director of the Libby Medical Program.

My initial comments concern the American Thoracic Society ATS document entitled Diagnosis and Initial Management of Non-malignant Disease Related to Asbestos. This was published in September 2004 in the ATS Journal.

EPA and SAB are relying on the ATS document to justify the selection of LPT or pleural plaques as an appropriate endpoint for the derivation of RfC. A paragraph on page 705 of this ATS document addresses the issue regarding the effects of pleural plaques on

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lung function.

The initial part of this paragraph suggests pleural plaques can cause a reduction of five percent or a loss of 140 MLs of FVC. The paragraph then goes on to state this has been a consistent -- this has not been a consistent finding. And longitudinal studies have not shown a more rapid decrement in pulmonary function in subjects with pleural plaques. Three references are cited.

The paragraph then says, Decrements when they occur are probably related to subclinical fibrosis. In other words, the decrements in pulmonary function are not due to LPT or pleural plaques. The paragraph concludes: Even so, most people with pleural plaques alone have well-preserved lung function.

The ATS document cites studies that support the hypothesis pleural plaques cause loss of pulmonary function. However, it also cites studies that provide the opposite point of view. Conclusion is that clearly these findings are scientifically inconsistent and should not be used to derive the RfC.

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I would next like to comment on the study Lung Function Radiographic Changes and Exposure Analysis of ATSDR data from Libby, Montana, USA, published in the European Respiratory Journal 2011 by D. Weil et al.

In this paper, Weil et al. reviewed the ATSDR B Reader reports from the medical testing program in Libby, Montana from 2000 and 2001. 482 participants were identified as having a pleural abnormality on PA chest x-rays by two out of three B Readers. The BMI of this group was 30.3, indicating obesity. The FVC percent predicted was 95.63 percent, which falls well within the normal range.

In the discussion of the paper, the following statements are made: Second paragraph, page 382, "Our review of the ATSDR data does not support the conclusion that pleural changes are associated with clinically significant reduced lung function."

Last paragraph on 382 states, "There was an expected detrimental effect on lung function due to cigarette smoking." Page 383, number 3 states, "With regard to the effect of pleural plaques on FEC in

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males, there was a small probably clinically insignificant reduction of 4.5 percent." Conclusion is that the decrease in FEC is most likely due to obesity and smoking and is not related to previous asbestos exposure.

My concluding comments are pleural plaques are merely markers of previous asbestos exposure and are not a disease pathway to adverse effects or directly cause adverse effects. The SAB panel should revise its opinion that LPT or pleural plaques are an appropriate endpoint to derive the RfC because the scientific literature does not support this position.

At the EPA teleconference on May 1, 2012, Dr. Lawrence Moore, a highly respected pulmonologist, presented public comments and submitted written comments entitled "Clinical Background Information and Comments on Recent Scientific Publications." And the draft EPA report, August 2011 -- (phone beeps) -- pointing to Libby amphibole asbestos.

Dr. Moore's comments provided excellent review of pleural plaques including their clinical effects as well as a review of several pertinent

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papers that the SAB panel may be considering. All members of the SAB panel are urged to review Dr. Moore's paper. Thank you.

DR. KANE: Thank you. All right. At this time does the panel have any questions specifically for Dr. Flynn? As most of these speakers are focusing their comments on LPT, I would like to ask members of the panel who have special expertise in this area to consider these.

Specifically did Drs. Newman or Redlich have something to add to this?

DR. NEWMAN: This is Lee Newman. Can you hear me?

DR. KANE: Yes.

DR. NEWMAN: Oh, good. I wasn't sure if I had the mute on. Yeah. No, I appreciate the comments that have been made today, and I've read the materials that were submitted as well.

We actually spent quite a bit of time going through this literature, and we also spent that time as a group discussing this. I understand that there are people who would have some points of disagreement

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around some of this literature, but I think the sum of it leads me the two conclusions: One, the statements that we've made as far as using the LPT as the endpoint are appropriate.

The one thing that I would consider us discussing further as a group here is the use of the word predictive. It sounds like people have gotten hung up on that term. And, you know, I think we could have a little discussion around whether we should use that term or use a term such as "associated with" as opposed to "predictive" when it comes to discussing the relationship of the localized pleural thickening to other asbestos-related endpoints. But otherwise I wouldn't be recommending any other changes in the document.

DR. KANE: Thank you, Dr. Newman. We will be discussing that in more detail when we get to that specific question from EPA.

Dr. Redlich?

DR. REDLICH: Yes. Carrie Redlich. I agree with Lee Newman.

DR. KANE: All right. As a panel member,

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not the chair, I would also like to offer my opinion. I am a board-certified anatomic pathologist. And when I am confronted with a patient at autopsy or a lung biopsy specimen or a lung resection specimen, the presence of pleural plaques would be listed on my pathologic anatomic diagnoses. It is a pathologic abnormality.

DR. REDLICH: I would just add one other comment. I think part of this confusion relates to the difference between a clinical practice and epidemiology studies and what we consider, you know, an endpoint such that -- (inaudible) -- a biologically relevant endpoint even if it is not favorable or is not -- because that question has been asked. And so the comments that it usually is not associated with severe -- I don't believe the severity of the lung abuse (ph). I think the question is is it a relevant health endpoint.

DR. KANE: Thank you, Dr. Redlich. Do other members of the panel have any thoughts on this issue?

DR. SALMON: This is Andy Salmon here. I

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think one of the things that we really need to keep in mind in this discussion is the point that was just made that, you know, this is an adverse pathological change which is -- (inaudible) -- observable. And from a public health point of view it's objectionable in its own right because of that.

You know if you ask the average person in the street is it all right for you to have these pathological changes in your body, they would probably say, no, it isn't. And that is the basis for the risk assessment that it's an adverse effect in its own right. Whether it has mechanistic implications or whether it has associations or predictions or other effects is an interesting question from the scientific and clinical points of view. But from the risk assessment points of view I think we need to simply say that, you know, this is a wonderful discussion to have, but the bottom line is we are looking at an adverse pathological change, and that that is -- because that is adverse and clinically observable, it's an appropriate endpoint to use for the risk assessment purpose.

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And the, you know, the question about mechanisms and clinical outcomes and whether it's associated or predicted, I mean, as an aside I will say I prefer the word "associated" because it doesn't make an assertion which we don't actually need to make in order to achieve the risk assessment process that we are aiming for.

So, anyway, I --

DR. REDLICH: I agree with all of that.

DR. MOOLGAVKAR: Can I respond to that, Dr. Kane?

DR. KANE: Yes.

DR. MOOLGAVKAR: If that is the way --

DR. KANE: Please identify yourself.

DR. MOOLGAVKAR: Yes. This is Dr. Moolgavkar. If that is the way the panel feels, then it should clearly state that. That is not what the current report reads.

It says it's predictive. And that has quite a different meaning than saying that it by itself is a pathological endpoint and we are taking that into consideration when we derive an RfC based on

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that.

I think that should be clearly stated. I don't think that the panel should be making these kinds of loose scientific statements about predictions.

DR. KANE: I think -- I think I would like to clarify something, that this is not a loose use of a term. I think that we have a problem here and that the panel is a group of experts from many different fields. And the word predictive means something different in an epidemiologic context than it would in a clinical context.

And we will be discussing very shortly about whether we should change "predictive" to "associated with," as that is one of the purposes why we are having this conference call to make final recommendations and changes in the draft document. So we will be considering that change in great detail very shortly. Thank you.

Does any other members of the panel have any comments or questions? Mr. Bussard? Do you have any specific comments or questions at this point?

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DR. BUSSARD: I am good. Thank you.

DR. KANE: Okay. We will be addressing EPA specific remarks very shortly. All right. If there are no more questions or comments, at this point I would like to thank the public speakers, the public commenters, and we will now return to the panel's draft -- discussion of the draft report.

We are going to begin with the section which has where there were little substantive changes were made earlier, Section 3.2.5 on the RfC. And in our deliberations this afternoon, because we have a lot to discuss, I would like to advise the panel to only consider major changes in the wording.

If there are only very simple typographical errors, they will be corrected. We've received some of your written comments, but we will be discussing substantive changes, and particularly focusing on questions where the EPA raised points for clarification as specific questions.

So we will start now on -- see what the question is here -- all right. We'll start on page 25. This is Section 3.2.5.1. And there were several

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charge questions under this section. And specifically the panel in our revisions made several changes. All right.

So before we get to that, I am going to return to the issue on page 19. And that was the issue on localized pleural thickening as the critical effect for derivation of the RfC. After this point is the time to ask the panel members to consider how we worded this in terms of using the terms "predictive" versus "associated with". And can we reach a consensus on whether we should edit this to use one term versus the other?

DR. NEWMAN: This is Lee Newman. Can you hear me?

DR. KANE: Yes.

DR. NEWMAN: Yes. I would propose that we change it from the word "predictive" to "associated with" and just put that on the table here. I think that Dr. Salmon's point is well-taken one, that we don't actually need that to make the -- in fact help support the case that EPA has made for using this as our endpoint.

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And so I think that's just a nice way of taking that away as, you know, it's sort of an unnecessary sideline issue that we can change by changing to the words "associated with".

DR. KANE: All right. Do other members of the panel have questions, comments?

DR. BONNER: This is Jamie Bonner. Can you hear me?

DR. KANE: Yes.

DR. BONNER: I would just second Lee's recommendation.

DR. KANE: Excellent. Any other alternate suggestions, questions from members of the panel?

DR. PETO: This is Julian Peto. Can you hear me?

DR. KANE: Yes, hello.

DR. PETO: Oh, hi. I wonder, I mean, as this is such a major issue which people have been so critical of and nobody's challenging the assertion that there isn't actually scientific evidence of substantial cause and effect, I do agree with, I mean, Dr. Moolgavkar's point that if that's what we are

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saying we should be explicit about it I think is a fair one.

And I just wonder whether how much difference it would make. I mean how difficult would it be for the EPA to base an RfC on the cancer endpoint and say that we feel that this is a substantial pathological change in its own right. And so the RfC's been calculated on that basis. But it would be possible to calculate an RfC on the basis of cancer alone and that would be the alternative value.

I mean that would seem a reasonable compromise because I do rather feel that, I mean, they have made quite a strong case that we were asserting something that wasn't scientifically supported. And to deal with it by changing predictive to associated without being absolutely explicit about what we are doing and why we are doing it seems rather satisfactory.

DR. SALMON: Andy Salmon here. I don't think that we have been unclear about the view that the LPT is an adverse endpoint in its own right and that that was an appropriate basis of an RfC. I think

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the unfortunate implication that we were saying something other than that is something which has been sort of corrected by imputation rather than anything that we intended to imply at any point.

And I think to some extent the critics of the proposed RfC have seized on this as an obvious point of confusion or weakness, but it's not one that was present in our original discussions to my recollection.

DR. KANE: Thank you.

DR. PETO: Is it the case that other RfCs have been based on science as distinct from symptoms? I mean if the -- I mean, you know, don't get into a great long semantic argument but, I mean, if it's a clinical sign which is detectable by an examination but it doesn't have health consequences in the in the normal sense.

DR. SALMON: This is risk assessment not clinical medicine. And one of the --

DR. PETO: Just to be clear about, I mean, if it really is driving the RfC then what's a very clear statement about what --

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DR. SALMON: There's a fairly clear statement in a number of documents about really the appropriate methodology for non-cancer risk assessment, including specification of degrees of severity and effect. And one of the critical things which is looked for is indicating that the clearly adverse effect is an irreversible pathological change in the structure of an organ or organ system.

And this clearly qualifies as that. It meets the criteria which are used in risk assessment for definition of an adverse effect in its own right. And that is entirely consistent with what has been done in other context in risk assessment.

Now, there are a lot of interesting questions around the clinical significance of this and how -- the degree to which it's associated with -- may progress to or otherwise be related to other endpoints, but those are not questions which we necessarily have the information to answer in this specific context. And my point is that we don't need to, and we haven't said that we need to.

DR. PETO: But do you think the suggestion

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that it would be useful to say if the RfC based on cancer would be, do you think it would be inappropriate to put that in?

DR. NEWMAN: This is Lee Newman. I don't think that that's an appropriate direction to go at this time, to answer your question. It's, you know, certainly the people who have provided comments have done their best to make the case that there is some clinical dispute here in the literature.

In fact, I think the literature stands and our review of it stands, that this -- that the localized pleural thickening is an adverse and critical effect. And so I don't think that we need to go on the path of suggesting that we need an alternative such as cancer.

DR. KANE: Does EPA have any comments on this?

MALE SPEAKER: I think you are in the right track that what we are looking for is guidance is it an adverse effect in and of itself, and then being careful that if you make statements about it being predictive or associated with something else, that

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that be a separate statement so that these things are sort of sequentially clear. Is it an adverse effect in and of itself.

Do I make a statement about whether it's associated with other effects. But to sort of make those two separate questions is very helpful.

DR. VU: All right. Agnes, this is Vanessa. May I provide some information?

DR. KANE: Yes.

DR. VU: So the agency's derived the reference concentration for non-cancer health endpoints and what Julian, when you raised the point of whether the agency should consider an RfC for cancer, so the agency's general process for assessing cancer risk is use what -- is considering the method to develop the inhalation cancer unit risk. And the RfC is mainly for the non-cancer health end points. So I just hope that's clear.

DR. KANE: Thank you, Vanessa. I that helps I think clarify that point.

DR. HEI: So, Agnes? This is Tom from Columbia University.

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DR. KANE: Yes.

DR. HEI: I think Vanessa clarified the issues, and based on the discussion that we have. It is perhaps a little unfortunate to choose a word predictive which by itself has implication for a mechanistic or pathological pathway which at the moment that doesn't want seem to support that.

So the words "associate with" tends to bypass all these complications and put us back on the right track. So I think that the previous suggestion to remove that and change the words and probably will be very helpful at this moment.

DR. KANE: Thank you, Tom. Any other members of the panel have any comments at this point?

DR. SHEPPARD: Yeah. This is Lianne Sheppard. Following up on this discussion on line 23 of page 19, it may be helpful to EPA if we had a sentence that says something to the effect of this is an adverse effect in and of itself, just to be completely clear. Maybe the wording could be enhanced to recognize the risk assessment aspect of that definition.

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DR. KANE: Do members of the panel --

UNIDENTIFIED MALE SPEAKER: I think clarity on that would be very helpful, I would agree.

DR. NEWMAN: So this is Lee Newman. You are suggesting something stronger than what's on page 19, line 13, where it says, radiographic evidence of localized pleural thickening in humans is the appropriate adverse and critical effect for the derivation of the RfC; you want to add something else right after that? Is that what you are saying.

DR. SHEPPARD: No. I was suggesting because the paragraph people seem to be struggling with is the next one where that issue is brought up again, but then it goes on to talk about how it's related to the other health outcomes, and that seems to be getting blended in a way that seems to be causing problems.

And so basically taking that, you know, taking some version of that, of what's said on line 13 and inserting it there on line 23 might help with making that distinction. So it -- what I'm understanding from this conversation, there's two

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points.

One is that it's an averse effect for in and of itself because of the way risk assessment is defined and the pathological changes. And then in addition it's associated with other health outcomes. And -- and I -- my understanding is those are being blended in a way that's kind of the message is being misinterpreted.

DR. REDLICH: Yes. This is Carrie Redlich. I think we are all pretty clear. I think for time's sake we could quickly edit this second paragraph.

DR. KANE: All right, Carrie. You want to give that a shot?

DR. REDLICH: Yes. But rather not with this group on the phone.

DR. KANE: I agree with you, but I think we all understand, at least I think from the members of the panel and from my point of view I understand what the issues are. And so Carrie will work and try to clarify the sentence on page -- on line 23, LPT is a structural pathological alteration of the pleura.

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Perhaps somewhere in there saying a adverse effect.
And then the lines 25 and 26 that talk about the association of LPT with other asbestos-related diseases as it's listed. And I think throughout this document and also as the EPA requested in its question number 1 in the letter to the administrator, the Executive Summary and any other place in the document, we should replace the word "predictive" with "associated with".
And I think that should clarify this issue. Is that clear to members of the panel? Any other questions or suggestions?
DR. HEI: I thought it's pretty fair.
DR. KANE: Okay. So, Carrie, you have an action item there. And I'm sure that we can clarify this. And I think these were very important points.
I'm glad that EPA brought it to our attention, the confusion by using these terms. Mr. Bussard, is that clear also.
DR. BUSSARD: I think we are clear. Thank you.
DR. KANE: Excellent. Excellent. All

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right. So that takes care of that item.
All right. Now, we'll go back to Section 3.2.5 beginning on page 25. There were significant changes in the panel's draft with respect to questions 1, 2, 3, 4 and 6.
So do any members of the panel have -- any of your review have you found any substantive issues that need further discussion or modification?
DR. SHEPPARD: Are we going to go through these line by line or do you want us just -- I mean question by question? Because we should probably make sure that we respond to these specific items that EPA addressed.
DR. KANE: That's what I was coming to next. We are not going to go through it line by line. I expect that members of the panel have reviewed this draft document and reviewed our changes. And --
DR. SHEPPARD: I'm sorry. I meant question by question.
DR. KANE: Right. Question by question. We can do that if you wish but if have, you know, if people have done this, their homework and have no

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problems with it, I think we can deal with it that way. And then we'll ask EPA or refer to EPA's questions specifically because that's the most important consideration here.
DR. SHEPPARD: I think we need discussion about their items number 4 and 5. And there may need to be some changes as a result of those.
DR. KANE: Yes. Right now we are on, yes, we'll be moving to those shortly after we are covering this section.
DR. SHEPPARD: Okay.
DR. KANE: Okay. So before we get to your questions four and five, Mr. Bussard, do you have any other questions on this section, particularly with respect to charge questions 1, 2, 3, 4 rand 6?
MR. BUSSARD: Other than the questions we have that articulate the question 3 -- I mean and the pages cited 28 through 31 or so, no. Thank you.
DR. KANE: Okay. Okay. Excellent.
DR. LIPPMANN: Mort here. Are you going to go to Issue 3?
DR. KANE: Yes, we will, but we'll do that

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after we are done with the RfC and IUR.
DR. LIPPMANN: Okay.
DR. KANE: Don't worry. We are not forgetting you, because some members of the panel cannot stay through the whole conference call. And these are the most substantive changes in the document.
All right. So there is a question now that we can deal with. There seems to be a question, a response to Question 1. There's some confusion, a little bit of confusion about the use of arithmetic -- geometric means versus arithmetic means. And in -- Jason (?), do you have any comments on that one, Question 1A and 1B?
UNIDENTIFIED FEMALE: I didn't -- what -- I'm not picking up where the confusion is. I didn't see that in the EPA notes. I thought the panel had discussed this and concluded what the -- with what the current draft. Oh, I'm --
DR. KANE: Diana, can you help us with this? Where specifically does this issue come up?
DR. WONG: Well, you are referring to the

APPENDIX C – 20

DATE

EPA-SAB...

The Honorable Lisa P. Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Subject: Review of EPA's Draft Assessment entitled *Toxicological Review of Libby Amphibole Asbestos* (August 2011)

Dear Administrator Jackson:

EPA's Office of Research and Development (ORD) requested the Science Advisory Board (SAB) to conduct a peer review of EPA's draft Integrated Risk Information System (IRIS) assessment, entitled *Toxicological Review of Libby Amphibole Asbestos (August 2011)*. The draft document is the first IRIS assessment specific to Libby Amphibole asbestos (LAA), a term used to refer to the mixture of amphibole mineral fibers of varying elemental composition that have been identified in the Rainy Creek complex near Libby, MT. In response to ORD's request, the SAB convened an expert panel to conduct this review. The SAB Panel was asked to comment on the scientific soundness of the hazard and dose-response assessment of LAA-induced cancer and non-cancer health effects.

The SAB finds the EPA's draft assessment to be comprehensive and generally clear, logical, and well written. We have provided recommendations to further enhance the clarity and strengthen the scientific basis for the conclusions presented. The SAB responses to the EPA's charge questions are detailed in the enclosed report. SAB major comments and recommendations are provided below:

- The SAB supports the derivation of an inhalation reference concentration (RfC) based on radiographic evidence of localized pleural thickening in an occupationally exposed Marysville OH cohort. The SAB finds the selection of the subcohort of 118 workers who began work in 1972 or later when exposure data were available and who had X-ray exams, with the full cohort of 434 workers used for confirmatory analyses to be clear and reasonable. However, the SAB finds that additional analyses are needed to strengthen and support the RfC. The SAB recommends that EPA include any X-ray abnormalities (localized pleural thickening, diffuse pleural thickening, or asbestosis) as the health outcome. The SAB also recommends that EPA conduct confirmatory analyses (to the

extent data permit) of pleural abnormalities using the recently published studies on the Libby workers cohort and the Minneapolis Exfoliation community cohort.

- The SAB agrees that localized pleural thickening has the appropriate specificity, and has a measurable relationship to altered lung function, and is a structural pathologic alteration of the pleura. The presence of localized pleural thickening itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer. The SAB has identified and provided the EPA with additional references and recommends that the agency to conduct a more detailed review of the literature to further support this conclusion.

- For exposure-response modeling of non-cancer endpoints, the SAB recommends that a clearer description be provided of how the "best" model was chosen. The SAB also recommends examining other exposure metrics besides the simple cumulative exposure, such as time weighting of exposures. In addition, more justification is needed for the selection of 10% extra risk as the benchmark response which is not consistent with EPA's guideline for epidemiological data.

- A composite uncertainty factor of 100 was applied to the point of departure to obtain the RfC. The SAB supports the intraspecies uncertainty factor of 10 to account for human variability and sensitive subpopulations. However, the SAB recommends that the EPA consider additional data and analysis for the application of a database uncertainty factor of 10.

- The SAB agrees that the weight of evidence for LAA supports the descriptor "Carcinogenic to Humans by the Inhalation Route", in accordance with EPA's *Guidelines for Carcinogen Risk Assessment*. The SABs also supports the EPA's conclusion that there is insufficient information to identify the mode of carcinogenic action of LAA, and therefore the default linear extrapolation at low doses is appropriate.

- The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation unit risk (IUR) and agrees that the use of the subcohort post 1959 for quantification is reasonable due to the lack of exposure information for many of the earlier workers. The SAB finds the use of lung cancer and mesothelioma as endpoints to be appropriate for the derivation of the IUR. However, the SAB recommends a more detailed discussion on how the use of mortality data rather than incidence data may have resulted in an undercount of both cancer outcomes.

- The SAB agrees that the agency clearly described the methods they selected to conduct the exposure-response modeling for lung cancer and mesothelioma. However, the SAB suggests that the agency provide a broader justification for its choice of statistical models to characterize the exposure response function. The SAB recommends that the Agency

evaluate the time dependence of disease by providing tabulation of mesothelioma mortality rates and lung cancer standardized mortality ratios by time since first exposure, duration of exposure, and period of first exposure for both the full and subcohort.

- There are several competing models- Weibull, and the two stage clonal expansion (TSCE) - that could have been used instead of or in addition to the Poisson and Cox models that might have provided very different estimates of risk, but these are not discussed in the document. Use of the TSCE model, for example, could allow for a more direct evaluation of, and possibly justification for, age-dependency of the IUR.

- The SAB believes the agency has been overly constrained by reliance on model fit statistics as the primary criterion for model selection. The SAB recommends graphical display of the fit to the data for both the main models and a broader range of models in the draft document to provide a more complete and transparent view of model fit.

- The EPA has summarized many sources of uncertainty, sometimes quantitatively, as well as the direction and magnitude of the likely impact of each source of uncertainty. However, the SAB identifies an important source of uncertainty, namely, model uncertainty, that might not be accounted for in the use of the 95% upper confidence limit on the inhalation unit risk (IUR) and the combined IUR. The SAB recommends that a more straightforward and transparent treatment of model uncertainty would be to estimate risks using a more complete set of plausible models for the exposure-response relationship, including the Cox and Poisson models. This sensitivity analysis, while not a full uncertainty analysis, would make explicit the implications of these key model choices.

The SAB appreciates the opportunity to provide the EPA with advice on this important subject. The SAB urges the agency to move expeditiously to finalize this IRIS document for Libby Amphibole Asbestos. We look forward to receiving the agency's response.

Sincerely,

believes additional analyses/cohorts are needed to strengthen and support the RfC. The SAB suggests that EPA include any X-ray abnormalities as the outcome (localized pleural thickening (LPT), diffuse pleural thickening (DPT), or asbestosis). The SAB also suggests that the EPA conduct analogous analyses (to the extent the data permit) of pleural abnormalities among the Libby workers cohort (Larson et al.,2012), and the Minneapolis Exfoliation Community cohort (Adgate et al.,2011; Alexander et al.,2012).

The SAB agrees that the radiographic evidence of localized pleural thickening (LPT) in humans is the appropriate adverse critical effect for the derivation of the RfC. LPT has the appropriate specificity and is not confounded by cigarette smoking. It is physiologically important due to its measurable relationship to altered lung function, and is a structural, pathologic alteration of the pleura. The reported findings are compatible with the animal data showing tissue injury and inflammation. Moreover, the presence of LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer, a point that the EPA should include as well. However, the SAB has identified additional relevant publications and a more detailed review of the literature is needed to further support this conclusion.

Use of Animal and Mechanistic Studies

In general, the SAB finds the laboratory animal studies listed in Tables 4-15, and 4-16 and summarized in Appendix D to be appropriate and complete. Laboratory animal studies using a variety of non-inhalation routes of exposure have been used to ascertain the potential fibrogenic and carcinogenic potential of the LA. While inhalation is regarded as the most physiologically relevant mean of fiber exposure in animals, there is no published study using this route of exposure in experimental animals. Therefore, the deposition of particles and fibers cannot be adequately addressed. However, inhalation studies have been conducted with tremolite. The relative potency of inhaled LAA should be compared with that of tremolite to add new information for refining the RfC for LAA.

Limited mechanistic studies using *in vitro* assay systems have utilized non-specific endpoints (e.g., pro-inflammatory cytokines, enzyme release and oxidative stress markers), and will probably not shed much light on the mechanisms of LAA-induced disease.

Carcinogenicity

Weight of Evidence Characterization

The SAB agrees that the weight of evidence for LAA supports the descriptor "Carcinogenic to Humans by the Inhalation Route", in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA,2005). The occupational studies showed dose-related increased risks of lung cancer and mesothelioma among workers exposed by inhalation, although the numbers of cases are small, particularly in the sub-cohort used from the Marysville, Ohio plant that had lower estimated levels of exposure. The case series in the community, while supportive, does not provide the same level of evidence for an association, or for the strength of the association. Effects from short term intra-tracheal instillation studies in mice and rats include altered gene expression, collagen induction, and inflammatory response, and are consistent with the early-stage pathological change induced by other

2. *Radiographic evidence of localized pleural thickening in humans was concluded by EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural thickening is associated with restrictive lung function, breathlessness during exercise and, for some individuals, chronic chest pain. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described. If a different health endpoint is recommended as the critical effect for deriving the RfC, please identify this effect and provide scientific support for this choice.*

The selection of radiographic evidence of localized pleural thickening (LPT) in humans is the appropriate adverse effect and critical effect for the derivation of the RfC. This is well supported by the lines of evidence presented in section 4.1.1.4.2. The section is scientifically supported and clearly described although, as described below, the SAB believes additional evidence is available and to further support this view and should be reported.

While other health endpoints might have been considered candidates for the critical effect for deriving the RfC, such as diffuse pleural thickening and small opacity profusion, none is superior to localized pleural thickening. LPT is found at a significantly elevated prevalence in the community of exposed individuals. Localized pleural thickening has the appropriate specificity and is not confounded by cigarette smoking. LPT is physiologically important due to its measurable relationship to altered lung function. LPT is a structural, pathologic alteration of the pleura. The findings reported in this section are compatible with the animal data showing tissue injury and inflammation. Additionally, the presence of LPT itself is predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer, a point that the EPA should include, as well. The SAB discussed that while it fully agrees with the merits of using LPT detected by chest radiograph and CT scan as the appropriate adverse effect and critical effect for the derivation of the RfC, this approach should not preclude EPA from using more sensitive diagnostic techniques that may identify earlier or more specific pleural changes in the future

.

Due to the landmark action of developing an RfC for LAA, the SAB discussed the need for the inclusion of a more detailed review of the literature to support the presence of a relationship between localized pleural thickening and both pathologic and physiologic abnormalities. There is additional literature that addresses and demonstrates the relationship between LPT and restrictive lung function that should be included. Published studies suggested by the SAB (Clin et al., 2011; Paris et al., 2009; Lilis et al., 1992) should be considered and include those referenced in the American Thoracic Society (ATS) Statement entitled, *Diagnosis and Initial Management of Nonmalignant Diseases Related to Asbestos: Official Statement of the American Thoracic Society*, (ATS,2004) (Miller et al., 1992; Miller, 2002; Schwartz et al., 1990; Jarvolm and Sanden, 1986; Hjortsberg et al., 1988; Oliver et al., 1988; Bourbeau et al., 1990; Ohlson et al., 1984; Ohlson et al., 1985; Sichletidis et al., 2006; Van Cleemput et al., 2001; Whitehouse (2004; Wilken et al., 2011). Consistent with that Statement, it is the view of the SAB that large cohort studies have shown a significant reduction in lung function, including diminished diffusing capacity and vital capacity attributable to LPT. The SAB also recommends that the EPA provide a more thorough review of the physiologic relationship between LPT found on chest x-ray and CT scan and lung function, not limiting itself to Libby amphibole asbestos.

The SAB also suggests that the EPA consider looking at LPT, DPT and small opacity profusion score together as an outcome. There is evidence that LPT is not always the first adverse effect that is detected

APPENDIX C – 21

EXCERPTS

Materials Submitted to the National Research Council
Part I: Status of Implementation of Recommendations

U.S. Environmental Protection Agency

Integrated Risk Information System Program

January 30, 2013

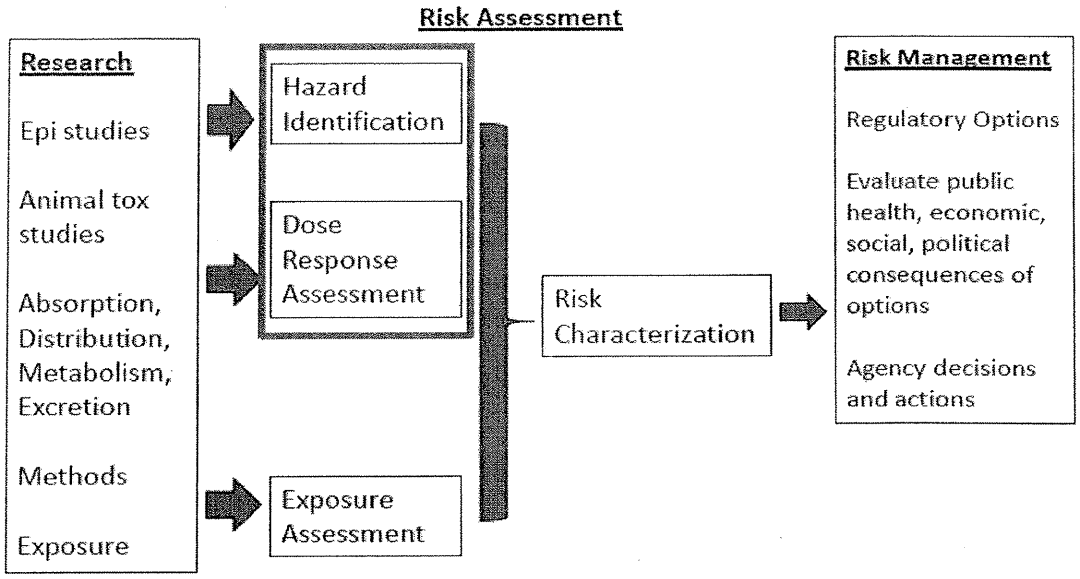
Table of Contents

I. Introduction

The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) Program develops human health assessments that provide health effects information on environmental chemicals to which the public may be exposed, providing a critical part of the scientific foundation for EPA's decisions to protect public health. In April 2011, the National Research Council (NRC), in their report *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*, made several recommendations to EPA for improving IRIS assessments and the IRIS Program. The NRC's recommendations were focused on Step 1 of the IRIS process, the development of draft assessments. Consistent with the advice of the NRC, the IRIS Program is implementing these recommendations using a phased approach and is making the most extensive changes to assessments that are in the earlier stages of the IRIS process.

Background on IRIS

IRIS human health assessments contain information that can be used to support the first two steps (hazard identification and dose-response analysis) of the risk assessment paradigm. IRIS assessments are scientific reports that provide information on a chemical's hazards and, when supported by available data, quantitative toxicity values for cancer and noncancer health effects. IRIS assessments are not regulations, but they provide a critical part of the scientific foundation for decisions to protect public health across EPA's programs and regions under an array of environmental laws (e.g., Clean Air Act, Safe Drinking Water Act, Comprehensive Environmental Response, Compensation, and Liability Act, etc). EPA's program and regional offices combine IRIS assessments with specific exposure information for a chemical. This information is used by EPA, together with other considerations (e.g., statutory and legal requirements, cost/benefit information, technological feasibility, and economic factors), to characterize the public health risks of environmental chemical and make risk management decisions, including regulations, to protect public health. IRIS assessments are also a resource for risk assessors and environmental and health professionals from state and local governments and other countries. Figure 1 illustrates where IRIS assessments contribute information within the risk assessment and risk management paradigms.



1 Adapted from the National Research Council risk assessment risk management paradigm (NRC 1983).

Figure 1. Risk Assessment Risk Management Paradigm (adapted from the National Research Council's paradigm, 1983). The red box shows the information included in IRIS assessments.

II. Charge to the NRC Expert Panel

In April 2012, EPA contracted with the NRC to conduct a comprehensive review of the IRIS assessment development process. The panel will review the IRIS process and the changes being made or planned by EPA and will recommend modifications or additional changes as appropriate to improve the process, and scientific and technical performance of the IRIS Program. The panel will focus on the development of IRIS assessments rather than the review process that follows draft development. In addition, the panel will review current methods for evidence-based reviews and recommend approaches for weighing scientific evidence for chemical hazard and dose-response assessments.

III. Overview of EPA's Implementation of NRC's Recommendations

EPA agrees with the NRC's 2011 recommendations for the development of IRIS assessments and plans to fully implement the recommendations consistent with the NRC panel's "Roadmap for Revision," which viewed the full implementation of their recommendations by the IRIS Program as a multi-year process. In response to the NRC's 2011 recommendations, the IRIS Program has made changes to streamline the assessment development process, improve transparency, and create efficiencies within the Program. The following sections outline the NRC's 2011 recommendations and provide an overview of how the IRIS Program is implementing the NRC's general and specific

recommendations. changes that have been made and will be made in response to the recommendations are provided in Appendices to this report.

In addition, chemical-specific examples demonstrating how the IRIS Program is currently implementing the NRC's 2011 recommendations have also been provided to the panel (see additional document provided, *Chemical-Specific Examples Demonstrating Implementation of NRC's 2011 Recommendations*). The examples cover literature search and screening, evaluation and display of individual studies, development of evidence tables, evidence integration, selecting studies for derivation of toxicity values, dose-response modeling output, and considerations for selecting organ/system-specific or overall toxicity values. The examples are not to be construed as final Agency conclusions and are provided for the sole purpose of demonstrating how the IRIS Program is implementing the NRC recommendations.

NRC's General Recommendations and Guidance

NRC Recommendations[1]:

- To enhance the clarity of the document, the draft IRIS assessment needs rigorous editing to reduce the volume of text substantially and address redundancies and inconsistencies. Long descriptions of particular studies should be replaced with informative evidence tables. When study details are appropriate, they could be provided in appendices.
- Chapter 1 needs to be expanded to describe more fully the methods of the assessment, including a description of search strategies used to identify studies with the exclusion and inclusion criteria articulated and a better description of the outcomes of the searches and clear descriptions of the weight-of-evidence approaches used for the various noncancer outcomes. The committee emphasizes that it is not recommending the addition of long descriptions of EPA guidelines to the introduction, but rather clear concise statements of criteria used to exclude, include, and advance studies for derivation of the RfCs and unit risk estimates.
- Elaborate an overall, documented, and quality-controlled process for IRIS assessments.
- Ensure standardization of review and evaluation approaches among contributors and teams of contributors; for example, include standard approaches for reviews of various types of studies to ensure uniformity.
- Assess disciplinary structure of teams needed to conduct the assessments.

Implementation:

➢ **New Document Structure** Implemented

In their report, the NRC recommended that the IRIS Program enhance the clarity of the document, reduce the volume of text, and address redundancies and inconsistencies. To improve the clarity of IRIS assessments, the IRIS Program has revised the assessment template to substantially reduce the volume of text and address redundancies and inconsistencies in assessments. The new template provides sections for the literature search strategy, study selection and evaluation, and methods used to develop the assessment.

[1] National Research Council, 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

➢ **Evidence Tables** Implemented

The IRIS Program has developed templates for evidence tables to standardize the presentation of reviewed studies in IRIS assessments. Once a literature search has been conducted and the resulting database of studies has been evaluated, evidence tables are developed to present information from the collection of studies related to a specific outcome or endpoint of toxicity. The evidence tables include studies that have been judged adequate for hazard identification and display available study results, both positive and negative results. The studies that are considered to be most informative will depend on the extent and nature of the database for a given chemical, but may encompass a range of study designs and include epidemiology, toxicology, and, other toxicity data when appropriate.

For more detailed information, see "Reporting Study Results" in the Evaluation and Display of Individual Studies section in the draft Handbook for IRIS Assessment Development in Appendix F.

A chemical-specific example of the implementation of this recommendation is available as "EXAMPLE 3 – Evidence Tables" in the Chemical-specific Examples Demonstrating Implementation of NRC Recommendations document.

Weight-of-Evidence Evaluation: Integration of Evidence for Hazard Identification

NRC Recommendations:

- Strengthened, more integrative and more transparent discussions of weight of evidence are needed. The discussions would benefit from more rigorous and systematic coverage of the various determinants of weight of evidence, such as consistency.
- Review use of existing weight-of-evidence guidelines.
- Standardize approach to using weight-of-evidence guidelines.
- Conduct agency workshops on approaches to implementing weight-of-evidence guidelines.
- Develop uniform language to describe strength of evidence on noncancer effects.
- Expand and harmonize the approach for characterizing uncertainty and variability.
- To the extent possible, unify consideration of outcomes around common modes of action rather than considering multiple outcomes separately.

Implementation:

➢ **Integration of Evidence for Hazard Identification** In Progress

The IRIS Program has strengthened and increased transparency in the weight-of-evidence for identifying hazards in IRIS assessments. Hazard identification involves the integration of evidence from human, animal, and mechanistic studies in order to draw conclusions about the hazards associated with exposure to a chemical. In general, IRIS assessments integrate evidence in the context of Hill (1965), which outlines aspects — such as consistency, strength, coherence, specificity, does-response, temporality, and biological plausibility — for consideration of causality

in epidemiologic investigations that were later modified by others and extended to experimental studies (U.S. EPA, 2005a).

All results, both positive and negative, of potentially relevant studies that have been evaluated for quality are considered (U.S. EPA, 2002) to answer the fundamental question: "Does exposure to chemical X cause hazard Y?" This requires a critical weighing of the available evidence (U.S. EPA, 2005a; 1994), but is not to be interpreted as a simple tallying of the number of positive and negative studies (U.S. EPA, 2002). Hazards are identified by an informed, expert evaluation and integration of the human, animal, and mechanistic evidence streams.

For more detailed information, see "Synthesis of Observational Epidemiology Evidence", "Synthesis of Animal Toxicology Evidence", and "Mechanistic Considerations in Elucidating Adverse Outcome Pathways" in the Evaluating the Overall Evidence of Each Effect section in the draft Handbook for IRIS Assessment Development in Appendix F.

See also Section 5 ("Evaluating the overall evidence of each effect") in the Preamble to IRIS Toxicological Reviews in Appendix B.

A chemical-specific example of the implementation of this recommendation is available as "EXAMPLE 4 – Evidence Integration" in the Chemical-specific Examples Demonstrating Implementation of NRC Recommendations document.

Currently, the IRIS Program is using existing guidelines that address these issues to inform assessments. In addition, the IRIS Program is taking a more systematic approach in analyzing the available human, animal, and mechanistic data is being used in IRIS assessments. In conducting this analysis and developing the synthesis, the IRIS Program evaluates the data for the:

- strength of the relationship between the exposure and response and the presence of a dose-response relationship;
- specificity of the response to chemical exposure and whether the exposure precedes the effect;
- consistency of the association between the chemical exposure and response; and
- biological plausibility of the response or effect and its relevance to humans.

The IRIS Program uses this weight of evidence approach to identify the potential hazards associated with chemical exposure.

The IRIS Program recognizes the benefit of adopting a formal weight-of-evidence framework that includes standardized classification of causality. In addition to the NRC task, in which the panel will review current methods for evidence-based reviews and recommend approaches for weighing scientific evidence for chemical hazard and dose-response assessments, the IRIS Program is planning to convene a workshop to discuss approaches to evidence integration. As part of this workshop, the various approaches that are currently in use will be acknowledged and compared for their strengths and limitations. The workshop will include scientists with expertise in the

classification of chemicals for various health effects. The workshop will be open to the public, and the details will be publicly announced.

The "Integration of Evidence Evaluation" section in the draft Handbook for IRIS Assessment Development in Appendix F is currently under development.

Selection of Studies for Derivation of Toxicity Values

NRC Recommendations:

- The rationales for the selection of the studies that are advanced for consideration in calculating the RfCs and unit risks need to be expanded. All candidate RfCs should be evaluated together with the aid of graphic displays that incorporate selected information on attributes relevant to the database.
- Establish clear guidelines for study selection.
- Balance strengths and weaknesses.
- Weigh human vs. experimental evidence.
- Determine whether combining estimates among studies is warranted.

Implementation:

➢ **Selection of Studies for Dose-Response Analysis** Implemented

The IRIS Program has improved the process for selecting studies for derivation of toxicity values as well as increasing the transparency about this process by providing an improved discussion and rationale. Building on the individual study quality evaluations (described under *Evidence Evaluation: Hazard Identification* in this report) that identify strengths and weaknesses of individual studies, for each health effect for which there is credible evidence of hazard, a group of studies are identified and evaluated as part of the hazard identification. In evaluating these studies for selecting a subset to be considered for the derivation of toxicity values, the basic criterion is whether the quantitative exposure and response data are available to compute a point of departure (POD). can be a no-observed-adverse-effect-level [NOAEL], lowest-observed-adverse-effect-level [LOAEL], or the benchmark dose/concentration lower confidence limit[BMDL/BMCL]).

Additional attributes (aspects of the study, data characteristics, and relevant considerations) pertinent to derivation of toxicity values are used as criteria to evaluate the subset of studies for dose-response analysis. Thus, the most relevant, informative studies are selected to move forward. The new document structure provides for transparent discussion of the studies identified for dose-response analysis.

For more detailed information, see "Selection of Studies for Derivation of Toxicity Values" in the Dose-Response Analysis section in the draft Handbook for IRIS Assessment Development in Appendix F.

See also Section 6 ("Selecting studies for dose-response analysis") in the Preamble to IRIS Toxicological Reviews in Appendix B.

Appendix B – Preamble to IRIS Toxicological Reviews

1. Scope of the IRIS Program

Soon fter EPA as established in 970, it was at the orefront of veloping isk assessment as science nd applying decisions rotect human health and the environment. The lean Air ct, for example, ndates that EPA provide "an ample rgin afety to protect health"; the Safe Drinking Water Act, that "no adverse effects e health persons may reasonably be anticipated o occur, allowing adequate margin afety." Accordingly, EPA uses formation e dverse effects chemicals exposure levels below which these effects are not anticipated to occur.

IRIS assessments ritically eview the publicly available tudies to dentify adverse health effects from long-term exposure to chemicals and to characterize exposure-response relationships. In terms et forth by the ional Research Council (NRC, 1983), IS assessments cover the hazard identification nd dose-response assessment eps of isk ssessment, not he exposure ssessment or isk haracterization steps at are onducted by EPA's program and regional ffices nd by er federal, state, and local health agencies at valuate pecific populations nd exposure cenarios. IRIS assessments re distinct from and do not address political, economic, and technical onsiderations that influence the design and selection of risk management alternatives.

An IRIS assessment may over a single chemical, a roup tructurally iologically elated chemicals, omplex mixture. eptions re chemicals currently used exclusively as pesticides, ionizing and non-ionizing adiation, and criteria ir pollutants isted under ection 108 of e lean ir ct (carbon noxide, lead, nitrogen oxides, ozone, particulate matter, and sulfur oxides).

Periodically, the RIS rogram asks r PA programs nd egions, other federal agencies, state health agencies, and the general public to nominate chemicals and mixtures for future assessment r eassessment. These agents may be nd in ir, water, soil, or sediment. Selection is ram and egional fice iorities and on vailability dequate information o evaluate the potential for dverse effects. The IRIS Program may assess other agents as an urgent public health need arises. IRIS also reassesses published.

2. Process for developing and peer-reviewing IRIS assessments

The process for developing IRIS assessments (revised in y 009) volves critical nalysis the pertinent studies, portunities or ublic input, and multiple levels of scientific eview. EPA vises draft assessments after each eview, and ternal drafts d omments ecome part of e ublic cord (U.S. PA, 2009).

Step 1. Development of a draft Toxicological Review (generally out -1/2 ths duration). he raft assessment onsiders all pertinent blicly ailable studies and applies onsistent criteria to evaluate study quality, identify ealth ffects, identify mechanistic events nd pathways, tegrate the evidence f ausation for each effect, nd derive ity values. A public dialogue meeting prior to the integration f evidence and derivation of toxicity alues romotes public discussion of the literature search, evidence, and key sues.

Step 2. Internal review by scientists in EPA programs and regions (2 months). The draft assessment is revised to address comments om ithin EPA.

Step 3. Interagency science consultation with other federal agencies and the Executive Offices of the President (1-1/2 onths). The draft ssessment is evised o address the interagency comments. The science consultation draft, teragency nts, and EPA's response to major omments become part of the public record.

Step 4. Public review and comment, followed by external peer review (3-1/2 months more, epending on e review rocess). EPA releases the draft ssessment for public review nd omment. Another blic dialogue meeting provides n portunity discuss the assessment rior o peer view. EPA addresses the public omments and releases raft or external peer review. The peer eviewers assess hether he evidence has been assembled nd evaluated cording to guidelines and whether e conclusions are justified by he evidence. The peer review eeting is open e public and includes time or ral ublic comments. The peer review draft, peer eview eport, and written public omments become part of the public cord.

Step 5. Revision of draft Toxicological Review and development of draft IRIS summary (2 months). The aft assessment is revised to reflect the peer eview comments, public comments, nd newly ublished studies that are critical e conclusions of the assessment. The disposition of eer review comments nd public ments ecomes part of the ublic record.

Step 6. Final EPA review and interagency science discussion with other federal agencies and the Executive Offices of the President (1-1/2 months). he draft assessment nd summary are revised to address A nd eragency comments. The science cussion draft, ritten agency comments, and EPA's esponse to major comments become art e ublic ecord.

Step 7. Completion and posting (1 month). The Toxicological Review d RIS mmary are posted on e IS web ite (http://www.epa.gov/iris/).

The remainder of this Preamble addresses step 1, the evelopment of ft Toxicological Review. IRIS assessments low tandard practices f evidence evaluation n n which are discussed n PA guidelines (U.S. EPA, 1986a, 986b, 1991, 1996, 1998, 2000, 005a, 2005b) nd ther methods (U.S. EPA, 1994, 2002, 2006a, 2006b, 2011, 2012a, 2012b). A practical draft *Handbook* is available for use by IRIS assessment eams (U.S. EPA, 2013). Transparent application f scientific dgment is of paramount importance. To rovide harmonized approach cross IRIS assessments, this Preamble summarizes concepts hese guidelines and emphasizes rinciples of eneral applicability.

3. Identifying and selecting pertinent studies

3.1 Identifying studies

Before eginning n assessment, A onducts a comprehensive earch the primary cientific literature. The iterature search follows standard practices nd ncludes he PubMed and ToxNet databases f the National Library of edicine, Web of cience, and other atabases ted n EPA's HERO system Health and nvironmental Research line, http://hero.epa.gov/). rches for nformation on mechanisms toxicity e inherently specialized and may include studies on ther gents that act through related mechanisms.

Each assessment pecifies he search strategies, keywords, and ut-off dates of iterature searches. EPA posts e esults e iterature search n e IRIS web ite and requests information from e ublic on additional studies and ngoing search.

EPA iders studies received through IRIS Submission Desk nd studies typically unpublished) bmitted e the oxic Substances Control Act or e Federal Insecticide, Fungicide, nd Rodenticide Act. aterial submitted onfidential Business mation is sidered only udes health and safety data that an be publicly eleased. If a study that may be critical to the conclusions of e assessment has not been peer-reviewed, EPA will have peer-reviewed.

EPA also examines the toxicokinetics of the agent to identify other chemicals (for example, major metabolites of the agent) lude e assessment q information is available, in rder to more ully lain e xicity of e agent and to suggest dose etrics for ubsequent modeling.

In assessments of chemical mixtures, mixture studies e preferred for eir ability eflect interactions mong omponents. The erature search seeks, in decreasing order eference (U.S. EPA, 1986a, 2000):

- Studies of the being assessed.
- Studies ufficiently similar mixture. In evaluating imilarity, the ssessment considers the alteration of mixtures in e environment hrough partitioning nd transformation.
- Studies of dividual hemical components of the mixture, if there re ot adequate studies of fficiently ar mixtures.

3.2 Selecting pertinent epidemiologic studies

Study esign the ey onsideration for selecting ertinent epidemiologic tudies from the results of the literature search.

- Cohort studies, case-control studies, some opulation-based surveys (for example, NHANES) provide the strongest epidemiologic idence, pecially when they collect information bout individual exposures effects.
- Ecological tudies (geographic correlation studies) relate exposures f by geographic area. They an rovide trong evidence if there are large exposure contrasts between geographic as, relatively ittle exposure ariation within study areas, and population migration is limited.
- Case ports igh or cidental exposure lack finition the ulation t risk nd the expected number of ses. hey can provide information bout rare effect or about the relevance of analogous results in animals.

The assessment briefly reviews ological studies and case reports ut eports tails only if ey suggest effects not identified by other studies.

3.3 Selecting pertinent experimental studies

Exposure route is a key design consideration for selecting ertinent experimental animal studies or uman inical studies.

- Studies f al, nhalation, ermal exposure volve passage rough n absorption barrier and are considered most pertinent to n v onmental exposure.
- Injection lantation tudies are often considered less pertinent but may provide valuable okinetic echanistic information. They lso may be seful for identifying effects n nimals eposition or absorption roblematic (for example, for particles d fibers).

Exposure duration is also a key esign consideration for selecting ertinent experimental animal studies.

- Studies of fects from chronic exposure are most pertinent to ifetime uman exposure.
- Studies fects from less-than-chronic exposure are pertinent but less preferred for identifying effects rom time uman exposure. uch tudies may be indicative of effects -than-lifetime human exposure.

Short-duration tudies involving imals or humans may provide okinetic or mechanistic information.

For developmental toxicity and reproductive toxicity, irreversible effects may result from a brief exposure during ritical period of development. Accordingly, specialized udy designs re used or hese effects U.S. EPA, 991, 1996, 1998, 2006b).

4. Evaluating the quality of individual studies

After the bsets of ertinent epidemiologic n experimental tudies ave een elected rom the literature ar hes, the assessment valuates the quality each ndividual study. This evaluation considers the esign, methods, conduct, nd documentation of each study, ut not whether the results are positive, negative, or null. The

objective is to identify the stronger, more informative studies based on a uniform evaluation f quality haracteristics across studies f similar esign.

4.1 Evaluating the quality of epidemiologic studies

The assessment evaluates ign and methodological spects at can crease or decrease the weight given to ach epidemiologic study n he overall evaluation (U.S. EPA, 1991, 1994, 996, 1998, 2005a):

- Documentation of study design, ethods, population haracteristics, nd results.
- Definition and selection of he tudy group and comparison group.
- Ascertainment of exposure to the chemical or ixture.
- Ascertainment of disease or health ffect.
- Duration xposure nd follow-up nd adequacy for assessing the occurrence of effects.
- Characterization of exposure during critical periods.
- Sample ize and statistical power to detect anticipated effects.
- Participation ates and potential or election bias as a result of the chieved participation rates.
- Measurement error (can lead to misclassification exposure, health outcomes, and other factors) and other types of information bias.
- Potential confounding nd other sources of bias addressed in e tudy design n analysis sults. The basis consideration founding expectation at the confounder is related to both exposure nd outcome and is sufficiently prevalent to result in bias.

For developmental toxicity, reproductive toxicity, neurotoxicity, and cancer there is further guidance on the nuances evaluating epidemiologic tudies of ese effects U.S. EPA, 1991, 1996, 1998, 005a).

4.2 Evaluating the quality of experimental studies

The assessment evaluates design and methodological spects at can crease or decrease the weight iven to ch experimental animal study, in-vitro tudy, or linical study (U.S. A, 1991, 994, 1996, 998, 2005a). Research involving uman ubjects considered only if conducted according to ethical principles.

- Documentation of tudy design, nimals study population, methods, basic ta, and results.
- Nature e ssay intended urpose.
- Characterization of the nature and extent of impurities nd contaminants e administered chemical or
- Characterization of e nd ing regimen (including e t exposure) and their adequacy licit effects, including latent effects.
- Sample sizes nd tistical power detect dose-related differences r rends.
- Ascertainment of urvival, vital signs, disease or effects, d use of eath.
- Control other ariables that could influence the occurrence of effects.

The ssessment uses statistical sts evaluate whether he observations may e due to hance. The standard for etermining statistical significance of esponse is a trend test or comparison tcomes n the exposed groups against those of concurrent controls. In some situations, examination of historical control ta from the same laboratory within a few ears of the tudy may mprove e nalysis. For n uncommon effect that is ot statistically significant compared with oncurrent controls, historical controls y show at the ffect unlikely to be due to chance. For a response at appears ignificant against urrent ontrol response at is nusual, istorical ontrols y offer ifferent interpretation (U.S. EPA, 2005a).

For evelopmental toxicity, reproductive , neurotoxicity, nd cancer there is further guidance on he nuances of evaluating experimental studies f these effects U.S. EPA,

1991, 1996, 1998, 2005a). In multi-generation studies, agents that produce developmental effects t doses that are not toxic e aternal animal re pecial concern. Effects at occur at doses ssociated with ild maternal toxicity are not assumed to result only from maternal toxicity. Moreover, maternal effects may reversible, hile ffects he fspring y be permanent U.S. EPA, 991, 1998).

4.3 Reporting study results

The assessment uses idence tables to present the sign nd key esults ertinent studies. There may be separate tables or each site of toxicity or type of tudy.

If rge mber tudies observe the me effect, e ssessment considers e tudy quality characteristics ection entify the strongest studies or pes tudy. The tables present details from these studies, and the assessment xplains the reasons r not reporting etails ther tudies r roups studies at not dd new information. Supplemental information provides eferences to all tudies onsidered, cluding those ot summarized in e bles.

The assessment discusses strengths and limitations that affect the interpretation ch study. If the interpretation of a study e assessment differs rom that of e dy uthors, the ssessment discusses the basis for the difference.

As a check on the selection and evaluation of pertinent udies, EPA asks peer reviewers to identify tudies at were not adequately considered.

5. Evaluating the overall evidence of each effect

5.1 Concepts of causal inference

For each ealth ect, the sessment evaluates the evidence as whole to determine whether t is reasonable to infer ausal association between exposure to the agent and the occurrence of the ect. his ference ased on information ertinent human tudies, animal studies, and mechanistic studies of adequate quality. Positive, negative, and null results are given weight according to study quality.

Causal ference involves scientific dgment, and he onsiderations e nuanced d mplex. Several health gencies ave eveloped frameworks or ausal inference, mong them the U.S. rgeon General (DHEW, 1964; DHHS, 2004), the nternational Agency for Research n Cancer 2006), nstitute of edicine 2008), and he .S. Environmental Protection Agency (2005a, 2010). Although eveloped or different purposes, the frameworks re imilar in nature and provide n tablished tructure d language for ausal inference. Each onsiders aspects of n ssociation at suggest ausation, discussed by Hill (1965) and elaborated by Rothman nd Greenland (1998) (U.S. EPA, 1994, 2002, 2005a).

Strength of association: The finding of relative isk with arrow onfidence intervals trongly uggests hat an association e to chance, bias, or other factors. Modest relative s may eflect a small range of exposures, agent of w potency, an ncrease in n ffect that is common, exposure misclassification, or other sources f bias.

Consistency of association: An inference f causation trengthened if elevated risks are bserved n independent tudies of different populations nd exposure scenarios. Reproducibility of indings constitutes one of the trongest arguments for ausation. Discordant results sometimes reflect differences tudy design, exposure, or onfounding actors.

Specificity of association: As riginally intended, this refers to one ause ociated with ne effect. urrent standing at many gents ause ltiple effects d ny effects have multiple causes make this ss informative aspect ausation, ess e effect is rare or nlikely ave ltiple causes.

Temporal relationship: A ausal interpretation requires at e precede development of the effect.

Biologic gradient (exposure-response relationship): Exposure-response relationships strongly ggest causation. A monotonic crease otthe ly attern consistent with usation. The presence of an exposure-response radient also weighs against bias d confounding s . ource of an ssociation.

Biologic plausibility: An inference of causation is trengthened by emonstrating plausible biologic mechanisms, vailable. Plausibility may reflect subjective prior beliefs ere insufficient understanding of e biologic process involved.

Coherence: An nference causation strengthened by upportive results rom animal xperiments, toxicokinetic tudies, and hort-term tests. Coherence may also e found er ines evidence, such s changing disease patterns in he population.

"Natural experiments": A change in exposure that rings about a change in disease frequency provides strong evidence, as tests e ypothesis of ausation. An example would be ntervention reduce exposure in e workplace nvironment that is followed y eduction of an adverse effect.

Analogy: Information uctural analogues r on chemicals that induce imilar mechanistic events can provide insight into causation.

These onsiderations are onsistent with guidelines for ystematic eviews at evaluate the quality nd eight of evidence. Confidence is increased if the magnitude ge, there is vidence n exposure-response relationship, or f ssociation was served and the ses would tend o decrease the magnitude the reported effect. Confidence is decreased r study imitations, inconsistency of esults, indirectness f evidence, imprecision, or reporting ias Guyatt et al., 2008a,b).

5.2 Evaluating evidence in humans

For each effect, the ssessment evaluates the evidence rom e pidemiologic dies as whole. to determine whether a credible sociation as been bserved d, if so, whether at association sistent with causation. In doing this, the assessment explores alternative explanations (such as chance, bias, and confounding) and draws a conclusion about whether these lternatives can satisfactorily explain ny bserved association.

To make ear ow much the epidemiologic evidence contributes to e overall weight of the evidence, the assessment may elect a tandard descriptor haracterize the epidemiologic evidence ssociation between exposure to the agent d occurrence f ealth ffect.

Sufficient epidemiologic evidence of an association consistent with causation: The evidence establishes ausal ssociation or which lternative explanations such as chance, bias, and onfounding an be ruled out with reasonable onfidence.

Suggestive epidemiologic evidence of an association consistent with causation: The evidence suggests ausal ssociation but chance, bias, or confounding annot e ruled out as xplaining the ssociation.

Inadequate epidemiologic evidence to infer a causal association: The available studies o not permit a clusion egarding e presence or absence of n ssociation.

Epidemiologic evidence consistent with no causal association: Several adequate studies covering e full ge f human exposures and considering usceptible populations, and for which alternative explanations ch bias and confounding can be ruled out, are mutually consistent in not finding an association.

5.3 Evaluating evidence in animals

For each effect, the assessment valuates the evidence rom e nimal experiments s whole to determine the extent to h indicate a potential for effects n mans. onsistent results across various species and strains increase confidence at similar results would occur in humans. Several concepts discussed by Hill (1965) are rtinent to the weight of experimental results: consistency of response, dose-response relationships, trength response, biologic plausibility, and coherence (U.S. EPA, 1994, 2002, 2005a).

In eighing vidence from multiple experiments, U.S. EPA 2005a) distinguishes

Conflicting evidence (that is, mixed positive and negative results the ame sex and strain using imilar tudy protocol)
Differing results (that is, positive results nd negative results are in ifferent exes or strains or use different study protocols).

Negative or null results do not invalidate positive results in a different experimental system. PA regards d bservations d looks explain fering results sing echanistic information (for example, physiologic metabolic differences across st systems) or methodological differences (for example, relative sensitivity e ests, fferences in e evels, insufficient sample ize, or dosing r data

It is l established that there re critical periods or ome evelopmental and reproductive fects. ccordingly, the assessment determines whether ritical periods have been adequately nvestigated U.S. EPA, 1991, 1996, 1998, 2005a, 2005b, 2006b). Similarly, the assessment determines whether he atabase is adequate to evaluate other critical sites and effects.

In evaluating evidence of genetic toxicity:

- Demonstration gene tations, chromosome errations, or neuploidy in humans xperimental mammals (*in vivo*) provides e rongest evidence.
- This is followed by positive results in lower organisms or in cultured cells (*in vitro*) or other genetic events.
- Negative results arry less weight, partly because ey cannot exclude e ossibility of effects in other tissues IARC, 2006).

For germ-cell tagenicity, EPA as defined categories f evidence, ranging om itive results of human germ-cell mutagenicity negative results for ll effects of oncern (U.S. EPA, 1986b).

5.4 Evaluating mechanistic data to identify adverse outcome pathways and modes of action

Mechanistic ata can be seful in answering several uestions.

- The iologic plausibility of a causal interpretation tudies.
- The generalizability of animal studies to humans.
- The usceptibility of particular populations or ifestages.

The focus e nalysis is o describe, if possible, *adverse outcome pathways* that lead to a health ffect. n dverse outcome pathway encompasses:

- *Toxicokinetic processes* of , distribution, metabolism, nd elimination that lead to e formation of an active t and its presence at the site of initial biologic interaction.
- *Toxicodynamic processes* that ad o ealth effect at this or another ite (also known s a *mode of action*).

For each effect, the assessment discusses the available formation on its *modes of action* and associated *key events* (*key events* being empirically bserv le, necessary r steps or biologic markers such teps; *mode of action* being a ries f key events olving interaction with ells, operational and anatomic changes, and resulting in disease). Pertinent information y also come rom studies of metabolites or ompounds at are structurally similar at act through mechanisms. Information on e of action is not required for a conclusion that the agent is causally related to an effect (U.S. EPA, 2005a).

The assessment addresses several questions about each ypothesized mode of action (U.S. EPA, 005a).

(1) Is the hypothesized mode of action sufficiently supported in test animals?
Strong upport r a ey event being necessary to a e of ction an ome from experimental challenge to the hypothesized mode of action, in which studies that

Evaluation and Display of Individual Studies

STUDY QUALITY EVALUATION

Study Quality Evaluation: Overview

- Be inclusive: t etter o de a study d aluate effects of potential limitations an o exclude a study and iminate any nformation the study could have provided
- Evaluate studies BEFORE developing evidence tables
- Series of ocused uestions; pplied stematically to all primary data studies identified elevant he screening steps
- Evaluation is ndpoint-specific; a given tudy aluating everal endpoints may have ifferent strengths nd imitations ith spect to ach endpoint

Study "quality," as defined erein, s a road erm encompassing terpretations regarding a variety of methodological features ., study esign posure measurement etails, study execution, data analysis nd presentation). The purpose of this step n he systematic eview process is not to eliminate udies, ut ather o evaluate studies with espect o otential methodological considerations hat ould affect he interpretation f or nfidence in he results. For larger atabases, n articular, this aluation can rovide a transparent means to onvey our assessment of a study's methodological strengths and limitations, and thus your ability o ely n the results. e esults of his systematic evaluation may also inform decisions about which studies to ove forward or dose-response modeling ivation

The systematic evaluation escribed in his step ould e nducted at an rly age assessment development, .e fter dentifying the relevant ources rimary data but efore developing evidence tables and characterizing hazards associated ith posure to hemical. All studies dentified elevant from the literature screening process hould e evaluated. Even a deficiency n ect of the udy is obvious, it he valuation of all of the component questions o hat ull record of the evaluation e maintained.

Examination f specific methodological features of each study can be ccomplished by applying ries of ocused starting point for generating these ssessment and endpoint ecific questions would be to consider the examples provided in Tables F-6 and F-7 for observational epidemiology and imal toxicology udies, espectively. Documentation important ethodological ures f a study may e an erative process, requiring odification an initial set of questions, as specific features of the chemical, endpoint(s), or study design(s) are discovered. It is essential that hese focused uestions be pplied uniformly to all studies evaluated. This will llow or mparison f the considered studies that is both stematic in design d ependent of the study results. Ideally, wo eviewers would ndependently dentify the relevant methodological details, and then compare their results and interpretations and resolve any differences.

For udies that amine more than ne endpoint or utcome, the evaluation process should be endpoint-specific, s the utility udy may ary for he ferent endpoints.

The methods section he paper ill generally rovide the majority of information needed for this aluation except, of course, for considerations elating to the level of detail of the reported esults). In some cases, however, study details may be presented elsewhere in the manuscript or report, such s the troduction r iscussion sections. dentification f ome study details may equire additional investigation, for example, by consulting ther publications describing the study or udies on he liability of an ay, or by contacting he udy uthors. n general, study uality evaluation hould be independent of considerations egarding he direction or magnitude of he ' esults.

It s useful to check the citation in one of the primary databases (e.g., PubMed) to see if there is any linked material, such ratum, supplementary pendix material, letter to the editor (and authors' reply) regarding the citation, or ompanion udy. is kind of preliminary work can prevent significant heartburn d eadaches in subsequent steps.

It s seful to record he pertinent ethodological features sy o form (e.g., a tabular format) so at these study details can be easily eviewed. ecause observational epidemiology and animal toxicology studies have fundamental differences, the documentation and evaluation of these studies will differ.

There may e situations, most mmonly hen tensive literature databases ist r a given chemical and effect, in hich n dividual study or sets of udies can be xcluded from further consideration. For example, acute animal toxicology studies ay cluded hen abundant bchronic and ronic exposure studies examining imilar dpoints are available.

The ollowing discussion tudy uality valuation ocused valuation observational epidemiology, animal toxicology, d human ontrolled posure studies. This approach could also be dapted r the evaluation of in itro studies d other ypes f studies relevant to mechanisms f action.

Study Quality Evaluation: Logistics

- Methods section of the study should rovide most of he nf mation you need;
- Study quality evaluation should be independent of considerations regarding the direction r gnitude f the study's results
- Look r rata, supplemental files, and ther aterial linked to the primary data citation or additional information bout the study
- Published correspondence (e.g., ters o the editor, editorials) may rovide additional ackground information mportant ethodological features.
- Ideally, use two *independent* reviewers, with procedures for disagreements to be reviewed d esolved

Evaluation of Observational Epidemiology Studies

The rocess of study evaluation is akin o tective ork. You need to investigate specific study ures hat ectly t he interpretation of the experimental results, including:

- exposure measures (reliability, validity, probability and el of exposure in ifferent situations or settings)

- outcome measures reliability, dity, prevalence in ifferent populations, disease course, relation een urvival and cess o ealth care or ther socioeconomic factors)
- confounders (strong risk actors or he come that are also known to be strongly associated with he exposure within he study)

These investigations may equire mini-reviews" and onsultation with experts in ifferent fields. Without this background understanding, you may t e able to curately aluate the studies.

Exposure assessment is pecially important in the environmental or occupational arena. The bility o correctly assify xposed" and "unexposed", te quantitative measures of exposure, and the range of exposure encompassed in the study is ey ifference between observational epidemiology and andomized clinical trials n which "exposure" (e.g., "intention o treat" or type of treatment) may be less subject to measurement error and the exposure contrast s less variable between studies.

As noted ove, an inclusive approach is enerally recommended: that is, it etter o include a study is systematic evaluation and xamine the impact of tential limitations, ather than exclude a study and thus lose any information it ould have provided. or demiology studies, to the extent possible, you want to assess ot st e "risk f bias," ut also he likelihood, direction, and magnitude of bias.

The study haracteristics that form the evaluation of observational epidemiology studies are summarized in able F-6. The first feature, the type of study esign, provides amework for the subsequent aluation; that s, the specific uestions and issues ill vary epending on he type of study. he other ures compass spects f the study opulations, exposure measures, outcome (effect) measures, and the analysis d resentation of results. Although eneral your evaluation he sults is eeded, for ample within the context of the evaluation of confounding, since confounding depends n he strength of various relationships (i.e., between the exposure and the potential confounder d between he potential confounder and he outcome).

A structured orm may be seful for ecording he key ures ed aluate a study. An example form is shown in Figure F-3; details of such a orm will eed o e modified ased n the specifics of the chemical, exposure scenarios, and effect measures nder study.

Study Quality Evaluation: Observational Epidemiology Studies

- As oted n he overview, the evaluation process is inclusive in ature, is conducted EFORE developing idence tables, uses eries of systematically applied, focused questions, and is end-point specific
- Do our etective work head f time: vestigate exposure measures, effect measures, and confounders for he chemical-effect der review
- To the extent possible, assess likelihood, direction, and magnitude of bias

Table F-6. General Considerations for Evaluation of Features of Epidemiology Studies

Feature	Example Questions or Details	Useful Information
Study design	Major types, based on approach to sample selection: cohort, case-control, nested case-control, population-based survey (e.g., NHANES), times series, case-crossover	Study methods
Study population; target population; setting	Where and when was the study conducted? What is the source(s) of exposure (environmental media, consumer products, occupational, an industrial accident, or other)? What was the recruitment process? How was eligibility determined? Does the study provide information on potential vulnerable or susceptible groups? Address: Potential generalizability of study results, potential for selection bias, potential to address effect modification	Geographic area, site (occupational, etc.), time period. Age and sex distribution, other details as needed (may include race/ethnicity, socioeconomic status); recruitment process; exclusion and inclusion criteria
Participation rate; follow-up	Did rates vary by exposure (or disease) status? Were there differences between individuals who did and did not participate, or who were or were not lost to follow-up? Is it known (or possible) that participation (or loss) is related both to exposure and disease status? Is there evidence of "healthy worker" or "healthy worker survivor" effect? Are differences likely to impact the observed associations (and if so, how)? Address: Potential for selection bias	Total eligible, participation at each stage and for final analysis group; loss to follow-up, denominators used to make these calculations; length of follow-up
Comparability (exposed and non-exposed; cases and controls)	How were potential differences between groups addressed in the study design (e.g. randomization, restriction, matching) and/or analysis (e.g. stratification, multivariate methods)? How were variables associated with exposure and with outcome, or which alter the association between exposure and outcome, addressed in the study? Address: potential for confounding and effect modification	"Table 1" type participant characteristic data, by group; approach to consideration of potential confounding (if applicable); strength of associations between exposure and potential confounders and between potential confounders and outcome
Exposure measures (procedure; range)	Are exposure estimates qualitative, semi-quantitative or quantitative? How well does the exposure protocol correctly classify or rank participants with respect to exposure? What is the likelihood of systematic (differential) error? What is the likelihood of random (non-differential) error? Does the protocol adequately characterize exposure during the relevant time window? What exposure range is spanned in this study? Address: potential for exposure misclassification (either non-differential or differential)	Describe, i.e., type of biomarker(s), occupational history, lifetime consumption, evidence from validation studies, variability within and between exposure groups
Outcome measures	What is source of outcome (effect) measure? How well do the outcome(s) measures correctly classify participants with respect to the outcome? What is the likelihood of systematic (differential) error? What is the likelihood of random (non-differential) error? Address: potential for outcome misclassification (either non-differential or differential)	Describe (i.e., source, how measured/classified, incident versus prevalent disease), evidence from validation studies
Data Presentation and Statistical Analysis	Is the analysis appropriate for the data and the study question? Are aspects of the data (i.e., non-normal distributions, correlation structure) adequately accounted for? Is the rationale for inclusion of variables in a model clear and logical? Are results presented with adequate detail? Is the study population of adequate size and composition to detect a true association (of a relevant effect size) between exposure and outcome? Were stratified analyses (effect modified) motivated by a specific hypothesis? Address: ability to interpret and level of confidence in results	How groups are compared (may include t-tests, ANOVA, regression models, etc.), what results are presented in text, tables, and figures, n exposed cases (case-control studies) or N cases among exposed (cohort studies)

APPENDIX C – 22

From: SandP8
To: Katherine Walker; Kane, Agnes; Diana-M Wong/DC/USEPA/US@EPA
Subject: Re: Language To Clarify Your View
Date: 10/01/2012 05:53 PM

Diane, Agnes:

I agree with Katy completely.

She said she'd reduce her commentary to a concrete suggestion about the text. I would concur (if that still matters) with any language suggestion she's comfortable with.

Scott

On Mon, Oct 1, 2012 at 5:27 PM, Katherine Walker <KWalker@healtheffects.org> wrote:
Yes. Will give it a whirl later. I was in a meeting when I wrote that. Will cut it down and resend. You will need to respond and concur or revise.

Sent from my iPhone

On Oct 1, 2012, at 5:04 PM, (b) (b) (6) [redacted]

As you know, I agree with you completely. Do you wanna make a specific suggestion about wording? Just omit mentioning the one point, or something broader?

Scott

On Mon, Oct 1, 2012 at 12:04 PM, Katherine Walker <<mailto:KWalker@healtheffects.org>KWalker@healtheffects.org<mailto:KWalker@healtheffects.org>> wrote:
I think the addition of 'may be' helps but the 'However..." that follows refers to just one of several recommendations we made that are targeted at trying to characterize the limitations or uncertainties that that may result from that choice, including the choice of models used to analyze a limited data set. I'm not sure i would want to single out the mortality v incidence issue alone.

I think we want to make the broader point - that they have made a number of data selection and analysis choices tha may be reasonable but that it is important to convey to risk analysts and to policy makers a broader perspective. That is the basis for a number of recommendation for sensitivity analyses that we made.

The NAS and others have made recommendations for 20 years or more that uncertainties need to be more clearly and quantitatively, if possible, portrayed. That was the spirit of our recommendations recognizing that it wasn't possible to do a full uncertainty analysis.

I think this is very important.

Katy

Sent from my iPhone

On Oct 1, 2012, at 11:37 AM, "Diana-M Wong" <<mailto:Wong.Diana-M@epamail.epa.gov>Wong.Diana-M@epamail.epa.gov<mailto:Wong.Diana-M@epamail.epa.gov><mailto:<mailto:Wong.Diana-M@epamail.epa.gov>Wong.Diana-M@epamail.epa.gov<mailto:Wong.Diana-M@epamail.epa.gov>>> wrote:

Scott,

Thank you for your response.

Based on your suggestion, the statement in the cover letter is revised to:

" The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation unit risk (IUR) and agrees that the use of the subcohort post-1959 for quantification may be reasonable due to the lack of exposure information for many of the workers in earlier years. The SAB finds it appropriate to use lung cancer and mesothelioma as endpoints for the derivation of the IUR. However, the SAB recommends a more detailed discussion and justification of how the use of mortality data rather than incidence data may have resulted in an undercount of cases of lung cancer and mesothelioma."

To be consistent, I will make similar change to line 27, page 3 of the Executive Summary of the August 30 draft. Please let me know if this change satisfies your concern.

Sincerely,

Diana Wong, Ph. D., DABT
Toxicologist and Designated Federal Officer
USEPA
Science Advisory Board Staff Office
MC: 1400R
1200 Pennsylvania Ave, N.W.
Washington, DC 20460

Phone:(202) 564-2049<tel:%28202%29%20564-2049>

<graycol.gif>SandP8 ---10/01/2012 10:59:09 AM---Diana, Agnes: Thanks for your suggested edit. I think it would be great. I apologize

From: (b) (6) [redacted]
To: Diana-M Wong/DC/USEPA/US@EPA
Cc: "<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com><mailto:<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com>>" <<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com><mailto:<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com>>>, Katherine Walker <<mailto:KWalker@healtheffects.org>KWalker@healtheffects.org<mailto:KWalker@healtheffects.org><mailto:<mailto:KWalker@healtheffects.org>KWalker@healtheffects.org<mailto:KWalker@healtheffects.org>>>, "Kane, Agnes" <<mailto:agnes_kane@brown.edu>agnes_kane@brown.edu<mailto:agnes_kane@brown.edu><mailto:<mailto:agnes_kane@brown.edu>agnes_kane@brown.edu<mailto:agnes_kane@brown.edu>>>
Date: 10/01/2012 10:59 AM
Subject: Re: Language To Clarify Your View

Diana, Agnes:

Thanks for your suggested edit. I think it would be great. I apologize for forcing you to read my mind about this. I suggested a much more modest change in the explanation promised to Agnes that I wrote after speaking to Katherine Walker last week:

1 do not agree that the use of the subcohort post-1959 for quantification is "reasonable" due to the lack of exposure information for many of the workers in earlier years. It *may* be reasonable, but I think it improper to say that it *is* reasonable. At best, it is a modeling choice that some but certainly not all people would make. In my estimation, the Agency has not sufficiently explored the question of whether or not the lack, or rather paucity, of exposure data from earlier years invalidates or inhibits inferences. Those statistical questions have not really been asked. Thus, I cannot "support the selection of the Libby worker cohort" as stated in the bullet's main clause. I have no problem with the rest of the text of the bullet. As a way forward, it might suffice to simply change "is" to "may be" in the third verb of the first sentence. I understand that the explanatory text on this matter persists in the body of the submission.

Sorry if this has been much ado about nothing, but the tone of the bullet seemed too much of a whitewash to accept as a reflection of what we had discussed in our meetings.

Thanks for your patience with me. It's been rather difficult for me personally these last few weeks. I hope that I will soon be out of the woods, to use a corny expression.

Best regards,
Scott

On Thu, Sep 27, 2012 at 5:16 PM, Diana-M Wong <<mailto:Wong.Diana-M@epamail.epa.gov>Wong.Diana-M@epamail.epa.gov<mailto:Wong.Diana-M@epamail.epa.gov><mailto:<mailto:Wong.Diana-M@epamail.epa.gov>Wong.Diana-M@epamail.epa.gov<mailto:Wong.Diana-M@epamail.epa.gov>>> wrote:

Scott,

My last communication to you on August 29 was to request for your suggested changes regarding the following paragraph in the cover letter:

" The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation unit risk (IUR) and agrees that the use of the subcohort post-1959 for quantification is reasonabl due to the lack of exposure information for many of the workers in earlier years. The SAB finds it appropriate to use lung cancer and mesothelioma as endpoints for the derivation of the IUR. However, the SAB recommends a more detailed discussion and justification of how the use of mortality data rather than incidence data may have resulted in an undercount of cases of lung cancer and mesothelioma."

Since you did not respond, I noted in the Panel Roster of the August 30 draft that you did not concur this draft.

During the quality review teleconference on Tuesday (September 25) by SAB, the SAB Chartered Board questioned the basis of your non-concurrence. Dr. Kane indicated that she received an e-mail from you that you were not feeling well and therefore unable to respond to her. Accordingly, the SAB Chair directed that I need to incorporate your suggested change or provide an explanation for your non-conccurrence. Based on my understanding of your concern, I proposed the following revised statement.

" The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation unit risk (IUR) and the use of the subcohort post-1959 for quantification due to the lack of exposure information for many of the workers in earlier years. However, the SAB recommends EPA utilize interval statistics to evaluate the potential impact of omitting the Libby workers hired before 1959 if deemed feasible. The SAB finds it appropriate to use lung cancer and mesothelioma as endpoints for the derivation of the IUR. However, the SAB recommends a more detailed discussion and justification of how the use of mortality data rather than incidence data may have resulted in an undercount of cases of lung cancer and mesothelioma."

I look forward to receiving your response. Thanks.

Sincerely,

Diana Wong, Ph. D., DABT
Toxicologist and Designated Federal Officer
USEPA
Science Advisory Board Staff Office
MC: 1400R
1200 Pennsylvania Ave, N.W.
Washington, DC 20460

Phone:(202) 564-2049<tel:%28202%29%20564-2049><tel:%28202%29%20564-2049>

Diana:

It is the first day of classes today, and am finding it difficult to be thorough in my review of the document you sent. I cannot always observe the deadlines that you set and inform me about.

I do not concur with this statement in the letter:

The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation unit risk (IUR) and agrees that the use of the subcohort post-1959 for quantification is reasonable due to the lack of exposure information for many of the workers in earlier years.

I thought I was paying close attention, but did not notice until now that earlier language had been so watered down to be a complete capitulation to what I continue to believe is a flawed idea.

I don't think I'm merely being grumpy here. Perhaps someone can talk me down, but I'm a bit surprised and disappointed. Unfortunately, I am very busy this week. I may be able to revisit this on Wednesday afternoon.

Regards,
Scott

EXPANDED FROM PRIOR PAGE TO INCREASE LEGIBILITY:

From: (b) (6)
To: Diana-N Wong/DC/USEPA/US@EPA
Cc: "<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com><mailto:<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com>>"
<<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com><mailto:<mailto:scott@ramas.com>scott@ramas.com<mailto:scott@ramas.com>>>, Katherine Walker
<<mailto:KWalker@healtheffects.org>KWalker@healtheffects.org<mailto:KWalker@healtheffects.org><mailto:<mailto:KWalker@healtheffects.org>KWalker@healtheffects.org<mailto:KWalker@healtheffects.org
>>>, "Kane, Agnes"
<<mailto:agnes_kane@brown.edu>agnes_kane@brown.edu<mailto:agnes_kane@brown.edu><mailto:<mailto:agnes_kane@brown.edu>agnes_kane@brown.edu<mailto:agnes_kane@brown.edu>>>
Date: 10/01/2012 10:59 AM
Subject: Re: Language To Clarify Your View

Diana, Agnes:

Thanks for your suggested edit. I think it would be great. I apologize for forcing you to read my mind about this. I suggested a much more modest change in the explanation promised to Agnes that I wrote after speaking to Katherine Walker last week:

I do not agree that the use of the subcohort post-1959 for quantification is "reasonable" due to the lack of exposure information for many of the workers in earlier years. It *may* be reasonable, but I think it improper to say that it *is* reasonable. At best, it is a modeling choice that some but certainly not all people would make. In my estimation, the Agency has not sufficiently explored the question of whether or not the lack, or rather paucity, of exposure data from earlier years invalidates or inhibits inferences. Those statistical questions have not really been asked. Thus, I cannot "support the selection of the Libby worker cohort" as stated in the bullet's main clause. I have no problem with the rest of the text of the bullet. As a way forward, it might suffice to simply change "is" to "may be" in the third verb of the first sentence. I understand that the explanatory text on this matter persists in the body of the submission.

Sorry if this has been much ado about nothing, but the tone of the bullet seemed too much of a whitewash to accept as a reflection of what we had discussed in our meetings.

Thanks for your patience with me. It's been rather difficult for me personally these last few weeks. I hope that I will soon be out of the woods, to use a corny expression.

Best regards,
Scott

APPENDIX C – 23

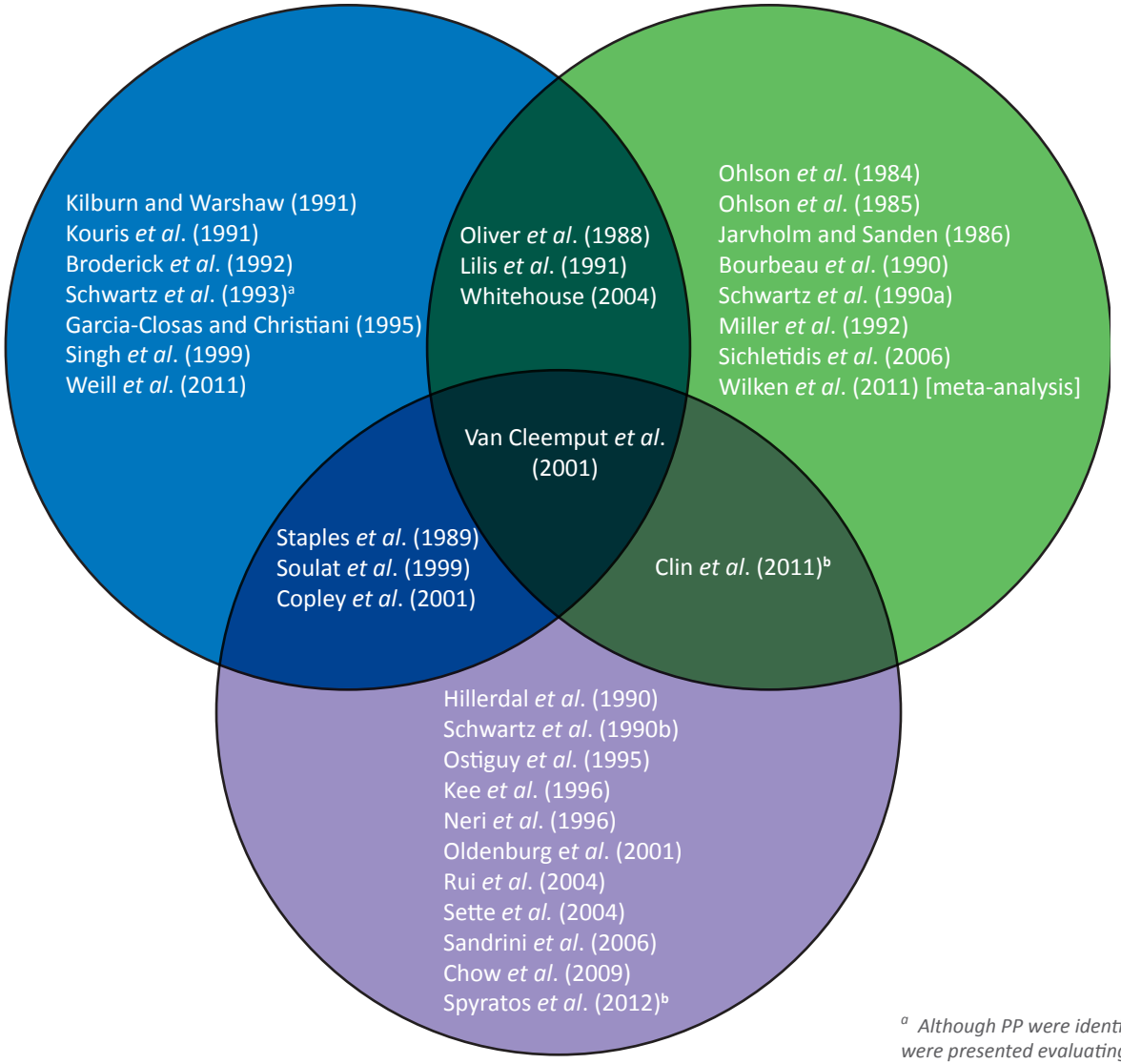
Laura E. Kerper, Ph.D.
Heather N. Lynch, MPH
Lawrence C. Mohr, M.D.*
Julie E. Goodman, Ph.D., DABT
*Medical University of South Carolina

SOT 2014 Annual Meeting
Abstract number 1811
Poster board 147

Do Asbestos-Induced Pleural Plaques Cause Lung Function Deficits?

While there is general agreement that pleural plaques are biomarkers of asbestos exposure, there is debate in the scientific community over whether pleural plaques cause lung function deficits. Many of the studies that addressed this issue were subject to certain limitations. In most studies, pleural plaques were diagnosed by radiography, which is less accurate than high resolution computed tomography (HRCT) and can lead to misdiagnoses. Some studies reported lung function changes in subjects that had lung abnormalities in addition to pleural plaques, so that the contribution of pleural plaques to deficits was unknown. To eliminate these sources of uncertainty, we conducted the first comprehensive analysis of the associations between pleural plaques and lung function based on epidemiology studies in which 1) pleural plaques were diagnosed by HRCT and 2) individuals were identified with pleural plaques and no other lung abnormalities. We identified and analyzed 16 relevant studies. We looked for patterns within and across studies and examined whether associations were reproducible. Only three of the 16 studies reported statistically significant associations between pleural plaques and some measure of lung function. Among these three studies, the lung function parameters were not consistent, suggesting that the associations were not likely causal. In addition, mean asbestos exposures in all three studies were higher in the subjects with pleural plaques than in the subjects without. This suggests that if the effects were not due to chance, the asbestos exposure itself, rather than pleural plaques, may have been responsible for observed lung function deficits. Taken as a whole, the direction of effect (*i.e.*, lung function deficit *vs*. improvement) varied among studies, indicating the absence of even subtle effects and that the lack of effect noted in the majority of studies was not a result of low statistical power. We conclude that there is no reliable association between the presence of pleural plaques in asbestos-exposed populations and lung function deficits.

Studies included in EPA, SAB, and HRCT study review of pleural plaques and lung function



[a] *Although PP were identified by HRCT, no analyses were presented evaluating PP alone.*

[b] *Published close to or after EPA analysis.*

GRADIENT

Pleural Plaques Diagnosed by High Resolution Computed Tomography (HRCT) and Lung Function in Asbestos-Exposed Populations.

This table summarizes associations between pleural plaques and lung function in studies in which 1) HRCT was used to diagnose or confirm the presence of pleural plaques, and 2) individuals with pleural plaques did not have other diagnosed lung abnormalities.

Study	No. of Participants	No. with Pleural Plaques Only	Cohort	Location	Asbestos Exposure Measure	Avg. Estimated Exposure	Measure of Lung Function	Result (Mean ± SD)		*p* value
								Control	Pleural Plaques	
Staples *et al.*, 1989	76	NR	Asbestos workers	US	Duration (mean years)	No PP: 14.5 With PP: 20.8	Air flow	NR	NR	>0.05
							Lung restriction	NR	NR	
							DL_{CO}	NR	NR	
Hillerdal *et al.*, 1990	23	13	Hospital pulmonary patients with occupational asbestos exposure	Sweden	Duration (mean years)	No PP: 0 With PP: 15-29	FEV_1, %	NR	98 ± 10	>0.05
							VC, %	NR	97 ± 11	>0.05
							FEV_1/VC	NR	98 ± 7	>0.05
							TLC, %	NR	96 ± 8	>0.05
							MVV, %	**NR**	**91 ± 11**	**<0.05**
							FEF_{50}, %	NR	95 ± 22	>0.05
							MEF/FEF_{50}, %	**NR**	**118 ± 27**	**<0.05**
Schwartz *et al.*, 1990	16	9	Sheet metal workers	US	Duration (years)	No PP: 33.3 ± 6.6 With PP: 30.3 ± 7.2	FEV_1, %	110.4 ± 9.1	100.1 ± 17.2	>0.05
							FVC, %	104.9 ± 6.7	96.0 ± 11.8	
							FEV_1/FVC	76.1 ± 6.4	75.1 ± 7.9	
							TLC, %	121.9 ± 12.5	116.7 ± 13.9	
							RV, %	120.7 ± 21.9	121.6 ± 42.5	
							DL_{CO}, %	111.6 ± 23.2	111.8 ± 16.3	
Ostiguy *et al.*, 1995	247	54	Copper refinery workers	Canada	Duration (years)	No PP: 25.7 ± 0.5 With PP: 26.8 ± 1.0	FEV_1, %	111	107	>0.05
							FVC, %	106	104	
							MMEF, %	114	106	
Kee *et al.*, 1996	106	44	Shipyard and construction workers	US	Duration (years)	26.5 ± 12	FEV_1/FVC	78 ± 7	74 ± 10	>0.05
							FVC, %	73 ± 19	78 ± 14	
							DL_{CO}, %	70 ± 23	88 ± 20	

Study	No. of Participants	No. with Pleural Plaques Only	Cohort	Location	Asbestos Exposure Measure	Avg. Estimated Exposure	Measure of Lung Function	Result (Mean ± SD)		*p* value
								Control	Pleural Plaques	
Neri *et al.*, 1996	119	50	Asbestos workers	Italy	Duration (years)	No PP: 4.8 ± 4.4 With PP: 9.1 ± 5.5	FEV_1	NR	NR	>0.05
							FVC	NR	NR	
							FEV_1/FVC	NR	NR	
							TLC	NR	NR	
							MEF_{25-75}	NR	NR	
							DLco	NR	NR	
Soulat *et al.*, 1999	170	84	Former insulation workers	France	Duration (years)	12.9 ± 0.6	FEV_1, %	108.4 ± 3.15	112.6 ± 2.40	>0.05
							FVC, %	108.9 ± 2.60	110.2 ± 2.03	
							MEF, %	111.1 ± 3.66	116.1 ± 2.96	
							MMEF, %	76.9 ± 4.53	81.1 ± 4.02	
Copley *et al.*, 2001	50	NR[a]	Patients with benign pleural disease	England	NR	NR	FEV_1	NR	NR	>0.05
							FVC	NR	NR	
							TLC	NR	NR	
							RV	NR	NR	
							Dco	NR	NR	
Oldenburg *et al.*, 2001	43	21	Asbestos workers	Germany	Duration (mean years)	30.7	FEV_1, %	86.58 ± 28.09	91.67 ± 20.25	>0.05
							FVC, %	89.89 ± 11.86	88.8 ± 13.89	
							FEV_1/FVC	94.9 ± 19.48	98.58 ± 13.48	
							MEF, %	93.07 ± 37.69	90.14 ± 36.79	
Van Cleemput *et al.*, 2001	73	51	Cement factory workers	Belgium	CEI	26.3 ± 12.6 f-years/ml	FEV_1, %	103.8 ± 13.7	104.1 ± 12.9	0.24
							VC, %	109.8 ± 14.9	110.5 ± 13.4	0.24
							FEV_1/VC	0.78 ± 0.07	0.78 ± 0.07	1.00
							PEF, %	108.7 ± 21.5	100.5 ± 23.3	0.48
							MEF, %	103.0 ± 35.7	109.2 ± 25.02	0.27
							TL_{CO}, %	97.2 ± 15.5	102.0 ± 16.5	0.93
Rui *et al.*, 2004	103	36	Asbestos workers	Italy	Duration (years)	No PP: 22 ± 6 With PP: 30 ± 6	FEV_1, %	**102 ± 13**	**95 ± 14**	**<0.05**
							VC, %	**96 ± 11**	**90 ± 10**	**<0.05**
							FEV_1/VC	78 ± 6	77 ± 7	>0.05
							TLC, %	**97 ± 9**	**91 ± 9**	**<0.05**
Sette *et al.*, 2004	82	NR	Cement workers	Brazil	Duration (years)	14.5 ± 10.1	Gas exchange	NR	NR	>0.05[a]

Study	No. of Participants	No. with Pleural Plaques Only	Cohort	Location	Asbestos Exposure Measure	Avg. Estimated Exposure	Measure of Lung Function	Result (Mean ± SD)		*p* value
								Control	Pleural Plaques	
Sandrini *et al.,* 2006	91	32	Patients with asbestos-related disorders	Australia	NR	NR	FEV_1, %	92 ± 16.9	93 ± 13.2	>0.05
							FVC, %	94 ± 13.5	95 ± 2.4	>0.05
Chow *et al*., 2009	86	26	Asbestos workers	Australia	NR	NR	FEV_1, %	91.65 ± 15.41	89.12 ± 16.41	>0.05
							FVC, %	91.88 ± 16.46	91.73 ± 16.04	
							VC, %	98.18 ± 15.80	100.0 ± 10.98	
							DL_{CO}, %	89.43 ± 15.26	86.69 ± 16.06	
Clin *et al*., 2011	2,743	403	Asbestos workers	France	CEI (exposure units x years)	No PP: 47.9 ± 83.1 With PP: 112.6 ± 128.6	FEV_1, %	**101.9 ± 19.2**	**97.9 ± 19.4**	**0.0032**
							FVC, %	**100.4 ± 16.6**	**96.6 ± 16.6**	**<0.0001**
							FEV_1/FVC	80.0 ± 7.9	79.2 ± 9.0	0.27
							TLC, %	**101.2 ± 16.0**	**98.1 ± 14.2**	**0.0494**
Spyratos *et al*., 2012	266	29	Cement factory workers	Greece	Mean concentration	1.7-6.49 f/ml	FEV_1, %	99.8 ± 15.2	92.6 ± 14.3	0.461
							FVC, %	99.6 ± 13.8	94.3 ± 12.5	0.536
							FEV_1/FVC	83.1 ± 10.4	78.1 ± 9.3	0.294
							MMEF, %	91.7 ± 30.4	71 ± 23.7	0.703
							TLC, %	93.3 ± 13	90.1 ± 7.7	0.983
							DL_{CO}, %	101.3 ± 15.8	100.5 ± 20.3	0.844

Notes:

Statistically significant results are in **bold** type.

CEI = cumulative exposure index; DL_{CO} = diffusing capacity for carbon monoxide; eCO = exhaled carbon monoxide (a marker of lung oxidative stress); FEF_{50} = flow at 50% of forced vital capacity; FE_{NO} = fractional exhaled nitric oxide (a marker of lung oxidative stress); FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high resolution computed tomography; MEF = forced expiratory flow at the level when 50% of the FVC remains exhaled; MEF_{25-75} = forced expiratory flow at the level when 25-75% of the FVC remains exhaled; MVV = maximal voluntary ventilation; NR = not reported; PP = pleural plaques; RV = residual volume; TLC = total lung capacity; TL_{CO} = transfer factor for carbon monoxide; VC = vital capacity.

(a) Presence of pleural plaques was evaluated as an independent variable.

References

Chow, S; Campbell, C; Sandrini, A; Thomas, PS; Johnson, AR; Yates, DH. 2009. "Exhaled breath condensate biomarkers in asbestos-related lung disorders." *Respir. Med.* 103(8):1091-1097.

Clin, B; Paris, C; Ameille, J; Brochard, P; Conso, F; Gislard, A; Laurent, F; Letourneux, M; Luc, A; Schorle, E; Pairon, JC. 2011. "Do asbestos-related pleural plaques on HRCT scans cause restrictive impairment in the absence of pulmonary fibrosis?" *Thorax* 66(11):985-991.

Copley, SJ; Wells, AU; Rubens, MB; Chabat, F; Sheehan, RE; Musk, AW; Hansell, DM. 2001. "Functional consequences of pleural disease evaluated with chest radiography and CT." *Radiology* 220(1):237-243.

Hillerdal, G; Malmberg, P; Hemmingsson, A. 1990. "Asbestos-related lesions of the pleura: Parietal plaques compared to diffuse thickening studied with chest roentgenography, computed tomography, lung function, and gas exchange." *Am. J. Ind. Med.* 18(6):627-639.

Kee, ST; Gamsu, G; Blanc, P. 1996. "Causes of pulmonary impairment in asbestos-exposed individuals with diffuse pleural thickening." *Am. J. Respir. Crit. Care Med.* 154(3 pt. 1):789-793.

Neri, S; Boraschi, P; Antonelli, A; Falaschi, F; Baschieri, L. 1996. "Pulmonary function, smoking habits, and high resolution computed tomography (HRCT) early abnormalities of lung and pleural fibrosis in shipyard workers exposed to asbestos." *Am. J. Ind. Med.* 30(5):588-595.

Oldenburg, M; Degens, P; Baur, X. 2001. "Asbest-bedingte Lungenfunktionseinschrän-kungen mit und ohne pleuraplaques (German)." *Atemw.-Lungenkrkh.* 27(8):422-423.

Ostiguy, G; Vaillancourt, C; Begin, R. 1995. "Respiratory health of workers exposed to metal dusts and foundry fumes in a copper refinery." *Occup. Environ. Med.* 52(3):204-210.

Rui, F; De Zotti, R; Negro, C; Bovenzi, M. 2004. "A follow-up study of lung function among ex-asbestos workers with and without pleural plaques." *Med. Lav.* 95(3):171-179.

Sandrini, A; Johnson, AR; Thomas, PS; Yates, DH. 2006. "Fractional exhaled nitric oxide concentration is increased in asbestosis and pleural plaques." *Respirology* 11(3):325-329.

Schwartz, DA; Galvin, JR; Dayton, CS; Stanford, W; Merchant, JA; Hunninghake, GW. 1990. "Determinants of restrictive lung function in asbestos-induced pleural fibrosis." *J. Appl. Physiol.* 68(5):1932-1937.

Sette, A; Neder, JA; Nery, LE; Kavakama, J; Rodrigues, RT; Terra-Filho, M; Guimaraes, S; Bagatin, E; Muller, N. 2004. "Thin-section CT abnormalities and pulmonary gas exchange impairment in workers exposed to asbestos." *Radiology* 14(9):560-565.

Soulat, JM; Lauque, D; Esquirol, Y; Depres, M; Giron, J; Claudel, R; Carles, P. 1999. "High-resolution computed tomography abnormalities in ex-insulators annually exposed to asbestos dust." *Am. J. Ind. Med.* 36(6):593-601.

Spyratos, D; Chloros, D; Haidich, B; Dagdilelis, L; Markou, S; Sichletidis, L. 2012. "Chest imaging and lung function impairment after long-term occupational exposure to low concentrations of chrysotile." *Arch. Environ. Occup. Health* 67(2):84-90.

Staples, CA; Gamsu, G; Ray, CS; Webb, WR. 1989. "High resolution computed tomography and lung function in asbestos-exposed workers with normal chest radiographs." *Am. Rev. Respir. Dis.*139(6):1502-1508.

Van Cleemput, J; De Raeve, H; Verschakelen, JA; Rombouts, J; Lacquet, LM; Nemery, B. 2001. "Surface of localized pleural plaques quantitated by computed tomography scanning: No relation with cumulative asbestos exposure and no effect on lung function." *Am. J. Respir. Crit. Care Med.* 163(3 pt. 1):705-710.

APPENDIX C – 24

EXCERPTS

AWARD/CONTRACT	1. THIS CONTRACT IS A RATED ORDER UNDER DPAS (15 CFR 350)	RATING	PAGE OF PAGES 1 32

2. CONTRACT (Proc. Inst. Ident.) NO.: DTRT57-09-D-30009

3. EFFECTIVE DATE: See Block 20C

4. REQUISITION/PURCHASE REQUEST/PROJECT NO.: 4E-7270

5. ISSUED BY — CODE: RVP-31

USDOT/RITA/Volpe Center
Contracts & Program Supppprt Service
55 Broadway RVP-31
Cambridge MA 02142-1001

6. ADMINISTERED BY (If other than Item 5) — CODE: RVP-31

U.S.DOT/RITA/Volpe Center
55 Broadway RVP-31
Cambridge MA 02142-1001

7. NAME AND ADDRESS OF CONTRACTOR (No., Street, City, Country, State and ZIP Code)

The University of Cincinnati
University Hall Goodman Ave Suite 5
PO Box 210222
Cincinnati OH 45221-0222

8. DELIVERY
[ ] FOB ORIGIN [X] OTHER (See below)

9. DISCOUNT FOR PROMPT PAYMENT
Net 30

10. SUBMIT INVOICES (4 copies unless otherwise specified) TO THE ADDRESS SHOWN IN: ITEM Block 12

CODE — FACILITY CODE

11. SHIP TO/MARK FOR — CODE: VNTSC

U.S. DOT/RITA/Volpe Center
125 Munroe Street
Receiving Dock
Cambridge MA 02142-1001

12. PAYMENT WILL BE MADE BY — CODE: VOLPE PAYMENT OFFIC

DOT/FAA Enterprise Services Center
Volpeinvoices@faa.gov

13. AUTHORITY FOR USING OTHER THAN FULL AND OPEN COMPETITION:
[ ] 10 U.S.C. 2304 (c) ( ) [X] 41 U.S.C. 253 (c) (1)

14. ACCOUNTING AND APPROPRIATION DATA: See Schedule

15A. ITEM NO	15B. SUPPLIES/SERVICES	15C. QUANTITY	15D. UNIT	15E. UNIT PRICE	15F. AMOUNT
	Continued				

15G. TOTAL AMOUNT OF CONTRACT: NTE $2,096,614.00

16. TABLE OF CONTENTS

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X	C	DESCRIPTION/SPECS./WORK STATEMENT	4-11
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X	F	DELIVERIES OR PERFORMANCE	14-15
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	L	INSTRS., CONDS., AND NOTICES TO OFFERORS	
	M	EVALUATION FACTORS FOR AWARD	

CONTRACTING OFFICER WILL COMPLETE ITEM 17 OR 18 AS APPLICABLE

17. [X] CONTRACTOR'S NEGOTIATED AGREEMENT (Contractor is required to sign this document and return 2 copies to issuing office.) Contractor agrees to furnish and deliver all items or perform all the services set forth or otherwise identified above and on any continuation sheets for the consideration stated herein. The rights and obligations of the parties to this contract shall be subject to and governed by the following documents: (a) this award/contract, (b) the solicitation, if any, and (c) such provisions, representations, certifications, and specifications, as are attached or incorporated by reference herein. (Attachments are listed herein.)

18. [ ] AWARD (Contractor is not required to sign this document.) Your offer on Solicitation Number ... including the additions or changes made by you which additions or changes are set forth in full above, is hereby accepted as to the items listed above and on any condition sheets. This award consummates the contract which consists of the following documents: (a) the Government's solicitation and your offer, and (b) this award/contract. No further contractual document is necessary.

19A. NAME AND TITLE OF SIGNER (Type or print): Deborah Galloway, Assoc. Vice President

20A. NAME OF CONTRACTING OFFICER: John P. Huss

19B. NAME OF CONTRACTOR — BY: Deborah Galloway (Signature of person authorized to sign)

19C. DATE SIGNED: 4/29/09

20B. UNITED STATES OF AMERICA — BY: John P. Huss (Signature of the Contracting Officer)

20C. DATE SIGNED: 5/1/09

NSN 7540-01-152-8069
PREVIOUS EDITION IS UNUSABLE

STANDARD FORM 26 (Rev. 4-85)
Prescribed by GSA
FAR (48 CFR) 53.214(a)

SECTION B - SUPPLIES OR SERVICES AND PRICES/COSTS

B.1 Contract Scope (MAY 1999)

The Contractor, acting as an independent Contractor and not as an agent of the Government, shall furnish all personnel, facilities, support, and management necessary to provide the services and/or supplies required under this contract and its associated task orders. The scope of this effort is defined in the Work Statement (see Section C of this document). Specific requirements will be stated in individual task orders.

B.2 Contract Line Items (MAR 2009)

CLIN	Description	
0001	**Support for exposure-response information pertinent to Libby vermiculite exposed workers for the Libby Superfund Program**	
0001AA	Task Order DTRTV-T9001 (Task Areas 1 and 2)	$339,389.00
0001AB	Task Area 3	$183,897.00
0001AC	Task Area 4	$901,869.00
0001AD	Task Area 5	$205,560.00
0001AE	Task Area 6	$25,103.00
0001AF	Task Area 7	$440,796.00
Total Estimated Cost		$2,096,614.00

NOTE: The Government intends to award the initial Task Order (line item 0001AA) with the award of this contract.

B.3 Type of Contract (SEP 2008)

The Government contemplates award of a Cost Reimbursement – No Fee, Indefinite Delivery/Indefinite Quantity (ID/IQ) Task Order contract resulting from this solicitation.

B.4 Minimum/Maximum Amount of Work (OCT 2008)

(A) The minimum guarantee (services) that shall be ordered under the contract by means of one or more task orders during the ordering period of this contract is $75,000.00. The maximum amount of services that may be ordered under all contracts during the ordering period of this

contract is $2,096,614.00. As more orders are issued under one contract, the value of orders, which can be issued under the remaining contract or contracts, drops by an equal amount.

(B) The maximum dollar amount is reached when the sum of the dollar amounts of all ordered supplies or services, under all awarded contracts equals the maximum amount stated in paragraph (A).

(C) Reaching the maximum amount does not preclude adjustments to the dollar amounts of existing placed orders, to complete actions of the placed orders, and which are made pursuant to existing contract authority, such as the Changes clause, as long as the maximum amount is not exceeded.

B.5 Type of Task Orders (OCT 2008)

The Government intends to issue completion, cost-reimbursement type task orders for all task orders issued under this contract.

SECTION C – DESCRIPTION/SPECIFICATIONS/WORK STATEMENT

C.1 Background

Between 1923 and the early 1990s, a mine near Libby, Montana, produced millions of tons of vermiculite ore. This vermiculite has been found to be contaminated with naturally-occurring Libby amphibole asbestos (LA), a known human health risk. The United States Environmental Protection Agency (EPA) initiated an emergency response action in November 1999 to address questions and concerns raised by citizens of Libby regarding possible ongoing exposures to asbestos fibers as a result of historical mining, processing, and exportation of asbestos-containing vermiculite. EPA began cleaning up Libby in 2000, and since then, the project has become part of its Superfund program and known as the "Libby Asbestos Project." The Environmental Engineering Division (RTV-4E) at the Volpe Center is supporting EPA Region 8 to provide emergency response and remedial program support for the Libby Asbestos Project.

The RTV-4E of the Volpe Center (hereafter referred to as simply, the "Volpe Center") is also supporting the work being done by the EPA Region 8 Technical Support Team for the Libby Superfund Site to develop of a Libby site-specific Reference Concentration (RfC) utilizing the extensive exposure-response information previously collected by the University of Cincinnati (UC) on Libby vermiculite exposed workers at the OM Scott Plant in Marysville, OH. The longitudinal research efforts concerning these workers provide a unique, exceptional and critically needed opportunity to assess the non-carcinogenic health effects associated with LA exposure. The RfC is an estimate of a continuous inhalation exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. The development of an RfC for the Libby community is vital to the understanding of the exposure-response relationship for asbestos-related non-cancer pulmonary health effects, which are highly prevalent in the Libby community, to help support the Baseline Risk Assessment (BRA). Further, the RfC will be used by EPA to help direct sampling efforts and to ensure that remediation efforts will be protective of public health for the Libby community.

The Volpe Center is specifically supporting the EPA Region 8 Technical Support Team for the Libby Superfund Site in the development of the most accurate Libby site-specific RfC by improving the scientific evidence that evaluates the pulmonary toxicity of LA. The improved scientific evidence will be achieved by (i) using more sensitive radiographic imaging and pulmonary function study techniques to assess health effects in comparison to estimated worker exposures, and (ii) collecting information to evaluate associations between exposures and reported non-pulmonary health endpoints (e.g., systemic autoimmune disease).

Thus, the development of a Libby site-specific RfC will be based upon available data acquired during the UC investigations and updated exposure information supplied by OM Scott, as well as new health information acquired by the contractor with the support of the Volpe Center. Accordingly, this Statement of Work (SOW) will consist of two phases of technical support: Phase I will encompass the "Exposure Reconstruction" phase of the project and Phase II will encompass the "Updated Health Information" phase of the project. The two phases may be performed concurrently to maintain project objectives and time frames.

C.2 Task Areas

The activities that the Contractor will be required to perform under this contract are identified in the following Task Areas. Please note that Task Areas 1 and 2 will constitute the first Task Order with the award of this contract. Task Areas 3 through 7 may be ordered separately via Task Orders. The Government will complete reviews of all contractor-deliverables identified in this section within fourteen (14) calendar days of receipt of deliverable.

Task Area 1: Evaluate and update existing exposure data-sets with new data provided by OM Scott

This task is part of Phase I of the support.

UC researchers began performing health studies of workers at the OM Scott Plant around 1980, with the original work published in 1984 (Lockey et al., *Am Rev Res Dis*, 1984, 129:952-6) and a subsequent follow-up study in 2005 (Rohs et al., *Am J Respir Crit Care Med*, 2008, 177(6):630-7). Recently, OM Scott supplied new fiber exposure data (post-1980) for the same cohort. Both the original pre-1980 dataset (encompassing information from the early 1960s to 1980) and post-1980 dataset were provided by OM Scott in hard-copy format to both UC researchers and EPA. However, it should be noted that UC researchers possess specific proprietary data about the details of the original jobs and associated tasks of the cohort individuals (such information was collected during the previous UC investigation in 1980).

The contractor will work with the Volpe Center in supporting EPA Region 8 investigators to organize, and code the new (post-1980) data supplied by OM Scott. As mentioned above, OM Scott also provided the original data (pre-1980) again. The pre-1980 data will be coded in the same format. The contractor will use this information to verify the accuracy of the original data set (currently possessed by UC researchers), and make any necessary updates and changes to the latter based on newly available data. The contractor shall evaluate the industrial hygiene data provided by OM Scott in the context of the site-specific and job description data currently possessed by UC researchers.

The deliverable for this task is the delivery of the exposure/industrial hygiene data (updated pre-1980 data and newly available post-1980 data). Prior to data entry of the pre and post-1980 data, UC will provide for Volpe review and approval a proposed format and contents for the data deliverables. The listing of potential variables follows:

Document id number (from which data were abstracted)
Date
Location/area
Job title
Task/activity
Routine or spill
Other activity in the area
Shift
Sample type (Personal or area)

Local Exhaust
General Ventilation
Housekeeping
Visible Dust
Analyte
Time: on, off
Duration
Sampling flow rate
Sampling result, with units
LOD, LOQ
% fiber
Fiber type
Respirator
Protective Clothing
Source of material
Lab doing analysis
Comments/remarks

The data must be: (i) in a format readily suitable for statistical analyses through established statistical analysis programs (such as Excel spreadsheets and/or SAS spreadsheets) and (ii) such that the data set is comprehensive in regard to exposure duration and activities to support epidemiological analysis.

Task Area 2: Develop new worker exposure estimates based upon all available exposure information

This task is part of Phase I of the support.

Fiber exposure estimates were previously developed by UC researchers (summary information published in Lockey et. al., *Am Rev Res Dis*; 1984, 129:952-6; 2005 follow-up study results in Rohs et al., *Am J Respir Crit Care Med*, 2008, 177(6):630-7). The objective of Phase I of the support is to work collaboratively with the Volpe Center in assisting EPA Region 8 investigators in developing an RfC for LA by utilizing and refining exposure and health data for OM Scott workers previously evaluated and followed by researchers at UC. Thus, the contractor in collaboration with the Volpe Center will assist EPA Region 8 investigators with making any identified necessary changes in previous fiber exposure estimates for workers at the Marysville site based on all available exposure information. It should be noted that EPA will develop the RfC, and that a finalized RfC is *not* a deliverable by the contractor.

To achieve the objective of Phase I, the contractor will utilize additional industrial hygiene measurements of fiber exposure and create a job exposure matrix, by year. The entire exposure matrix shall then be re-evaluated by a team (consisting of Federal employees, as well as employees of the contractor to whom this contract is awarded) with expertise and experience in exposure reconstruction in order to ensure the final exposure reconstruction will optimally reflect actual job exposure. In order to perform these tasks, the contractor will provide support in two areas: (i) exposure reconstruction, (ii) and exposure-response analysis.

The addition of any fiber exposures after 1980 per Task Area 1 and the refinement of the overall exposure reconstruction per this Task Area 2 will improve the accuracy of each worker's cumulative fiber exposure estimation.

The contractor will also provide support (likely, bio-statistical expertise) to the Volpe Center in assisting EPA investigators in re-analyzing the exposure-response relationship between exposure to fiber and the demonstrated chest radiographic changes (Rohs et al., *Am J Respir Crit Care Med*, 2008, 177(6):630-7) in light of any refinement and modifications to the exposure assessments.

In addition, the contractor will review toxicity exposure assessment work previously performed by the EPA. Expertise in this area will be critical in reviewing this work, and will be performed by an individual, highly experienced and well recognized in the area of exposure response analysis to identify point of departure for operational derivation of the RfC. This will include evidence-based rationale for health effects and response measures as well as suggestions for residual uncertainties to be addressed by standard US EPA methodology (US EPA, 1994).

The contractor will also support the Volpe Center in meeting with investigators from the Government with expertise in dose estimation from human exposure data. The purpose of these meetings is to establish what additional variables can be retrieved from the exposure data set and job exposure matrix to facilitate a dose response analysis. If, and when, the Government completes development of a dose estimation from human exposure data model, the contractor will review the model and submit a proposal and budget to complete a dose response analysis. In order to identify point of departure for operational derivation of the RfC, the contractor will also provide support that is highly experienced and well recognized in the area of dose response analysis.

Throughout the performance of this task, the contractor will support the Volpe Center in coordinating with EPA investigators. For planning purposes, coordination will likely involve more than one contracted personnel, each for an average of ten hours per month, for six to eight months, as well as participation in approximately three one-day meetings (location to be decided). Additionally, various working teleconferences with the Volpe Center, EPA, and principal experts should be expected each month.

Deliverables for this task are:

(1) A job exposure matrix (i.e. annual estimates of fiber levels by job) that incorporates additional industrial hygiene measurements. The matrix shall be accompanied with a report detailing the development of the matrix – i.e., describing the derivation of the raw data, documenting decision points, and documenting data-collection input assumptions. Iterative drafts of these items will be submitted to the Volpe Center for review and approved per a schedule to be agreed to by the Volpe Center within fourteen (14) calendar days after the completion of Task Area 1.

(2) A new exposure response analysis as described above (re-analyzing the exposure-response relationship between exposure to fiber and the demonstrated chest radiographic changes (Rohs et

al., *Am J Respir Crit Care* Med, 2008, 177(6): 630-7) in light of any refinement and modifications to the exposure assessments) will be performed. The analysis will be presented in tables and a report, the details and timelines to be prepared by the contractor, which are subject to approval by the Volpe Center after the award of the contract. Similar to the first deliverable of Task Area 2, the analysis must be accompanied by all relevant information detailing the analyses – explanation(s) of the model(s) used, statistics run, and electronic copies of the spreadsheets used in statistical programs.

Task Area 3: Support the technical and administrative planning for collection of additional health information

This task is part of Phase II of the support.

The objective of Phase II is to support the Volpe Center in assisting EPA Region 8 investigators to improve the scientific evidence evaluating the pulmonary toxicity of LA. This objective will be achieved by the contractor obtaining additional evidence through follow-up worker interviews and using more sensitive radiographic imaging and pulmonary function study techniques. Such additional information will ultimately be used by the EPA investigators to assess health effects in comparison to estimated worker exposure for development of the most accurate RfC for the Libby site.

In keeping with the objective of Phase II of the support, the contractor shall develop the Study Protocol to collect additional health information from participating workers including, but not limited to, performing updated worker interviews, CT Scans for asbestos-related pulmonary disease, and pulmonary function tests with diffusion capacity. The Study Protocol is to be structured and organized such that it will meet all applicable Federal regulations, including current criteria established by the EPA's Human Subjects Review Board (HSRB); it is expected that the contractor will have experience developing reports with such a structure and that the contractor will have its own institutional review board (IRB). Iterative drafts of the Study Protocol will be submitted to the Volpe Center for review and discussion per a schedule to be created by the Volpe Center in conjunction with the order of the Task Order encompassing this Task Area. The Protocol will be finalized by the contractor, following review and approval of the protocol by the Volpe Center. A planning meeting at a location, to be determined, will occur.

Specific deliverables for this task are:

- A Study Protocol that contains, among other information, specific details of the composition of the study cohort, medical procedures to be performed, and how those medical procedures are to be performed;
- Updated worker questionnaires;
- Data collection tools;
- Consent forms;
- Assistance to the Volpe Center in supporting the EPA with HSRB reviews;
- Additional supporting documentation to be determined during the development and review of the Study Protocol.

All of the deliverables must first be reviewed and approved by the Volpe Center prior to finalization, in order to ensure that information collected via the Study Protocol will be able to be used to evaluate associations between exposures and reported non-pulmonary health endpoints (e.g., systemic autoimmune disease).

Task Area 4: Collect health data to update health response information

This task is part of Phase II of the support.

The contractor shall provide all resources and equipment necessary to implement the Study Protocol developed in Task Area 3. The contractor will locate, recruit, and collect new health information from the participating worker cohort (estimated to not exceed 300 participants) both from worker interviews, medical testing, and other means per the protocols developed in Task Area 3. As pulmonary function tests vary widely by the quality and training of the technician, only participants living within a 50 mile radius of the selected clinical facility in Marysville, Ohio will be recruited for pulmonary function testing. The contractor will mail each participant a personalized summary letter including test results and any appropriate health counseling. This task may also include limited travel for purposes of project coordination.

Task Area 5: Prepare, and populate with newly collected data [and existing/new data from OM Scott], the data-set structure for updated health response information

This task is part of Phase II of the support.

In order to organize the health information collected as part of Task Area 4, as well as integrate this new information with the data-set created as part of Tasks Areas 1 and 2, the contractor shall prepare a data-set structure for review. The data-set structure shall be developed such that it will present data in the most useable format to evaluate exposure (concentration and time) and health effects (circumscribed pleural disease, diffuse pleural disease, interstitial disease).

Once the data-set structure is reviewed and in a format approved by the Volpe Center for use, the contractor shall (1) enter into the data-set structure coded and organized data collected as part of Task Area 4, and (2) integrate into this data-set, the information entered and organized per Task Areas 1 and 2.

During the development of the data-set structure, as well as during the population of the data-set, ongoing communication shall take place between the contractor, the Volpe Center, and EPA investigators, so that to ensure the data-set meets the needs of the Volpe Center in assisting EPA investigators. Such communication may include a meeting at a location, to be determined.

Task Area 6: Transfer data-set to Federal government

This task is part of Phase II of the support.

The contractor shall provide the Volpe Center with the populated data-set structure, as developed in Task Area 5; however, all data shall be provided without individual identifying factors (e.g.,

name, social security number) but rather though use of codes. The contractor shall also provide technical documentation on data-set structure, use, and analyses. This task will involve communication with the Volpe Center and EPA investigators to ensure full understanding of the data.

Task Area 7: Assist with specific areas of data interpretation, analyses, technical reviews, and preparation of written draft and final reports

This task is part of Phase II of the support.

The contractor will support the Volpe Center in assisting EPA Region 8 investigators in interpreting and analyzing specific areas of data delivered as part of Task Area 6. Emphasis will be on evaluating the association between asbestos exposure and pulmonary disease as identified through medical testing including CT scans, chest X-rays, pulmonary function testing, medical questionnaires, and other assessments as indicated and agreed upon during the development of the Study Protocol and review of the data delivered as part of Task Area 6. Evaluation of clinical results will follow standard epidemiologic methods and best practices (e.g., evaluation of chest x-rays by at least two of three physicians with special expertise and training in reading chest x-rays for asbestos-related changes, known as "B-Readers") to help ensure the greatest quality and applicability of study findings. The contactor will also provide any additional draft information or data that may help facilitate this collaborative effort. The contractor will provide expert advice and consultation on data analysis, synthesis, and preparation of written reports.

Specific deliverables for this task are:

(1) Summary report of Phase II study, including, at minimum, the following sections of information: materials and employed methods; presentation of results (with identifying factors removed) of all tests, surveys, and questionnaires used in the analysis available from Task Areas 5 and 6; discussion of findings; and, conclusion(s).

(2) A record of all substantive decisions made regarding data collection, data input, data management, meaning of assigned data variables ("data dictionary"), data analyses, and data interpretations.

(3) An exposure-response analysis, the results of which would be presented in a summary report. The summary report should also include information on all test methods and strategies which have been evaluated, findings of various methods, rationale for approaches used for final analyses of the data, sensitivity analyses of the results, and a thorough discussion of any interpretations and findings.

Throughout the performance of Task Area 7, ongoing communication will take place among the contractor, the Volpe Center, and EPA investigators in order to ensure a shared understanding of project progress, important decisions that will affect study outcomes, Volpe Center expectations, and any issues and problems which may arise. For planning purposes, such collaboration will likely average six-eight hours of regularly scheduled interactions per month, likely involving more than one contracted personnel, for nine to twelve months. Additionally, various working

teleconferences and meetings (at a location, to be determined) with the Volpe Center, EPA, and principal experts should be expected each month.

SECTION D – PACKAGING AND MARKING

D.1 Preservation and Packaging (MAY 1999)

Preservation, packing and packaging of articles called for herein shall be in accordance with good commercial practices to assure delivery at destination.

D.2 Marking (MAY 1999)

When applicable, all items submitted to the Government shall be clearly marked as follows:

A. NAME OF CONTRACTOR

B. CONTRACT NUMBER

C. TASK ORDER NUMBER, (IF APPLICABLE)

D. DESCRIPTION OF ITEMS CONTAINED THEREIN

E. CONSIGNEE'S NAME AND ADDRESS, AND

If applicable, packages containing software or other magnetic media shall be marked on external containers with a notice reading substantially as follows: "CAUTION: SOFTWARE/MAGNETIC MEDIA ENCLOSED. DO NOT EXPOSE TO HEAT OR MAGNETIC FIELDS."

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EXCERPTS

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 5 2012

MEMORANDUM

SUBJECT: Response to the OIG Draft Report, "Follow-Up Report: Better Planning, Execution, and Communication Could Have Reduced Delays in Completing the Libby Asbestos Toxicity Assessment (Assignment No. OPE-FY10-0012)"

FROM: Mathy Stanislaus, Assistant Administrator
Office of Solid Waste and Emergency Response (OSWER)

James B. Martin, Regional Administrator
Region 8

Lek G. Kadeli, Acting Assistant Administrator
Office of Research and Development (ORD)

TO: Arthur Elkins, Jr., Inspector General
Office of Inspector General (OIG)

The memorandum transmits the Environmental Protection Agency's (EPA's) response to the Office of Inspector General (OIG) Draft Report entitled, "Follow-Up Report: Better Planning, Execution, and Communication Could Have Reduced Delays in Completing the Libby Asbestos Toxicity Assessment (Assignment No. OPE-FY10-0012)." EPA appreciates the opportunity to comment; however, in general, we have significant concerns with the OIG's Draft Report. The OIG Draft Report fails to acknowledge EPA's major strides in improving the understanding of the health effects of exposure to Libby amphibole asbestos, substantially reducing the exposure levels of the citizens of Libby through our cleanup efforts, and coordinating with community health organizations and the Agency for Toxic Substances and Disease Registry (ATSDR) to address the Public Health Emergency (PHE) in Libby, MT and the surrounding communities. Instead, the OIG Draft Report focuses primarily on EPA not meeting the initial draft Libby Action Plan (LAP) project timelines, which the OIG acknowledges as unachievable, without acknowledging our accomplishments or the fact that EPA's delay in meeting research timelines did not impede the conduct of the extensive cleanup activities that have occurred to date. While EPA appreciates the diligence with which the OIG has conducted their review of the LAP

Region 8 adheres to the Federal Acquisition Regulations (FAR) with regard to Interagency Agreements (IAs). As such, Region 8 has ensured that work assignments issued through IAs are within the scope of those agreements and will continue to do so.

The EPA disagrees with the OIG finding that the contract work was outside of the scope of the IA. The contract with the University of Cincinnati (UC) included work essential to the development of a site-specific RfC for use in the Libby, MT risk assessment and in support of risk management decisions and remedy selection. As such, the work was integral to Superfund site cleanup actions. The site-specific risk assessment includes site-specific exposure measurements and toxicity values. Where no toxicity values are available, site-specific values are needed. Development of the RfC was initially scoped as a site-specific endeavor. This work was and continues to be as important and relevant to site cleanup and remedy selection as was the site exposure monitoring and could be carried out in parallel to continued cleanup efforts.

The OIG is correct in that the interagency agreement is specifically for work to support site cleanup and remediation activities for Libby, MT and the surrounding community. However, EPA disagrees with the OIG's interpretation that only individuals physically located in Libby, MT can perform actions under this IA. There are many aspects of the work supporting cleanup activities for Libby, MT that are appropriately performed at locations outside of the physical vicinity of Libby, MT. Examples of this include sample analysis, contract management, and project management functions. Similarly, the UC scientists do not need to be physically located in Libby, MT to conduct their scientific study in support of the site-specific RfC. Thus, EPA disagrees with the OIG's finding that the Volpe IA was an inappropriate contracting mechanism based on the requirement that all work conducted under this IA must occur physically in Libby, MT.

Alternative Remedy: No corrective action needed. Region 8 adheres to the FAR with regard to IAs.

5) Assistant Administrator for Research and Development develop a priority list for pending and ongoing research.

EPA Response: Nonconcur

EPA does not concur with the recommendation to develop a new process for setting priorities across the Office of Research and Development (ORD) for pending and ongoing research. EPA believes that this draft OIG recommendation is overly broad, the criteria are vague, and the recommendation is beyond the scope of the investigation. EPA's mission is complex and encompasses working on many high-priority activities. EPA has a research planning process that sets priorities for funding and conducting research across the ORD's laboratories and centers. This ORD planning process obtains input from EPA programs and Regional Offices as well as from the scientific community and advisory groups such as the EPA's SAB and Board of Scientific Counselors for planning its research and making decisions about which research is conducted.

With respect to toxicity assessments specifically, ORD has a process of soliciting nominations for Integrated Risk Information System (IRIS) assessments. This process solicits input from EPA programs, Regional Offices, and the public regarding Agency and public need and public health impact. That process involves periodic input from EPA offices and a Federal Register notice seeking nominations and information from the public.

EPA did determine that assessing the toxicity of Libby amphibole asbestos was a high priority. EPA assembled a team with the appropriate expertise within and outside of the Agency and assigned a high priority to development of an assessment of the toxicity of Libby amphibole asbestos.

However, EPA disagrees with any implication that the declaration of a PHE made completion of the *Toxicological Review of Libby Amphibole Asbestos* the primary or highest-priority toxicity assessment for EPA. The PHE declaration accomplished its main purpose, which was to trigger provisions under CERCLA to allow the Federal government to provide health care to the population in Libby, MT. This health care was provided by ATSDR and the local community health agencies, not by EPA. More importantly, neither asbestos removal actions nor public health actions in Libby, MT have been delayed pending a final *Toxicological Review of Libby Amphibole Asbestos.*

EPA strongly disagrees with any OIG findings or implications that other toxicity assessments being conducted by ORD were not of equally high public health consequence. The OIG did not evaluate the public health impacts of any of the other Toxicological Assessments being conducted by EPA. They did not, for example, evaluate the public health significance of completing assessments of the toxicity of formaldehyde, trichloroethylene (TCE), or perchloroethylene (PERC). TCE and PERC are constituents of concern at over 700 sites on the National Priorities List, and formaldehyde is a chemical with very widespread exposure in both indoor and outdoor air. All of these assessments were nominated and selected per the IRIS process described above.

EPA does acknowledge that some portion of the delay in the Toxicological Review was due to EPA work completing other equally high-priority assessments. However, as noted, EPA believes that there are multiple high-priority assessments, and the most efficient use of EPA's expert staff and resources often entails staff with particular expertise working on more than one priority assessment at the same time. The OIG did not evaluate ORD's process for priority setting, which places this recommendation outside the scope of the OIG investigation.

EPA also disagrees with any implied finding that the delay in completing the *Toxicological Review of Libby Amphibole Asbestos* was due solely to competing demands. As EPA explained to OIG staff, there were multiple reasons the draft toxicological review took longer than initially expected. The OIG should present the other factors which impacted project timelines, as noted below.

- The time needed to complete the exposure-response modeling for the Libby amphibole asbestos IRIS assessment was initially underestimated. Modeling of epidemiology data is complex and as such it is difficult to predict the level of effort and resources needed until one evaluates the data and begins to conduct the modeling.
- The time needed to resolve legal issues regarding the protection of personal medical information in data shared between National Institute for Occupational Safety and Health (NIOSH) and EPA was longer than anticipated.
- A science-based decision to update the cancer mortality data for the Libby worker cohort was made in order to provide more information on rates of mesothelioma. This increased the amount of time needed to update the NIOSH database that EPA used for the exposure response modeling, as well as the time needed to conduct additional exposure response modeling with these new data.

- The RfC was originally begun as a site-specific toxicity value, which does not require the intra-agency, interagency, and external peer review process that accompanies an IRIS document. Thus, the original draft RfC schedule did not include time for these review steps in the IRIS process or the corresponding time needed to craft appropriate responses to comments and document revisions. The shift to an IRIS document also resulted in additional work on model evaluation and other content development.

Alternative Remedy: No corrective action needed. EPA believes the existing prioritization approach used by ORD/ National Center for Environmental Assessment (NCEA) is appropriate and adequate.

Agency Responses to Findings in the OIG Draft Report

A) Original Project Milestones Were Ambitious

A.1) OIG finding (Page 7)

"We found that the milestones established for accomplishing these studies were ambitious and there was a high risk of the milestones not being completed on time. Consequently, since establishing corrective actions under its April 2007 follow-up response, EPA has twice revised these milestones."

EPA Comments: Nonconcur

- EPA does not agree with the OIG's interpretation that the draft timelines provided in April 2007 should be the baseline against which the EPA's progress on LAP projects should be evaluated.
- The draft project timelines were submitted to the OIG while EPA was still determining the scope and resources required for each project (see "*Draft Planned Completion Dates for Individual Studies*," in EPA's April 2007 follow-up response). In addition, with respect to the five National Health and Environmental Effects Research Laboratory (NHEERL) studies, EPA stated at the time "*... however, this date is tentative pending the completion of the detailed workplans.*" Further, EPA made the OIG aware that workplans had not been developed as of the date of the April 2007 memo for all 12 proposed studies, stating that "*detailed workplans are currently being developed and will include consultation with other Agencies ....*" As project planning continued, EPA refined the initial timelines to reflect the more detailed project scoping and planning.
- EPA does acknowledge that the initial draft project milestones submitted to the OIG were ambitious. Updated milestones and project plans were developed in 2008, after detailed workplans were peer-reviewed. These updated milestones and project plans were presented in public meetings in 2008. September 2009 is when EPA initially notified the OIG of revisions to the draft initial milestones, followed by a formal request for extension dated October 20th 2009.

Proposed revised text:

"The EPA provided the OIG with *Draft Planned Completion Dates for Individual Studies* which were ambitious and specifically noted that some of the completion dates were "*tentative pending the completion of the detailed workplans.*" As project planning continued, EPA developed completion dates that reflected a better understanding of the scope, level of effort, and time

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EXCERPTS

EPA's Response to Selected Major Interagency Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of Libby Amphibole Asbestos

August 25, 2011

Purpose:
The Integrated Risk Information System (IRIS) assessment development process of May 2009, includes two steps (Step 3 and 6) where White House offices and other federal agencies can comment on draft assessments. The following are EPA's responses to selected major interagency review comments received during the Interagency Science Consultation step (Step 3) for the draft IRIS Toxicological Review of Libby Amphibole Asbestos (dated May 2011). All interagency comments provided were taken into consideration in revising the draft assessment prior to posting for public comment and external peer review. The complete set of all interagency comments is attached as an appendix to this document.

For a complete description of the IRIS process, including Interagency Science Consultation, visit the IRIS website at www.epa.gov/iris.

Topic #1: Terminology - *NIOSH commented on several issues regarding the current terminology and definitions of terms relevant to asbestos. A key comment was the need for clarity in the use of the term "Libby Amphibole asbestos" for the mixture of mineral fibers that forms the basis of this assessment.*

> **EPA Response:** EPA agrees with the need to use clearly defined terminology when discussing asbestos and related mineral fibers. The terminology of asbestos and related mineral fibers is an ongoing issue in the field of asbestos research. Usage of the term 'asbestos' depends in part on the framework or context: commercial use, regulatory, geologic (hand samples), mineralogic (composition), and analytical (size aspect ratio, regulatory). EPA has included in the text clarification of the terminology when used, and has added a glossary of asbestos terms to the Toxicological Review to clarify how the definitions of the asbestos-related terms are used in this assessment. For the purposes of this document, EPA uses the term "Libby Amphibole asbestos" to identify the mixture of amphibole mineral fibers of varying elemental composition (e.g. winchite, richterite and tremolite, etc), which have been identified in the Rainy Creek complex near Libby, MT as described in Section 2.2 of the Toxicological Review. A geological description

Appendix

OMB Staff Working Comments on EPA's Libby Amphibole Asbestos draft Toxicological Review (page numbers refer to the draft dated May 2011) **and Draft Charge to External Reviewers**

June 15, 2011

General Science Comments:

- We recommend consideration of the following questions and additions to ensure that the final RfC of 1x 10^{-5} fibers/cc is realistic.
  - As EPA is proposing an RfC that is at or below background levels, we suggest a discussion of current levels of detection and analytical sensitivity to ensure that the RfC is realistic and implementable. In addition, EPA should clarify how the RfC, in fibers/cc relates to s/cc (structures/cc).
  - Page 2-23, states that ambient air in schools, in 2006/7 ranged from 0.0022 to 0.039 f/cc in the Libby community. If one assumes that the level was less in 2006/7 (when sampling was conducted) compared to the 1950s, wouldn't we expect most if not all of the population to show pleural thickening? Does EPA have information about the rates of pleural thickening in the Libby community, and if so, could EPA compare the predictions from the analysis with actual rates?
  - Page 2-27, notes that background air samples in homes were below 0.0016 f/cc when the air was not disturbed, and modeled to be 0.001 and 0.25 f/cc during renovations. Table 2-3 shows all area and personal samples to be orders of magnitude above the RfC. If the RfC is accurate, does this mean that most of the homeowners in the US (page 2-26 notes that 80% of the vermiculate used in US homes came from Libby) should be showing pleural thickening?
  - According to the HSDB, ambient air levels are generally less than 5 x 10^{-5} fibers/cc. In addition (see http://books.google.com/books?id=rR4ewu4IfmsC&pg=PA26&lpg=PA26&dq=asbestos+how+many+ng+to+a+fiber&source=bl&ots=Os8L5aPaqP&sig=eOrVAN6mtuwvRA_IflgvrsfIlAE&hl=en&ei=GxK_TdK5DM6ztweS-bnNBQ&sa=X&oi=book_result&ct=result&resnum=1&ved=0CEMQ6AEwAA#v=onepage&q&f=false) the table below shows that throughout the US, air in schools and US cities is above the proposed RfC. Again, this would seem to suggest that the we would see a large amount of pleural thickening. What do we know about the current rates in the US?

Table 2-1. Summary of asbestos exposure samples in different environments

Sample set	Sample No.	Measured concentration (ng/m³) Median	Measured concentration (ng/m³) 90th %ile	Equivalent concentration (fibers/cc)* Median	Equivalent concentration (fibers/cc)* 90th %ile
Air of 48 U.S. cities	187	1.6	6.8	0.00005	0.00023
Air in U.S. school rooms without asbestos	31	16.3	72.7	0.00054	0.00242
Air in Paris bldgs with asbestos surfaces	135	1.8	32.2	0.00006	0.00107
Air in U.S. bldgs with cementitious asbestos	28	7.9	19.1	0.00026	0.00064
Air in U.S. bldgs with friable asbestos	54	19.2	96.2	0.00064	0.00321

Source: Modified from Ref.17. *Based on conversion factor of 30μg/m³ = 1 fiber/cc.

- Page 4-30, line 22, notes that the exposures in group 1 (the non-exposed group) in Marysville Ohio studies was 0.049 fibers/cc, and the levels in the low-exposure groups were 1.2-1.5 fibers/cc before 1974. How do the levels of pleural thickening in these non-exposed and low-exposure groups compare to the levels EPA would expect considering that these exposures are orders of magnitude above the RfC?
- Page 4-34, table 4-10, shows that at the lowest exposure (0.12 fiber/cc) the number of workers was only 7%. If the RfC is correct, shouldn't a much greater percentage have shown changes?
- It would also be helpful to provide a clear discussion regarding US background rates of pleural thickening and how these may be impacted by age and or smoking. This comparison information would be helpful when EPA discusses the radiographic changes in the Libby cohort. It would be helpful for EPA to have a specific charge question on the background rate chosen for the RfC analysis.
- For the RfC analysis and for exposure reconstruction, EPA assumes 365 days of exposure per year for workers and 24hr/day exposure. Further discussion about why this was chosen (rather than a 40-hour work week with holidays and vacation) would be helpful. EPA may also want to consider a charge question relating to these assumptions.
- In discussing the RfC, perhaps greater discussion and weight could be given to potential confounders such as age and smoking. Further discussion in 5.2.1 would be helpful.
- Table 5-3 clearly shows a dose response for local thickening, but a similar relationship is not seen for the other changes (until the highest dose is reached). We also note that the lowest exposures here (0.061 fibers-yr/cc), where minimal effects are seen, is orders of magnitude above the RfC.

- The approach to deriving the RfC raises the following questions.
  - Cohorts:
    - Page 5-10 notes that exposure estimates were developed, and are shown in App F. Has this analysis by the Univ. of Cincinnati undergone independent

APPENDIX C – 27

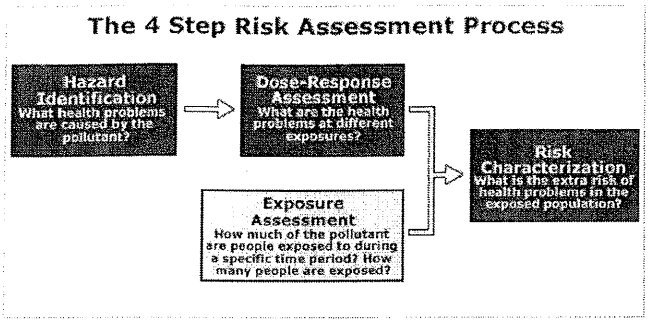
http://www.epa.gov/risk/exposure.htm

EPA United States Environmental Protection Agency

Risk Assessment

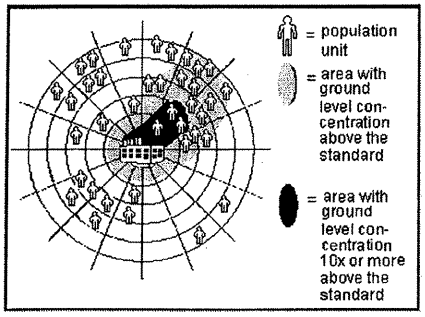
Step 3 - Exposure Assessment

Step 3 - Exposure Assessment: To calculate a numerical estimate of exposure or dose.



EPA defines exposure as 'contact between an agent and the visible exterior of a person (e.g. skin and openings into the body)'. Exposure assessment is the process of measuring or estimating the magnitude, frequency, and duration of human exposure to an agent in the environment, or estimating future exposures for an agent that has not yet been released. An exposure assessment includes some discussion of the size, nature, and types of human populations exposed to the agent, as well as discussion of the uncertainties in the above information. Exposure can be measured directly, but more commonly is estimated indirectly through consideration of measured concentrations in the environment, consideration of models of chemical transport and fate in the environment, and estimates of human intake over time.

Different Kinds of Doses. Exposure assessment considers both the exposure pathway (the course an agent takes from its source to the person(s) being contacted) as well as the exposure route (means of entry of the agent into the body). The exposure route is generally further described as intake (taken in through a body opening, e.g. as eating, drinking, or inhaling) or uptake (absorption through tissues, e.g. through the skin or eye). The applied dose is the amount of agent at the absorption barrier that is available for absorption. The potential dose is the amount of agent that is ingested, inhaled, or applied to the skin. The applied dose may be less than the potential dose if the agent is only partly bioavailable. The internal dose or absorbed dose is the amount of an agent that has been absorbed and is available for interaction with biologically significant receptors within the human body. Finally, the delivered dose is the amount of agent available for interaction with any specific organ or cell.



Range of Exposure. For any specific agent or site, there is a range of exposures actually experienced by individuals. Some individuals may have a high degree of contact for an extended period (e.g. factory workers exposed to an agent on the job). Other individuals may have a lower degree of contact for a shorter period (e.g. individuals using a recreational site downwind of the factory). EPA policy for exposure assessment requires consideration of a range of possible exposure levels. Two common scenarios for possible exposure are "Central Tendency" and "High End". "Central Tendency" exposure is an estimate of the average experienced by the affected population, based on the amount of agent present in the environment and the frequency and duration of exposure. "High End" exposure is the highest dose estimated to be experienced by some individuals, commonly stated as approximately equal to the 90th percentile exposure category for individuals.

Quantifying Exposure. There are three basic approaches for quantifying exposure. Each approach is based on different data, and has different strengths and weaknesses; using the approaches in combination can greatly strengthen the credibility of an exposure risk assessment.

- **Point of Contact Measurement** - The exposure can be measured at the point of contact (the outer boundary of the body) while it is taking place, measuring both exposure concentration and time of contact, then integrating them;
- **Scenario Evaluation** - The exposure can be estimated by separately evaluating the exposure concentration and the time of contact, then combining this information;
- **Reconstruction** - the exposure can be estimated from dose, which in turn can be reconstructed through internal indicators (biomarkers, body burden, excretion levels, etc) after the exposure has taken place (reconstruction).

For more information on exposure assessment methods, see the "Guidelines for Exposure Assessment", May 1992.

Next Step is Step 4

Last updated on Tuesday, July 31, 2012

APPENDIX C – 28

EXCERPTS

-Working Draft-

March 20, 2012

PHASE V
SAMPLING AND ANALYSIS PLAN
FOR OPERABLE UNIT 3
LIBBY ASBESTOS SUPERFUND SITE

Part A: Kootenai River
Surface Water, Sediment, and Activity-based Sampling

Prepared for and with oversight by:

U.S. ENVIRONMENTAL PROTECTION AGENCY
Region 8

Prepared by:

CDM Smith

CDM Federal Programs Corporation
555 17th Street, Suite 1100, Denver, Colorado 80202

Section 1 Project Overview

This section provides a summary of the purpose and organization of this document.

1.1 Purpose of this Document

This document is a Sampling and Analysis Plan (SAP) that describes data collection efforts that will be conducted during Phase V Part A of the remedial investigation (RI) for Operable Unit (OU) 3 of the Libby Asbestos Superfund Site (the Site). This SAP contains the elements required for both a field sampling plan (FSP) and quality assurance project plan (QAPP), and has been developed in basic accordance with the U.S. Environmental Protection Agency (EPA) *Requirements for Quality Assurance Project Plans, EPA QA/R-5* (EPA 2001) and the *Guidance on Systematic Planning Using the Data Quality Objectives Process – EPA QA/G4* (EPA 2006). While this QAPP is organized differently than the recommended structure in the QA/R-5 guidance, all the required elements are presented. **Table 1-1** provides a cross-reference where information for each QA/R-5 element is located in this QAPP. This document is organized as follows:

Section 1 – Project Overview

Section 2 – Background and Problem Definition

Section 3 – Data Quality Objectives

Section 4 – Sampling Program

Section 5 – Sample Preparation and Analysis Requirements

Section 6 – Quality Assurance/Quality Control

Section 7 – Data Management

Section 8 – Assessment and Oversight

Section 9 – Data Validation and Usability

Section 10 – References

1.2 Project Management and Organization

Project Management

Figure 1-1 presents the organizational chart for the OU3 team and illustrates the lines of authority and communication between the agencies and contractors. The EPA is the lead regulatory agency for Superfund activities within OU3. The EPA Remedial Project Manager (RPM) for OU3 is Christina Progess, EPA Region 8. Ms. Progess is a principal data user and decision-maker for Superfund activities within OU3.

Sample Analysis

Each sediment sample will be analyzed for LA in accordance with Libby site-specific SOPs. The coarse fraction (if any) will be examined using stereomicroscopy, and any particles of LA will be removed and weighed in accordance with SRC-LIBBY-01, referred to as "PLM-Grav". One of the fine ground fraction aliquots will be analyzed by PLM using the visual area estimation method in accordance with SOP SRC-LIBBY-03, referred to as "PLM-VE". Mass fraction estimates of LA and optical property details will be recorded on the Libby site-specific laboratory bench sheets and electronic data deliverable (EDD) spreadsheets.

5.1.3 Analysis of ABS Air

Two samples are collected during each ABS event for each actor (i.e., a high volume filter and a low volume filter). The high volume filter will be analyzed in preference to the low volume filter. If the high volume filter is deemed to be overloaded, the low volume filter should be analyzed in preference to performing an indirect preparation on the high volume filter to avoid potential bias associated with indirect preparation[d]. If the low volume filter is deemed to be overloaded, an indirect preparation (with ashing) may be performed in accordance with the procedures in SOP EPA-LIBBY-08.

Analysis Method

All ABS air samples collected as part of this investigation shall be prepared and analyzed for LA using TEM in basic accordance with ISO 10312:1995(E) (ISO 1995), with all applicable project-specific laboratory modifications. These modifications include the most recent versions of LB-000016, LB-000029, LB-000066, LB-000067, and LB-000085.

Target Analytical Sensitivity

The level of analytical sensitivity needed to ensure that analysis of ABS air samples will be adequate is derived by finding the concentration of LA in ABS air that might be of potential concern, and then ensuring that if an ABS sample were encountered that had a true concentration equal to that level of concern, it would be quantified with reasonable accuracy. This process is implemented below:

---

[d] Indirect preparation has the potential to increase the number of LA structures recorded during TEM analysis, which may bias resulting air concentrations high (Berry *et al.* 2011).

Step 1. Calculation of Risk-Based Concentrations

Cancer. The basic equation for calculating the risk-based concentration (RBC) for cancer is:

RBC(cancer) = Maximum Acceptable Cancer Risk / (TWFc * IUR)

For cancer, the maximum acceptable risk is a risk management decision. For the purposes of calculating an adequate TAS, a value of 1E-05 is assumed.

No data are presently available on the frequency or duration of human exposures that occur in OU3, and the EPA has not established default parameters that are applicable for the exposure scenario of potential concern. Therefore, the following exposure parameters were selected based on professional judgment and conversations with outfitters who frequent the Kootenai River:

- The exposure time (ET) parameter was based on an assumed value of 2 hours per day.
- In Libby, assuming recreational activities along the Kootenai River are likely to occur mainly between May and October (about 24 weeks per year) at a frequency of seven days per week, the exposure frequency (EF) parameter for the number of days per year spent recreating along the Kootenai River was estimated to be about 170 days.
- At present, no site-specific data exist that provide information on the exposure duration (ED) of recreational visitors. In the absence of data, a conservative value of 30 years was assumed.

Based on these exposure parameters, the TWFc is 0.0470 (2/24 * 170/365 * 30/70 = 0.0166). The proposed LA-specific IUR is 0.17 $(PCM\ s/cc)^{-1}$. Based on these values, the RBC for cancer is 0.0035 LA PCME s/cc.

Non-Cancer. The basic equation for calculating the RBC for non-cancer effects is:

RBC(non-cancer) = (Maximum Acceptable HQ * RfC) / TWFnc

For non-cancer, the maximum acceptable HQ is 1. The TWFnc is 0.0548 (2/24 * 170/365 * 30/60 = 0.0194). The proposed LA-specific RfC is 0.00002 LA PCM s/cc. Based on these values, the RBC for non-cancer is 0.00103 LA PCME s/cc.

Because the non-cancer RBC is lower than the cancer RBC, the non-cancer RBC is used to derive the target analytical sensitivity, as follows.

Step 2: Determining the Target Analytical Sensitivity

The target analytical sensitivity (TAS) is determined by dividing the RBC by the target number of structures to be observed during the analysis of a sample with a true concentration equal to the RBC:

$$TAS = RBC / Target\ Count$$

The target count is determined by specifying a minimum detection frequency required during the analysis of samples at the RBC. This probability of detection is given by:

$$Probability\ of\ detection = 1 - Poisson(0, Target\ Count)$$

Assuming a minimum detection frequency of 95 percent, the target count is 3 structures. Based on this, the target analytical sensitivity is:

$$TAS = (0.00103\ s/cc) / (3\ s) = 0.00034\ cc^{-1}$$

Maximum Number of LA Structures

As described in Section 5.1.1 above, there is little change in the relative uncertainty when structure counts are greater than 25. Therefore, the count-based stopping rule for TEM should utilize a maximum structure count of 25 LA structures.

Maximum Area to be Examined

The number of grid openings that must be examined (GOx) to achieve the target analytical sensitivity is calculated as:

$$GOx = EFA / (TAS \cdot Ago \cdot V \cdot 1000 \cdot f)$$

where:

EFA = Effective filter area (assumed to be 385 mm^2)
TAS = Target analytical sensitivity $(cc)^{-1}$
Ago = Grid opening area (assumed to be 0.01 mm^2)
V = Sample air volume (L)
1000 = L/cc (conversion factor in L/cc)
f = Indirect preparation dilution factor (assumed to be 1 for direct preparation)

A total of about 235 grid openings will need to be examined to achieve the target analytical sensitivity, assuming an air sample volume of 480 liters (60 minute sample duration x 8 liters/minute flow rate) and that the filter is able to be prepared directly (i.e., f = 1). If an indirect preparation is necessary, the number of grid openings that will need to be examined is inversely proportional to the dilution needed (i.e., an f of 0.1 will increase the number of grid openings by a factor of 10).

In the event that analysis of the low volume sample is needed (due to particulate overloading on the high volume filter) or if an indirect preparation of the low volume sample is necessary, it is possible that the number of grid openings that would need to be examined to achieve the target analytical sensitivity may be cost or time prohibitive. In order to limit the maximum effort expended on any one sample, a maximum area examined of 20 mm^2 is identified for this project. Assuming that each grid opening has an area of about 0.01 mm^2, this would correspond to about 2,000 grid openings.

Counting Rules

Because of the high number of grid openings that are needed to achieve the target analytical sensitivity, all ABS samples will be examined using counting protocols for recording PCME structures only (per ISO 10312 Annex E). That is, filters will be examined at a magnification of 5,000x, and all amphibole structures (including not only LA but all other amphibole asbestos types as well) that have appropriate SAED patterns and EDXA spectra, and having length > 5 µm, width ≥ 0.25 µm, and aspect ratio ≥ 3:1 will be recorded on the Libby OU3-specific TEM laboratory bench sheets and EDD spreadsheets. Data recording for chrysotile, if observed, is not required (but presence should be noted in the analysis comments).

Stopping Rules

The TEM stopping rules for all ABS air field samples from this investigation should be as follows:

1. Count a minimum of two grid openings from each of two grids.
2. Continue counting until one of the following is achieved:
   a. The target analytical sensitivity (0.00034 cc^{-1}) is achieved.
   b. 25 PCME LA structures have been observed.
   c. A total filter area of 20 mm^2 has been examined (this is approximately 2,000 grid openings).

When one of these criteria has been satisfied, complete the examination of the final grid opening and stop.

APPENDIX C – 29

From: Brattin, Bill <brattin@srcinc.com>
Sent: Thursday, May 30, 2013 12:47 AM
To: Tim Hilbert
Cc: Benson, Bob; Berry, David
Subject: follow-up question

If a diagnosis of Pleural Plaque (1980) may not be DPT, but is not LPT, that means there are really 3 categories of pleural thickening:

a) LPT
b) DPT
c) Other pleural thickening

If so, are there workers in 2004 who might have "Other" pleural thickening, such that LPT + DPT is not the same as "Any Pleural Thickening" ??

****

Bill Brattin
SRC, Inc.
999 18th Street Suite 1150
Denver CO 80202
Phone: 303-357-3121
Fax: 303-292-4755
e-mail: brattin@srcinc.com

From: Hilbert, Timothy (hilbertj) <HILBERTJ@UCMAIL.UC.EDU>
Sent: Friday, May 17, 2013 2:42 PM
To: Brattin, Bill
Cc: Benson, Bob
Subject: RE: Is this right?

Correct.

Pleural plaques = LPT.

The other category (pleural thickening) could meet the current definition of DPT or LPT.

Jim recommends they all just be called PT.

From: Brattin, Bill [mailto:brattin@srcinc.com]
Sent: Friday, May 17, 2013 2:33 PM
To: Hilbert, Timothy (hilbertj)
Cc: 'Bob Benson (Benson.Bob@epamail.epa.gov)'
Subject: Is this right?

Tim

See if the following is correct:

In 1980, the data for x-ray results included two categories that are related to pleural thickening:

a) Pleural plaques
b) Some other category (not sure what it is called)

Until the recent discussion with Jim, the pleural plaques were identified as LPT and the other category was identified as DPT.
Based on Jim's recent input, it is clear pleural plaques are the same as LPT, but the other category cannot be assigned DPT, because it could be either LPT and/or DPT (at least based on the current definition of DPT).
For this reason, he has recommended that these two categories be combined and simply identified as "pleural thickening".

Is that right?

****

Bill Brattin
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Phone: 303-357-3121
Fax: 303-292-4755
e-mail: brattin@srcinc.com

RE: Additional Data Needed

Hilbert, Timothy (hilbertj) to: Benson.Bob 11/09/2010 11:15 AM

From: "Hilbert, Timothy (hilbertj)" <HILBERTJ@UCMAIL.UC.EDU>
To:
Cc: "Lockey, James (lockeyje)" <lockeyje@UCMAIL.UC.EDU>, "Lemasters, Grace (lemastgj)" <LEMASTGJ@ucmail.uc.edu>, "Rice, Carol (ricech)" <ricech@ucmail.uc.edu>, "Borton, Eric (bortonek)" <BORTONEK@UCMAIL.UC.EDU>

Bob, There are two issues with providing you with this information. First, we only have approximately half of the actual B-reader forms from the 1980 study. From the master thesis we know who the 10 people are with pleural changes and the one person with interstitial changes. However, since only 501 of the 513 participants had a usable X-ray, we can't say for sure that the remainder were negative since 12 didn't have a usable 1980 Xray. The second issue is that the ILO B-reader form that was used for the 1980 study is an older version than the one used in 2004 and does not as clearly differentiate between diffuse (pleural thickening that involves CPA blunting) and discrete pleural thickening. Most likely the distribution is as follows: 6 discrete pleural thickening, 3 diffuse pleural thickening, and 1 with both discrete and diffuse. So in summary we can tell you who the one person from 1980 with interstitial changes is, we can tell you who the 10 with pleural changes are and our best estimation if they are discrete or diffuse, and we cannot definitively tell you that the balance of the 513 are all negative because 12 people didn't have films and we don't know who they are.
One possibility in moving forward is for us to assume the 12 without X-rays were negative. Then we could supply you with a spreadsheet as you requested, being fairly certain of its accuracy.
Please let us know
Tim

-----Original Message-----
From: Benson.Bob@epamail.epa.gov
[mailto:Benson.Bob@epamail.epa.gov]
Sent: Monday, November 01, 2010 3:45 PM
To: Hilbert, Timothy (hilbertj)
Cc: brattin@srcinc.com; Jill Lundell
Subject: Additional Data Needed

Our modeling efforts have led us to need the data used in the Lockey et
al. (1984) publication.
This is what we need:
ID number (same as that in final UC report)
x-ray date (for the 1984 publication)
Health outcome for each worker in the 1984 publication (comparable to
the health outcomes in the final UC report - discrete, diffuse, interstitial)
We can use the Asbestos Other in the final UC report.

APPENDIX C – 30

Response to Comments on RfC Draft

Bob Benson to: HILBERTJ, David Berry 04/23/2010 11:50 AM

From: Bob Benson/R8/USEPA/US

To: HILBERTJ@UCMAIL.UC.EDU, David Berry/R8/USEPA/US@EPA

Tim,
Please distribute to the UC Group and Leslie. I don't have his email address.

Responses to LS, UC, DB.doc

To: UC Group, Leslie Stayner, and David Berry

From: Bob Benson

Re: Comments on the draft RfC for Libby Amphibole

Thank you all for taking the time to review the draft assessment. Your comments revealed a number of places where the document needs revision. I will use most of your editorial suggestions. There are some places where we "are not on the same page" and need to get there.

Page 1, Introduction
The wording in the Introduction is that used for all IRIS assessments. I don't think I should change from the canned language.

Page 8
My paragraph on the Multi-Path Particle Dose Model was poorly worded. The advantage of using the MPPD model is that it can use information on the concentration of the particle in inspired air, deposition in specific areas of the respiratory tract, and clearance from those areas to estimate the biologically effective dose in the target tissue. Then the model is used to back calculate to a concentration of fibers in air that will lead to that biologically effective dose in the target tissue. This approach can account for overload and saturation of clearance mechanisms that cannot be taken into account with only data on concentration of fibers in air and prevalence of adverse response. In either case the RfC is still expressed as the concentration of fibers in air. I will clarify the wording and delete wording that promises that a future revision will incorporate the modeling.

Page 9
Studies in laboratory animals are in progress at RTP. However, I do not have any confidence that they will be finished and citable in the time frame needed to incorporate them into this assessment.

Page 10
The Sullivan publication doesn't define SRR. I assume it is Standardized Risk Ratio and is calculated using the referent group with a value of 1.0.

Page 12
I will probably drop Table 4-2.

Page 16, Table 4-8
I don't know why the Amandus study did not show statistically significant results in the reanalysis by Armstrong presented in Table 4-8. The effects were all significant in the original analysis presented in Table 4-6 and Table 4-7. We don't have the data necessary for a reanalysis.

Page 17
I will add a summary of the Vinikoor et al. study to Section 4.2.2.

Page 18
I am intending to report in Table 4-9 what was published in 1984. I will change the wording to conform to the published paper, not the job titles from the thesis, and will use the number of significant as reported in the publication.

Page 19
I am assuming that UC will provide some better data on background exposure in Marysville for the new exposure reconstruction.

How did you calculate the 65% of all living workers from the original study?

Page 20
Throughout the document I will report the number of significant digits used in the published work.

Page 23
I will delete the "any radiographic change" line from Figure 5, but only present one figure. Because discrete and diffuse pleural changes occur in different anatomical locations, I do not think it is appropriate to combine them.

Page 24
The correct value is 80/280 from Rohs.

Page 26
The questions about the Whitehouse, Noonan, and Pfau studies are reasonable. I will try to incorporate the relevant information from the publications. If I can't find the relevant information, are you suggesting the studies are not valid and should not be included? Because there is no exposure response information in any of the papers, I am including them only as a summary of published literature. They are not used in the quantitative determination of the LEC05. The immunotox results, however, do play an important role in the database uncertainty factor and need to be included in the document.

Page 27
I am summarizing here from ATS (2004). Do you have alternative suggestions for wording?

Page 29
I agree that only weak data support surface charge and surface reactivity as causative factors. I will look for references. Do you have some in mind?

Page 30
I am "borrowing" Figure 6. I will change the title to focus on MOA for changes in the respiratory tract. The focus of the figure is not autoimmune disease and I don't think

Annie would want to include that as an independent endpoint in her figure. Do you think plaques need a separate line distinct from those at the bottom (translocation to pleura, leading to inflammation and cellular proliferation, leading to remodeling and leading to pleural fibrosis)? If so, I can make a suggestion to Annie to include plaques.

Non-cancer effects in the respiratory tract are included in the MOA figure.

Page 31
I will include the 95% LCL in Table 5-1. I am trying in the Table to make a clear comparison of the dose-response for the three studies. I agree that the approach of dropping the two high doses from McDonald is not a good way of doing this. The problem is that McDonald presented the exposure reconstruction in Table 4-4 for the full cohort. However, Amandus (Table 4-6) lumped all workers with exposure >86 into one group. As they were studying overlapping cohorts, the >86 group from Amandus will certainly contain workers with exposures comparable to what was presented by McDonald. I think using the data in Table 4-8 where the exposure groupings are comparable would work better. Is this acceptable?

Page 32
I will include a clearer rationale for selecting the Rohs study as the principal study in Section 5.1.1. Reasons will include a superior exposure reconstruction, lower cumulative exposure, a longer latency period after exposure to allow radiographic changes to appear, more recent radiographic analysis (I am assuming here that film quality and reader qualifications have advanced since 1986. Correct?), and the increased prevalence of irreversible, but less serious, changes in the respiratory tract at lower exposure. Therefore, this using these results will provide better public health protection. Should any reasons be deleted or added?

Page 32
I don't clearly understand the distinction being made between survival data and cross-sectional data. Leslie's paper on chrysotile dimensions and respiratory disease used the Cox Regression as the only statistical method of analysis for what seems to me to be a comparable situation to Marysville, except the chrysotile paper was a mortality study. What am I missing?

Page 33
The distinction I am trying to make between the logistic regression and the benchmark dose analysis is using individual data for the logistic regression analysis versus grouped data for the benchmark dose analysis, not whether the function is linear or logistic. Do you have a suggestion for alternative wording to clarify?

Page 34
RfCs are expressed as continuous exposure (24 hrs/day, 365 days/year for a lifetime of about 70 years). I will clarify the wording.

Whether this is a large or small study depends on your point of view. It is small relative to many epidemiological studies, but large compared to the typical laboratory animal study used by EPA to derive reference values. The point I was trying to make is that this study is large enough to detect a 5% increase in the adverse response given the size of the cohort used in the analysis. I will adjust the wording.

Page 35
The limit of detection is certainly important. However, this is a risk management issue. If compliance with a health based standard cannot be verified using existing analytical methods, then EPA typically uses the limit of detection as the compliance standard.

Page 37
The issue about the latency period and increased adverse responses appearing later is important. I can include "with conventional x-ray techniques" and add a sentence stating that if more sensitive health assessment techniques are used (HRCT), the prevalence of adverse responses is likely to be higher. Do you have some suggested wording?

Page 38
The issue I am trying to deal with by using Figure 8 is whether there is a bias because we have no industrial hygiene data before 1972. This is extremely important and could be a showstopper for NCEA.

I am trying to find a good way of showing that the slopes of the curves (full cohort versus those hired after 1972) are relatively similar, not identical. Therefore, there is not a huge error resulting from the fact that we have no industrial hygiene data before 1972 when the facility might have been dustier with an increased concentration of Libby Amphibole fibers. Do you have any suggestions on how to present this more clearly or some other way of dealing with the issue?

Page 39
Is this RfC biased high or low? This is extremely important! Here is my logic. The uncertainty factor is 30. The exposure at the LEC05 is estimated as 0.07 fibers-yr/cc. If the exposure really needed to get to the LEC05 is 0.14, then exposure is underestimated. The RfC using 0.07 fibers-yr/cc and the 30 UF is 0.002; The RfC using 0.14 fibers-yr/cc and the 30 UF is 0.005. Therefore, underestimating the exposure in this situation is health protective.

Page 45
Using the Cox Proportional Hazard Regression is an important issue for NCEA. This is an area where I need some expert advice and a very strong rationale why this methodology is not appropriate for the data we have. As I read Leslie's paper on chrysotile fibers where the Cox Regression was the only statistical method used, I don't see a difference in the two situations. Am I missing something?

Page 46
Is deleting covariates appropriate? Again, this is extremely important!

I am not aware of any information that suggests that smoking, body mass index, and sex are independent risk factors for discrete or diffuse pleural thickening. Why should they be included in the regression analysis to calculate the LEC05? I grant that body fat could cause misdiagnosis of pleural thickening, but showing no statistically significant correlation should allow the conclusion that this is not an independent risk factor for the effect. Including covariates was also an issue raised by Suresh Moolgavkar in the criminal trial.

Cox model and stop time? I made a wording error here. Because the calculation was successful, I think the correct term here is that the lag time is zero. Because there was only a relatively small increase in exposure after 1980 and the long latency period between end of exposure and evaluation of health endpoint, including a lag time did not improve the fit. I think this was the same reasoning used in Leslie's paper on chrysotile fibers. What is the correct wording to use to avoid a misinterpretation?

Page 46
Why include Benchmark Dose Modeling? EPA rarely has individual exposure and health outcome data to use in a risk assessment. We usually have only grouped data from epidemiological studies or laboratory animal studies. Therefore, most EPA risk assessors do not have experience evaluating individual data. Most EPA risk assessors, however, have familiarity with Benchmark Dose methodology and most trust the results. Therefore, I am including the Benchmark Dose results as a bridge to convince EPA risk assessors that the analysis of the individual data for Libby Amphibole is reliable because the results using the two different methods are about the same.