EHC 240: Chapters

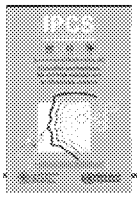
7 Risk characterization

8 Maximum residue limits for pesticides and veterinary drugs

9 Principles related to specific groups of substances

Annex: Glossary of Terms

World Health Organization



EHC 240: what it is and what not

- Risk assessment guidance for all food chemicals
- Describes testing strategy and general principles for testing but does not give test protocols
- Makes reference to existing guideline study protocols (OECD, EPA, FDA)
- Focus on interpretation of studies, including considerations of study design, GLP etc.
- **De**scriptive guidance, not **pre**scriptive
- Electronic publication in individual chapters – for update

World Health Organization

Future Work and Challenges

- GEMS/Food databases – exposure assessment
- Veterinary drugs: *A hypothesis driven decision tree approach for the safety evaluation of residues of veterinary drugs*
- Risk benefit assessments
- Cumulative and Aggregate exposure and risk assessment

World Health Organization

"Only if we act together can we respond effectively to international food safety problems and ensure safer food for everyone"

Dr Margaret Chan – Director-General

World Health Organization

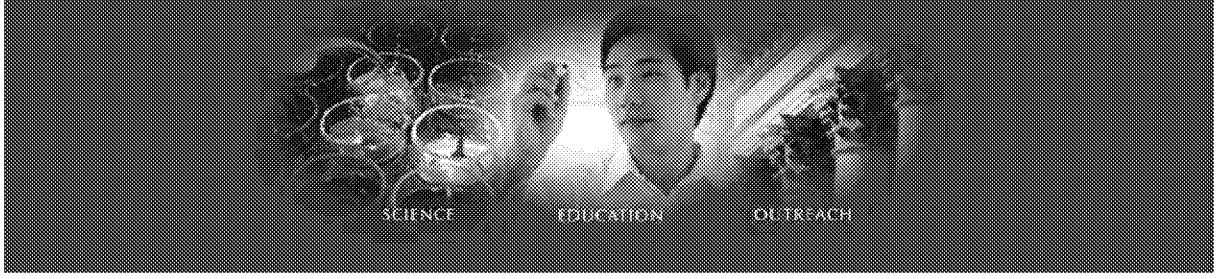
A Twenty-five Year Saga of Alternative Toxicological Methods Research

Pew Charitable Trust Food Safety Workshop

IIVS Institute for Sciences

Rodger D. Curren, Ph.D.

Institute for In Vitro Sciences
Gaithersburg, Maryland • 6 April 2011



Institute for In Vitro Sciences

Founded as a non-profit in 1997

"Advancing science & animal welfare together"

- Science

  Working with industry, academic labs and government agencies worldwide, IIVS provides testing *in vitro* testing for over 1,000 materials/yr.

- Education

  Workshops, hands-on training, international committees, etc.

- Outreach

  Direct interaction with regulatory agencies, animal welfare organizations, and the general public, internationally.

IIVS

What are "Alternatives"?

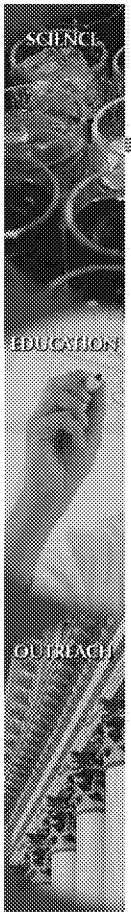
Commonly thought of as "just" 3Rs methods

Non-animal replacements for acute topical toxicities

…but the learnings of the last 25 years can apply to most any new test

- a new analytical method
- a new animal test
- a Tox21 test
- …..

IIVS



Progression of New Test Method(ology)s

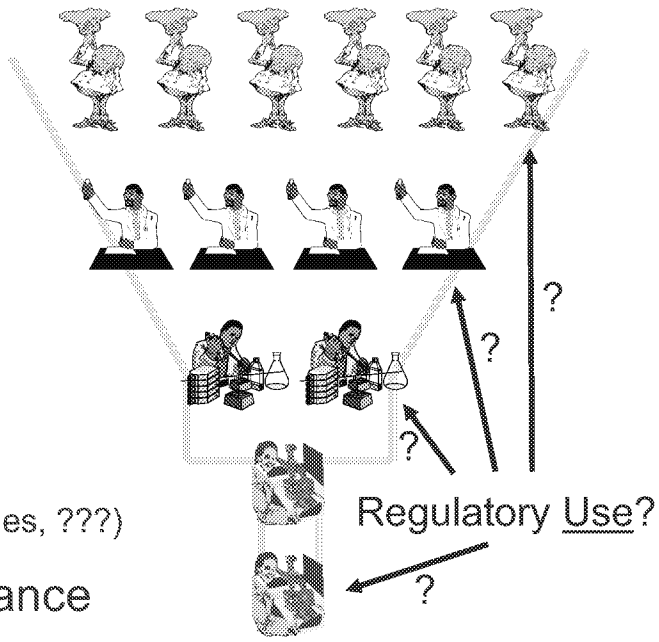
Basic Research

Development & Optimization

Prevalidation

Validation
(ICCVAM, ECVAM, Agencies, ???)

Regulatory Acceptance



IIVS

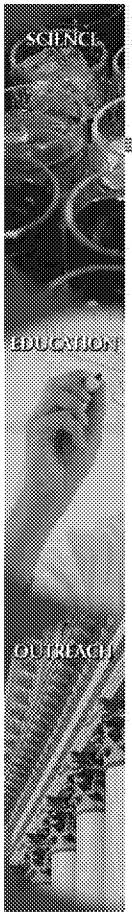
What Is Validation?

Validation is the scientific process used to show that an alternative test really "works", and to define the areas within which the test can be used with confidence. Validation has become a requirement for test methods.

- Is the test (method) reliable and relevant?
- What is its applicability domain?
- What is its predictive capacity (performance characteristics)?

History shows that this works best if it is an hypothesis testing activity. Propose what you think the test does, then perform a blinded study to confirm. …just like validating a computational method.

IIVS



What Is The Target For Validation?

For almost all of the "alternatives" activities, the target (gold standard) has been the animal test. The regulatory requirement was an animal toxicity test, so matching that has been the demand.

"We don't want the tests to predict what could happen in humans, we want to protect humans" - anonymous, EPA

…but the target of validation can be anything – an adverse human health effect, fish toxicity, serum cholesterol levels, etc. The same rules should apply.

IIVS

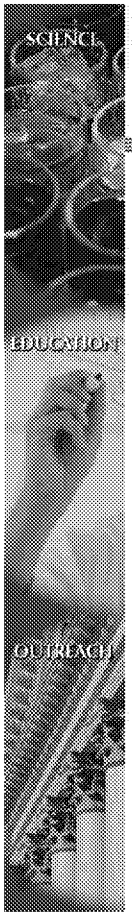
Why Has Validation Been So Slow?

It's taken years (decades!) for some of the current *in vitro* tests to become OECD Test Guidelines.

- Many tests did just not perform well enough to be validated!
- The "gold" standard of animal test results was a difficult hurdle
- The variability of animal tests was often not considered
- Generally necessary to use historic (perhaps unreliable) animal data
- There was likely overkill in some validation study designs
- Scientists can't follow protocols
- Funding was sometimes difficult to find.

…but things have improved. Recently some tests have become OECD Test Guidelines within a year of entering the system!

IIVS



Performance Characteristics

Sensitivity and Specificity are <u>developers</u> statistics.

Positive and Negative predictive values are <u>users</u> statistics.

- Paraphrased from Alvin Feinstein, M.D. (1975)

A user (industrial toxicologist, regulator, etc) wants to know what the chances are that a decision is correct.

If the test comes up positive, what is the likelihood that the material is toxic? …or vice versa?

IIVS

Food for Thought

Sensitivity (SN) = % of positives correctly identified
Specificity (Sp) = % of negatives correctly identified

A test with Sn = 90%; Sp = 90%
Prevalence of positives = 20/200 = 10%

Tested Condition	Known Condition: *Positive*	Known Condition: *Negative*
Positive	18	20
Negative	2	180

Positive predictive value = 18/38 = 47% (less than a coin flip)
Negative predictive value = 180/182 = 99%

Food for Thought #2

A "screening" test has to be very sensitive (picks up almost all positives), but doesn't have to be that specific (can have false positives).

A test with Sn = 95%; Sp = 70%
Prevalence of positives = 100/10000 = 1%

Tested Condition	Known Condition: *Positive*	Known Condition: *Negative*
Positive	95	3000
Negative	5	7000

Positive predictive value = 95/3095 = 3.1% Compare with original.
Negative predictive value = 7000/7005 = 99.93%

Method Adoption: Speed Vs. Validation Detail

IIVS

Current Situation For Validation

Path 1

Regional Validation Bodies

- ICCVAM
- ECVAM
- JaCVAM
- KoCVAM
- etc.

Loosely organized under ICATM

Provide information to regional regulators, e.g. EPA, FDA, ECHA.

Also propose test guidelines to OECD

Path 2

Direct Agency Validation

- EPA
- FDA
- CPSC

Especially for agency-specific test requirement

Example EPA's anti-microbial cleaning products eye irritation program.

Also propose test guidelines to OECD

IIVS

Key Concepts for Successful Adoption

- Must provide a value to the user: faster, more predictive, fewer animals, etc.
- Validation process should be transparent; determined by blinded challenge testing, not post hoc.
- All stakeholders should participate
- It helps to have champions within agencies, industry, etc.
- Regulatory reviewers must be adequately trained to understand the method and the supporting data

IIVS

NICEATM

National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods

Introduction to NICEATM and ICCVAM

RADM William S. Stokes, D.V.M., DACLAM
Director, NICEATM
Executive Director, ICCVAM
(Presented by Ray Tice, NTP)

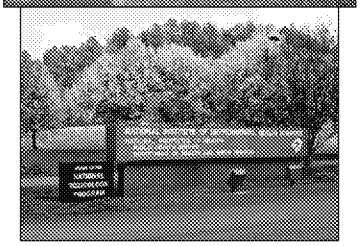
Pew Workshop on Enhancing FDA's Evaluation of Science to Ensure Chemicals Added to Human Food are Safe

April 6, 2011
Washington, DC

What is ICCVAM?

- The **I**nteragency **C**oordinating **C**ommittee on the **V**alidation of **A**lternative **M**ethods was established by the NIEHS in 1997
- Members represent the heads of 15 U.S. Federal regulatory and research agencies
- Duties prescribed by law:
  - Advise on test method development and validation
  - Conduct technical reviews of new safety testing methods
  - Transmit formal recommendations to Federal agencies
  - Promote regulatory acceptance of valid methods
  - Foster national and international harmonization of test methods
- Began as ad hoc committee, 1994
- Standing committee, 1997
- ICCVAM Authorization Act of 2000
  - Permanent committee under NICEATM

What is NICEATM?



- The **N**ational Toxicology Program (NTP) **I**nteragency **C**enter for the **E**valuation of **A**lternative **T**oxicological **M**ethods
- A Center of the U.S. NTP, headquartered at the National Institute of Environmental Health Sciences, NIH, DHHS
  - NIEHS is one of the 27 NIH Institutes and Centers
  - NTP coordinates toxicology testing programs across the federal government
  - Located in Research Triangle Park, North Carolina
- Administers and provides scientific support for the **Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)**
- Conducts international validation studies

National Toxicology Program NTP

The 15 ICCVAM Member Agencies

Regulatory Agencies (7)

- Consumer Product Safety Commission
- Department of Agriculture[1]
- Department of the Interior[1]
- Department of Transportation
- Environmental Protection Agency[1]
- Food and Drug Administration[1]
- Occupational Safety and Health Administration

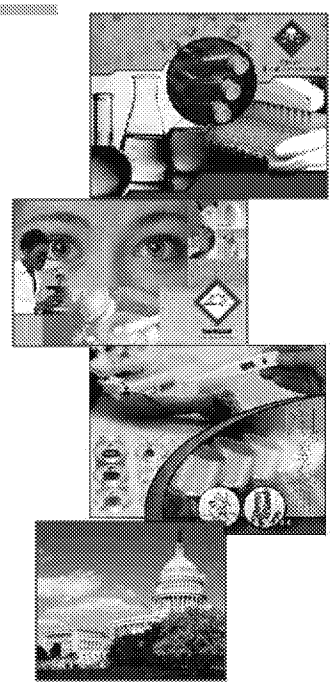
Research Agencies (8)

- Agency for Toxic Substances and Disease Registry
- National Institute for Occupational Safety and Health-CDC
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Library of Medicine
- National Institutes of Health
- Department of Defense
- Department of Energy

[1] Also has research component

NICEATM and ICCVAM Progress

- 40 alternative safety testing methods accepted/endorsed by U.S. and international agencies since 1999
  - Can significantly reduce, refine, and replace animal use
  - Most adopted as international test guidelines and guidances
- Recommendations for R&D, translation, and validation activities to further advance methods



What is Validation?

- A determination of the usefulness and limitations of a test method for a specific purpose[1]
- The process by which the *reliability* and *relevance* of a test method are established for a specific purpose[1]
  - *Reliability:* A measure of the extent to which a test method can be performed reproducibly within and among laboratories over time.
  - *Relevance:* The extent to which a test method will correctly predict or measure the biological effect of interest.
- Adequate validation of a new test method is a prerequisite for it to be considered for use in regulatory decision-making by U.S. Federal agencies.
  - *Agencies must determine the method to be valid for its intended purpose prior to requiring, recommending, or encouraging its use* (P.L. 106-545)

[1]ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods; NIH Pub. No. 03-4508, 2003, NIEHS, Research Triangle Park, NC. http://iccvam.niehs.nih.gov/docs/guidelines/subguide.htm

ICCVAM Validation Criteria[1]

1. Clear statement of proposed use
2. Biological basis/relationship to effect of interest
3. Formal detailed protocol
4. Reliability assessed
5. Relevance assessed
6. Limitations described
7. All data available for review
8. Data quality: *Ideally GLPs*
9. Independent scientific peer review

[1]Adopted from: Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods; NIH Pub. No. 97-3981, 1997, NIEHS, Research Triangle Park, NC. http://iccvam.niehs.nih.gov/docs/guidelines/validate.pdf

ED_002435_00000659-00054

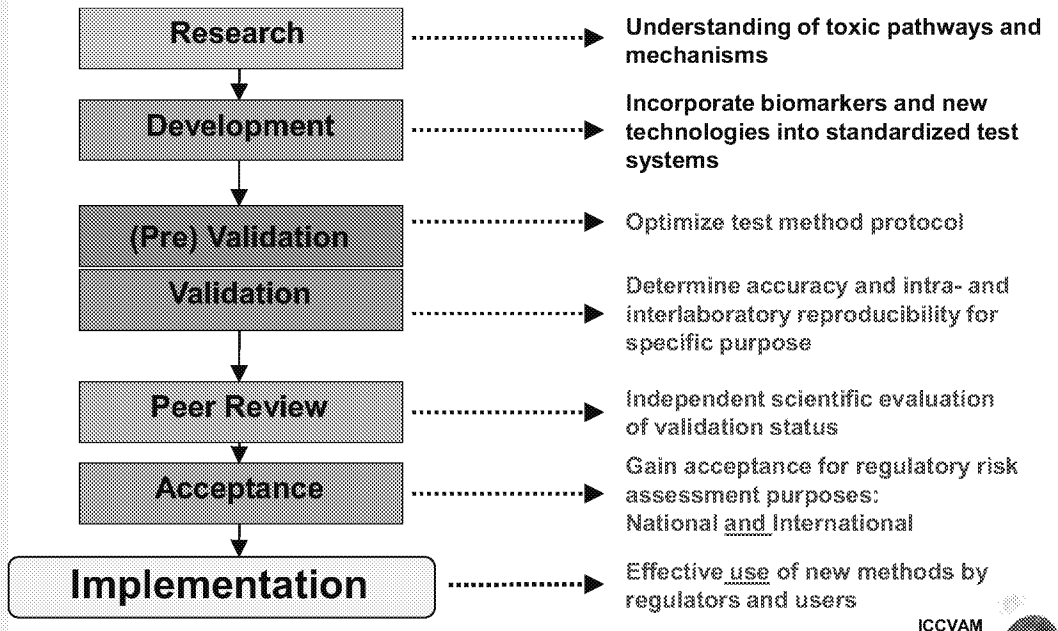
ICCVAM Acceptance Criteria[1]

1. Fits into the regulatory testing structure
2. Adequately predicts the toxic endpoint of interest
3. Generates data useful for risk assessment
4. Adequate data available for specified uses
5. Robust and transferable
6. Time and cost-effective
7. Adequate animal welfare consideration (3Rs)

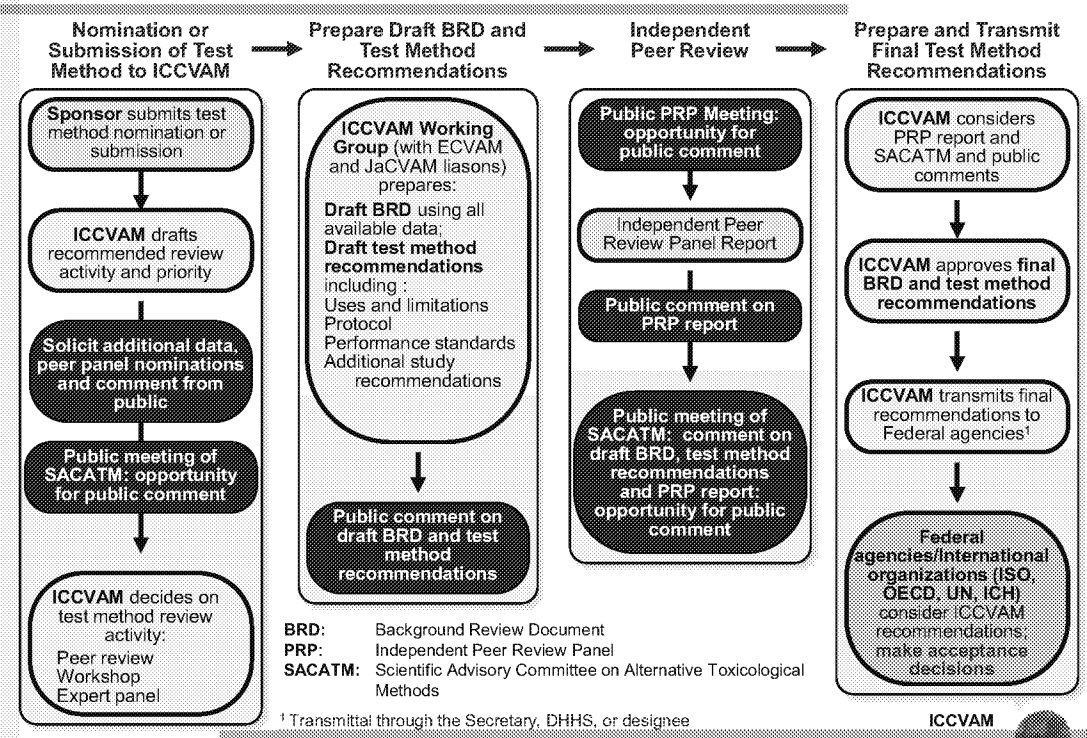
   The proposed use of the test method will provide for equivalent or improved protection of human and/or animal health, or the environment.

[1]Adopted from: Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods; NIH Pub. No. 97-3981, 1997, NIEHS, Research Triangle Park, NC. http://iccvam.niehs.nih.gov/docs/guidelines/validate.pdf

Translating New Science and Technology Into Regulatory Safety Assessment Methods and Approaches



ICCVAM Test Method Evaluation Process

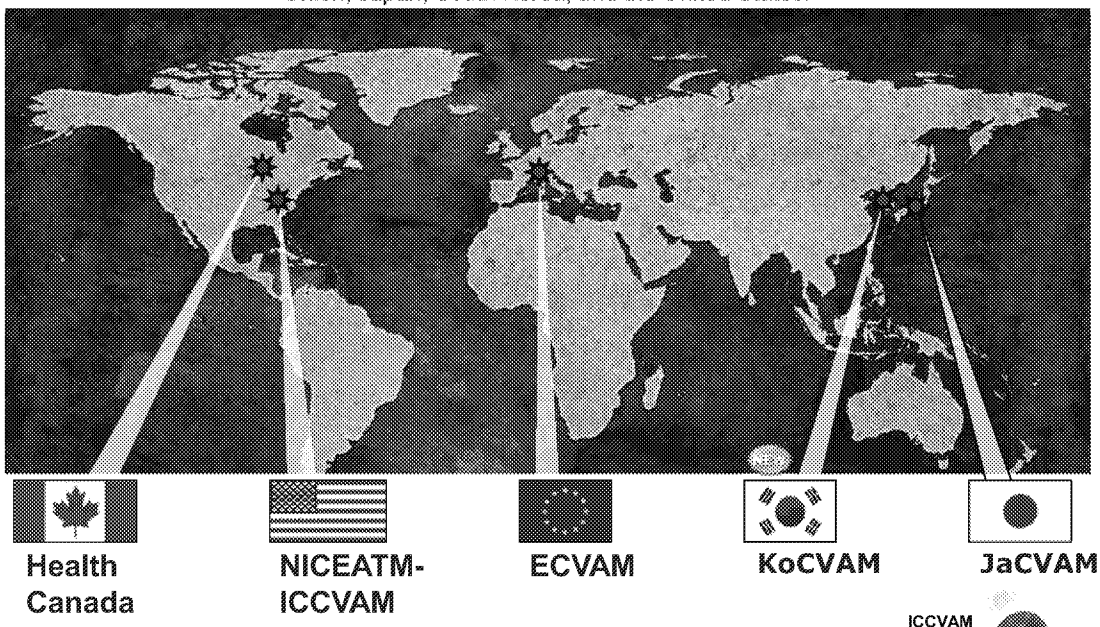


BRD: Background Review Document
PRP: Independent Peer Review Panel
SACATM: Scientific Advisory Committee on Alternative Toxicological Methods

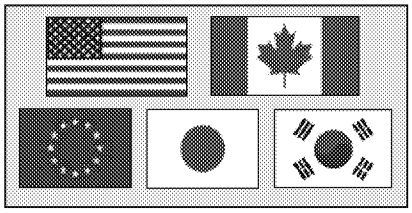
[1] Transmittal through the Secretary, DHHS, or designee

International Cooperation on Alternative Test Methods (ICATM)

ICATM is a **voluntary** international cooperation of national organizations: Canada, the European Union, Japan, South Korea, and the United States.



International Cooperation on Alternative Test Methods: Purposes and Goal



- Promote consistent and enhanced cooperation, collaboration, and communication among national validation organizations
- Achieve greater efficiency and effectiveness
- Incorporate transparency and stakeholder involvement
- Speed international adoption of valid alternative methods
- Complete the translation of science and technology into improved public health prevention tools
- Goal: Maintain/improve protection of people, animals, and/or the environment while reducing, refining, and replacing animals where scientifically feasible

ICCVCAM and ICATM Contributions: Adoption of International Test Guidelines, 2009-2010

Allergic Contact Dermatitis (skin sensitization)

TG 429: Skin Sensitization (LLNA) → Up to 40% decrease in animals used

TG 442A: Skin Sensitization (LLNA: DA)
TG 442B: Skin Sensitization (LLNA: BrdU-ELISA) → " Green" test methods (radioisotopes not required)

Skin Irritation

TG 439: *In Vitro* Skin Irritation → First *in vitro* test methods for this purpose

Genetic Toxicity

TG 487: In Vitro Mammalian Cell Micronucleus Test → Non -animal alternative to the in vivo micronucleus test

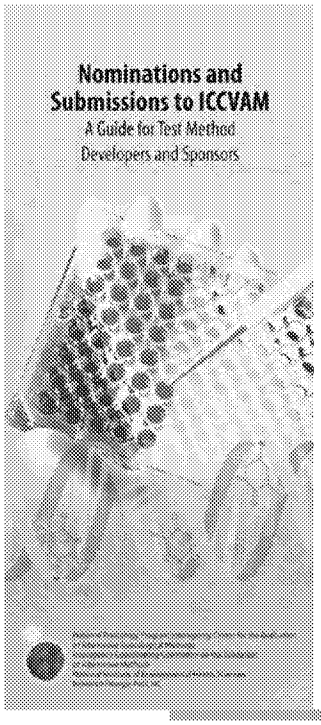
Ocular Toxicity

TG 437: Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants

TG 438: Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants

→ Ocular corrosives and severe irritants can be identified without testing in animals

Nominations and Submissions to ICCVAM



- Advances in science and technology are expected to yield new methods applicable to regulatory safety testing
  - Tox 21, ToxCast, etc.
- NICEATM and ICCVAM seek nominations and submissions for:
  - Validation studies
  - Formal evaluations
  - Other activities
- Of particular interest are methods with potential to:
  - Provide improved safety or hazard assessment
  - Reduce, refine, and replace the use of animals
- Nominations and Submissions accepted from any individual or organization
- Contact NICEATM for more information

Thank you for your attention.

NICEATM-ICCVAM

http://iccvam.niehs.nih.gov/

Email: niceatm@niehs.nih.gov

This presentation may not necessarily reflect the official position of any U.S. Agency.

Validation of Toxicity Tests: Lessons Learned

Leon H. Bruner DVM, PhD
Senior Vice President Science & Regulatory Affairs
The Grocery Manufacturer's Association

Context

- Role of the toxicologist working in the food industry and in regulatory agencies is similar in the following respects:
  - Make decisions on safety
    - food ingredients
    - finished products
  - Decisions need to be correct in order to ensure that public health is protected

Constraints on the decision-making process

- Knowledge of toxicity is incomplete
- Extrapolation from surrogate testing
  - QSAR and other computer model-based methodologies
  - *In vivo* tests
  - *In vitro* tests
  - Other information that may be available
- Proving the negative

Confidence comes from the generation of data from trusted tests

- Mechanistic basis
- The test conducted in different laboratories returns the same result(s)
- Knowledge that predictions of toxicity will lead to decisions that are protective of public health in a risk assessment

Validation: Studies to assess whether results are reproducible in different laboratories at different times by different investigators and whether the observed results are adverse or can predict adverse effects

Establishing the Validity of a Toxicity Test

- Mechanistic basis:
  - Is defined
  - Related to the endpoint of interest
  - Assessed and agreed by qualified scientists
- Reliability
  - The reproducibility of results obtained from multiple laboratories is demonstrated
- Predictive Capacity:
  - A defined prediction model is tested and shown to deliver correct predictions of toxicity

Testing the validity of a toxicity test is relatively easy if it is sufficiently developed

- What is needed to test validity:
  - Clearly defined toxicity test (SOPs and protocols) and prediction model
  - Qualified participants
  - Reference set of test substances; identity unknown to participating laboratories
  - Statistical support
  - Logistical support
  - Financial support

What did we learn when test performance was rigorously assessed?

- Despite the claims of test sponsors the results showed some of the toxicity tests:
  - Not reproducible between laboratories
  - Did not provide correct predictions of toxicity

A toxicologist simply cannot trust that toxicity test results serve as the basis for making critical public safety decisions unless the validity of the test has been rigorously assessed

Is the issue under discussing relevant?

Other learning applicable to this workshop

- The issues associated with test validation have been extensively discussed and tested
  - Apply to the field of possible tests:
    - Computer models
    - In Vivo
    - In Vitro
    - Pathways
  - Don't reinvent the wheel
  - Build on what others have already done
  - Innovate, innovate, innovate
  - Keep the science solid

Final thought

- It is easy to assess validity
  - Mechanistic basis
  - Reproducibility
  - Predictive capacity
- It is very difficult to develop valid tests

AGENDA

Orientation for New Members of the Board of Scientific Counselors

National Center for Environmental Health (NCEH)/
Agency for Toxic Substances and Disease Registry (ATSDR)
May 17, 2011 (Tuesday)
Centers for Disease Control and Prevention
4770 Buford Highway, Atlanta, Georgia 30341
(Building 106 - Conference Room 9A)

Tuesday, May 17, 2011

2:10 p.m. – 2:15 p.m.	**Welcome and Introductions** Christopher Portier, Ph.D., Director, NCEH/ATSDR
2:15 p.m. – 2:45 p.m.	**Overview of NCEH/ATSDR, Office of the Director** Tom Sinks, Ph.D., Deputy Director, NCEH/ATSDR
2:45 p.m. – 3:15 p.m.	**Overview of NCEH/ATSDR Divisions** 1) Division of Emergency & Environmental Health Services (10 minutes) Sharunda Buchanan, Ph.D., M.S. 2) Division of Environmental Hazards & Health Effects (10 minutes) Josephine Malilay, Ph.D., M.P.H 3) Division of Health Assessment & Consultation (10 minutes) William (Bill) Cibulas, Ph.D.
3:15 p.m. – 3:30 p.m.	**BREAK**
3:30 p.m. – 4:10 p.m.	4) Division of Health Studies (10 minutes) Anne Sowell, Ph.D. 5) Division of Laboratory Sciences (10 minutes) James (Jim) Pirkle, Ph.D. 6) Division of Regional Operations (10 minutes) Tina Forrester, Ph.D. 7) Division of Toxicology & Environmental Medicine (10 minutes) Moiz Mumtaz, Ph.D.
4:10 p.m. - 4:30 p.m.	**Logistics (Travel and Honoraria)** Sandra Malcom and Shirley Little: Office of Science

Message

From: Flowers, Lynn [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1A4411C874D041B9A8BADFC32B91BD70-FLOWERS, LYNN]
Sent: 3/23/2011 12:11:31 PM
To: Winner, Darrell [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=860556f5cd0f4855839907bcc90b2c41-Winner, Darrell]; Cogliano, Vincent [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=51f2736376ac4d32bad2fe7cfef2886b-Cogliano, Vincent]; Clark, Becki [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a906e07f1cd143b9a3c2ddab813b8140-Clark, Becki]; Jones, Samantha [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=eac77fe3b20c4667b8c534c90c15a830-Jones, Samantha]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]
Subject: FYI----FROM NTP---Action item - 122911 - Correspondence from Greg Dolan
Attachments: [Untitled].pdf

FYI-----we need to keep in mind that the FRN for methanol (noncancer) is going to come out before the press release. See letter form Greg Dolan below....

----- Forwarded by Lynn Flowers/DC/USEPA/US on 03/23/2011 08:08 AM -----

From: Lynn Flowers/DC/USEPA/US
To: "Bucher, John (NIH/NIEHS) [E]" <bucher@niehs.nih.gov>
Date: 03/23/2011 08:08 AM
Subject: Re: FW: Action item - 122911 - Correspondence from Greg Dolan - Pls prepare draft response

John:
I regret to say that the draft press release has not yet made it to our press office for their consideration. We are working on it today but understand that even if we got it to them today, they would likely need a bit of time (maybe as much as two weeks) before the actual release.

If your recall, we have provided a short statement to the insideepa and we have now posted an identical statement has been placed on the internet along with our draft methanol assessment. The statement on our website is as follows:

Notice

[Mar 2011] **UPDATE:** Following a report from the National Toxicology Program (NTP), EPA has placed the external peer review of the draft IRIS Methanol Toxicological Review on hold. The NTP report (referred to in EPA's June 15, 2010 press release) recommended that pathology reviews be carried out to resolve differences of opinion in the diagnoses of certain tumors reported in a methanol research study completed by the Ramazzini Institute. Therefore, EPA and the National Institute of Environmental Heath Sciences plan to jointly sponsor an independent Pathology Working Group (PWG) review of select studies conducted at the Institute. More information regarding the PWG work will be made publicly available in the near future.

We are also planning on releasing a FR Notice announcing the peer review (and additional public comment) on just the noncancer portion of the methanol assessment. At that time, we will edit the above statement to be more specific to indicate our plans for the noncancer portion of the assessment.

Call or email if you have any additional questions. We will keep you up to date.
Lynn

Lynn Flowers, PhD, DABT
Acting Associate Director for Health
National Center for Environmental Assessment
Office of Research and Development
U.S. EPA

Mailing address:
1200 Pennsylvania Ave., NW (8601P)
Washington, DC 20460
Phone: 703-347-8537
FAX: 703-347-8699

Physical location:
Two Potomac Yard (North Building)
2733 S. Crystal Drive
Arlington, VA 22202

From: "Bucher, John (NIH/NIEHS) [E]" <bucher@niehs.nih.gov>
To: Lynn Flowers/DC/USEPA/US@EPA
Date: 03/22/2011 11:09 AM
Subject: FW: Action item - 122911 - Correspondence from Greg Dolan - Pls prepare draft response

Hi Lynn, just wanted to let you know that I am preparing a response to the attached, and I was wondering whether your press release is imminent? Thanks, John
--

------ Forwarded Message
From: "Daye, Joyce (NIH/NIEHS) [E]" <daye1@niehs.nih.gov>
Date: Thu, 10 Mar 2011 12:23:57 -0400
To: "Bucher, John (NIH/NIEHS) [E]" <bucher@niehs.nih.gov>
Cc: "Wolfe, Mary (NIH/NIEHS)" <wolfe@niehs.nih.gov>, "Jung, Paul (NIH/NIEHS) [E]" <paul.jung@nih.gov>
Subject: Action item - 122911 - Correspondence from Greg Dolan - Pls prepare draft response

Please open the attached document. This document was digitally sent to you using an HP Digital Sending device.

------ End of Forwarded Message

[Untitled].pdf

Message

From: Everhart, Cheryl (ATSDR/OA/OD) [bqf5@cdc.gov]
Sent: 4/22/2011 5:18:46 PM
To: Cogliano, Vincent [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=51f2736376ac4d32bad2fe7cfef2886b-Cogliano, Vincent]
CC: Portier, Christopher (CDC/ONDIEH/NCEH) [cip7@cdc.gov]
Subject: Call with Dr. Portier

Good afternoon Vince,

Hope you are ready for a wonderful weekend! Dr. Portier would like to speak with you this afternoon if you have time.

What times are you available this afternoon after 2:30? If so, what number would I be able to reach you?

Thank you,

Regards,

Cheryl Everhart
Executive Assistant to Dr. Christopher Portier
National Center for Environmental Health/
Agency for Toxic Substances and Disease Registry
Office: 770-488-0636
Fax: 770-488-3385
E-Mail: bqf5@cdc.gov

Message

From: Clark, Becki [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=A906E07F1CD143B9A3C2DDAB813B8140-CLARK, BECKI]
Sent: 12/2/2010 9:02:31 PM
To: Flowers, Lynn [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1a4411c874d041b9a8badfc32b91bd70-Flowers, Lynn]; Cogliano, Vincent [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=51f2736376ac4d32bad2fe7cfef2886b-Cogliano, Vincent]; Jones, Samantha [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=eac77fe3b20c4667b8c534c90c15a830-Jones, Samantha]; Bussard, David [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cf26b876393e44f38bdd06db02dbbfe5-Bussard, David]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Gatchett, Annette [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f12d699a71f84e21bddbb876dae7f96c-Gatchett, Annette]
CC: CN=Linda Tuxen/OU=DC/O=USEPA/C=US@EPA; CN=Audrey Hoffer/OU=DC/O=USEPA/C=US@EPA
Subject: Call with John Bucher - the latest news on Ramazzini
Attachments: Appendix 1 updated.doc; RI Proposal EPL - edits23-11-10accepted.doc; Ramazzini Technical agreement-draft-23-11-2010.doc

Becki Clark
Acting Director
National Center for Environmental Assessment
(703) 347-8551

----- Forwarded by Becki Clark/DC/USEPA/US on 12/02/2010 03:57 PM -----

From: "Bucher, John (NIH/NIEHS) [E]" <bucher@niehs.nih.gov>
To: Becki Clark/DC/USEPA/US@EPA
Date: 12/02/2010 03:19 PM
Subject: Files

Becki, Lynn, Vince
Attached are very rough drafts of a Technical agreement that was prepared by the Ramazzini, and a draft protocol for the path data review that was initially prepared by EPL and subsequently modified by Morando, Fiorella and myself, and an addendum with costs for doing a complete pathology data review prepared by the Ramazzini according to the guidelines we discussed on the phone today. As I indicated, this really reflects the maximum work that could be performed and may well be more than is needed to satisfy your needs. John

PS clearly these are rough drafts and should have limited distribution.

Appendix 1 updated.doc | RI Proposal EPL - edits23-11-10acc... | Ramazzini Technical agree...

Message

From: Deener, Kathleen [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=B9A2FF1C086249EA8F6414AFDE8A5E54-DEENER, KATHLEEN]
Sent: 1/3/2011 3:24:59 PM
To: Clark, Becki [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a906e07f1cd143b9a3c2ddab813b8140-Clark, Becki]; Flowers, Lynn [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1a4411c874d041b9a8badfc32b91bd70-Flowers, Lynn]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Cogliano, Vincent [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=51f2736376ac4d32bad2fe7cfef2886b-Cogliano, Vincent]
Subject: Fw: Jan 4 Meeting with The Administrator: Drinking Water Strategy - Contaminants Group Discussion
Attachments: Jackson DW Strategy Groups Jan 4 2011 v7.ppt

As mentioned by Fred on our call with OSP this morning...

----- Forwarded by Kathleen Deener/DC/USEPA/US on 01/03/2011 10:19 AM -----

From: Fred Hauchman/DC/USEPA/US
To: Kathleen Deener/DC/USEPA/US@EPA
Date: 01/03/2011 10:00 AM
Subject: Fw: Jan 4 Meeting with The Administrator: Drinking Water Strategy - Contaminants Group Discussion

.....

Fred S. Hauchman
Director, Office of Science Policy
Office of Research and Development
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W. (8104R)
Washington, D.C. 20460
(202) 564-6705 - office
(202) 565-2911 - fax
hauchman.fred@epa.gov

----- Forwarded by Fred Hauchman/DC/USEPA/US on 01/03/2011 09:59 AM -----

----- Original Message -----
From: Eric Burneson
Sent: 12/30/2010 02:36 PM EST
To: Barbara Bennett; Bob Perciasepe; Bob Sussman; Carrie Wehling; Charles Imohiosen; Cynthia Dougherty; Elizabeth Doyle; Eric Burneson; Erica Jeffries; Jennifer Orme-Zavaleta; Miguel Flores; Nancy Stoner; Pamela Barr; Paul Anastas; Peter Grevatt; Peter Silva; Richard Keigwin; Sally Gutierrez; Steve Owens; Steven Bradbury; Wynne Miller; Yvette Selby-Mohamadu
Cc: Bobbi White; CatherineM Davis; Christopher Busch; Diane Thompson; Donald Maddox; Georgia Bednar; Jody Ramsey; Joyce Crowley; Keara Moore; Margie Fehrenbach; Martha Workman; Mike Shapiro; Nathan Gentry; Phil Oshida; Rhonda Robinson; Stephanie Washington; Teri Porterfield; Daniel Gerasimowicz; Ann Campbell; Jordan Dorfman; Simma Kupchan
Subject: Jan 4 Meeting with The Administrator: Drinking Water Strategy - Contaminants Group Discussion

Attached for your information please find the briefing document we have prepared for the January 4 meeting with the Administrator on the Drinking Water Strategy. We have prepared the attached document in coordination with the Office of Research and Development and the Office of Chemical Safety and Pollution Prevention.

Jackson DW
Strategy Groups ...

Eric Burneson
Acting Deputy Director
Office of Ground Water and Drinking Water

202-564-5250

Appointment

From: Burke, Thomas [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=39FFC3DD34EA495B9A31E61B778FBBEC-BURKE, THOM]
Sent: 1/12/2015 8:54:50 PM
To: Burke, Thomas [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=39ffc3dd34ea495b9a31e61b778fbbec-Burke, Thom]; Olden, Kenneth [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8979224c77ea4d559f70cab1688f28aa-Olden, Kenneth]; Cogliano, Vincent [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=51f2736376ac4d32bad2fe7cfef2886b-Cogliano, Vincent]; Perovich, Gina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6e3c19d7f4db41bfa2477aa27ad83945-Perovich, Gina]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]
CC: Flowers, Lynn [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1a4411c874d041b9a8badfc32b91bd70-Flowers, Lynn]

Subject: IRIS and IRIS Workplan
Location: 41209 RRB/via video

Start: 1/20/2015 7:30:00 PM
End: 1/20/2015 8:15:00 PM
Show Time As: Out of Office

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

NOTICE

This report has been written as part of the activities of the EPA Science Advisory Board, a public advisory committee providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use. Reports of the EPA Science Advisory Board are posted on the EPA website at http://www.epa.gov/sab.

ED_002435_00001461-00004

U.S. Environmental Protection Agency
Science Advisory Board
Libby Amphibole Asbestos Review Panel

CHAIR

Dr. Agnes Kane, Professor and Chair, Department of Pathology and Laboratory Medicine, Brown University, Providence, RI

MEMBERS

Dr. John R. Balmes, Professor, Department of Medicine, Division of Occupational and Environmental Medicine, University of California, San Francisco, CA

Dr. James Bonner, Associate Professor, Toxicology, North Carolina State University, Raleigh, NC

Dr. Jeffrey Everitt, Director, Department of Laboratory Animal Science, GlaxoSmithKline Pharmaceuticals, Research Triangle Park, NC

Dr. Scott Ferson, Senior Scientist, Applied Biomathematics, Setauket, NY

Dr. George Guthrie, Focus Area Leader, Geological and Environmental Sciences, National Energy Technology Laboratory, U.S. Department of Energy, Pittsburgh, PA

Mr. John Harris, Principal, LabCor Portland, Inc, Portland, OR

Dr. Tom Hei, Professor and Vice-Chairman, Radiation Oncology, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY

Dr. David Kriebel, Professor and Chair, Dept. of Work Environment, School of Health & Environment, University of Massachusetts Lowell, MA

Dr. Morton Lippmann, Professor, Nelson Institute of Environmental Medicine, New York University School of Medicine, Tuxedo, NY

Dr. John Neuberger, Professor, Preventive Medicine and Public Health, School of Medicine, University of Kansas, Kansas City, KS

Dr. Lee Newman, Professor of Medicine, Division of Environmental and Occupational Health Sciences, School of Public Health, University of Colorado, Aurora, CO

Dr. Michael Pennell, Assistant Professor, Division of Biostatistics, College of Public Health, Ohio State University, Columbus, OH

Dr. Julian Peto, Professor, Department of Epidemiology and Population Health , London School of Hygiene and Tropical Medicine, London, UK

Dr. Carrie Redlich, Professor of Medicine, Internal Medicine, School of Medicine, Yale University, New Haven, CT, United States

ED_002435_00001461-00005

Dr. Andrew G. Salmon, Senior Toxicologist, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA

Dr. Elizabeth A. (Lianne) Sheppard, Professor, Biostatistics and Environmental & Occupational Health Sciences, School of Public Health, University of Washington, Seattle, WA

Dr. Randal Southard, Professor of Soils, AES Dean's Office, University of California at Davis, Davis, CA

Dr Katherine Walker, Senior Staff Scientist, Health Effects Institute, Boston, MA

Dr. James Webber, Research Scientist, Wadsworth Center, New York State Department of Health, Albany, NY

Dr. Susan Woskie, Professor, Work Environment, Health and Environment, University of Massachusetts Lowell, Lowell, MA

SCIENCE ADVISORY BOARD STAFF

Dr. Diana Wong, Designated Federal Officer, U.S. Environmental Protection Agency, Washington, DC

ED_002435_00001461-00006

U.S. Environmental Protection Agency
Science Advisory Board
FY 2012

CHAIR

Dr. David T. Allen, Gertz Regents Professor of Chemical Engineering and the Director of the Center for Energy and Environmental Resources, Department of Chemical Engineering, University of Texas, Austin, TX (Chair since November 2012)

Dr. Deborah L. Swackhamer, Professor and Charles M. Denny, Jr. Chair in Science, Technology and Public Policy, Hubert H. Humphrey School of Public Affairs and Co-Director of the Water Resources Center, University of Minnesota, St. Paul, MN (Chair until September 2012)

MEMBERS

Dr. George Alexeeff, Acting Director, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA

Dr. Pedro Alvarez, Department Chair and George R. Brown Professor of Engineering, Department of Civil & Environmental Engineering, Rice University, Houston, TX

Dr. Joseph Arvai, Svare Chair in Applied Decision Research, Institute for Sustainable Energy, Environment, & Economy, Haskayne School of Business, University of Calgary, Calgary, Alberta, Canada

Dr. Claudia Benitez-Nelson, Full Professor and Director of the Marine Science Program, Department of Earth and Ocean Sciences, University of South Carolina, Columbia, SC

Dr. Timothy J. Buckley, Professor and Chair, Division of Environmental Health Sciences, College of Public Health, The Ohio State University, Columbus, OH

Dr. Patricia Buffler, Professor of Epidemiology and Dean Emerita, Department of Epidemiology, School of Public Health, University of California, Berkeley, CA

Dr. Ingrid Burke, Director, Haub School and Ruckelshaus Institute of Environment and Natural Resources, University of Wyoming, Laramie, WY

Dr. Thomas Burke, Professor, Professor and Jacob I and Irene B. Fabrikant Chair in Health, Risk and Society Associate Dean for Public Health Practice, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

Dr. Terry Daniel, Professor of Psychology and Natural Resources, Department of Psychology, School of Natural Resources, University of Arizona, Tucson, AZ

Dr. George Daston, Victor Mills Society Research Fellow, Product Safety and Regulatory Affairs, Procter & Gamble, Cincinnati, OH

Dr. Costel Denson, Managing Member, Costech Technologies, LLC, Newark, DE

ED_002435_00001461-00007

Dr. Otto C. Doering III, Professor, Department of Agricultural Economics, Purdue University, W. Lafayette, IN

Dr. Michael Dourson, President, Toxicology Excellence for Risk Assessment, Cincinnati, OH

Dr. David A. Dzombak, Walter J. Blenko, Sr. Professor of Environmental Engineering , Department of Civil and Environmental Engineering, College of Engineering, Carnegie Mellon University, Pittsburgh, PA

Dr. T. Taylor Eighmy, Senior Vice President for Research, Office of the Vice President for Research, Texas Tech University, Lubbock, TX

Dr. Elaine Faustman, Professor and Director, Institute for Risk Analysis and Risk Communication, School of Public Health, University of Washington, Seattle, WA

Dr. John P. Giesy, Professor and Canada Research Chair, Veterinary Biomedical Sciences and Toxicology Centre, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Dr. Jeffrey K. Griffiths, Professor, Department of Public Health and Community Medicine, School of Medicine, Tufts University, Boston, MA

Dr. James K. Hammitt, Professor, Center for Risk Analysis, Harvard University, Boston, MA

Dr. Barbara L. Harper, Risk Assessor and Environmental-Public Health Toxicologist, and Division Leader, Hanford Projects, and Program Manager, Environmental Health, Department of Science and Engineering, Confederated Tribes of the Umatilla Indian Reservation (CTUIR), West Richland, WA

Dr. Kimberly L. Jones, Professor and Chair, Department of Civil Engineering, Howard University, Washington, DC

Dr. Bernd Kahn, Professor Emeritus and Associate Director, Environmental Radiation Center, Georgia Institute of Technology, Atlanta, GA

Dr. Agnes Kane, Professor and Chair, Department of Pathology and Laboratory Medicine, Brown University, Providence, RI

Dr. Madhu Khanna, Professor, Department of Agricultural and Consumer Economics, University of Illinois at Urbana-Champaign, Urbana, IL

Dr. Nancy K. Kim, Senior Executive, Health Research, Inc., Troy, NY

Dr. Cecil Lue-Hing, President, Cecil Lue-Hing & Assoc. Inc., Burr Ridge, IL

Dr. Floyd Malveaux, Executive Director, Merck Childhood Asthma Network, Inc., Washington, DC

Dr. Judith L. Meyer, Professor Emeritus, Odum School of Ecology, University of Georgia, Lopez Island, WA

ED_002435_00001461-00008

Dr. James R. Mihelcic, Professor, Civil and Environmental Engineering, University of South Florida, Tampa, FL

Dr. Christine Moe, Eugene J. Gangarosa Professor, Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA

Dr. Horace Moo-Young, Dean and Professor, College of Engineering, Computer Science, and Technology, California State University, Los Angeles, CA

Dr. Eileen Murphy, Director of Research and Grants , Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ

Dr. James Opaluch, Professor and Chair, Department of Environmental and Natural Resource Economics, College of the Environment and Life Sciences, University of Rhode Island, Kingston, RI

Dr. Duncan Patten, Research Professor, Hydroecology Research Program , Department of Land Resources and Environmental Sciences, Montana State University, Bozeman, MT

Dr. Stephen Polasky, Fesler-Lampert Professor of Ecological/Environmental Economics, Department of Applied Economics, University of Minnesota, St. Paul, MN

Dr. C. Arden Pope, III, Professor, Department of Economics, Brigham Young University, Provo, UT

Dr. Stephen M. Roberts, Professor, Department of Physiological Sciences, Director, Center for Environmental and Human Toxicology, University of Florida, Gainesville, FL

Dr. Amanda Rodewald, Professor of Wildlife Ecology, School of Environment and Natural Resources, The Ohio State University, Columbus, OH

Dr. Jonathan M. Samet, Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA

Dr. James Sanders, Director and Professor, Skidaway Institute of Oceanography, Savannah, GA

Dr. Jerald Schnoor, Allen S. Henry Chair Professor, Department of Civil and Environmental Engineering, Co-Director, Center for Global and Regional Environmental Research, University of Iowa, Iowa City, IA

Dr. Gina Solomon, Senior Scientist, Health and Environment Program, Natural Resources Defense Council, San Francisco, CA

Dr. Daniel O. Stram, Professor, Department of Preventive Medicine, Division of Biostatistics, University of Southern California, Los Angeles, CA

Dr. Peter Thorne, Professor and Head, Occupational and Environmental Health, College of Public Health, University of Iowa, Iowa City, IA

ED_002435_00001461-00009

Dr. Paige Tolbert, Professor and Chair, Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA

Dr. John Vena, Professor and Department Head, Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia, Athens, GA

Dr. Robert Watts, Professor of Mechanical Engineering Emeritus, Tulane University, Annapolis, MD

Dr. R. Thomas Zoeller, Professor, Department of Biology, University of Massachusetts, Amherst, MA

SCIENCE ADVISORY BOARD STAFF

Dr. Angela Nugent, Designated Federal Officer, U.S. Environmental Protection Agency, Washington, DC

ED_002435_00001461-00010

TABLE OF CONTENTS

Abbreviations and Acronyms ix
1. EXECUTIVE SUMMARY 1
2. INTRODUCTION 7
3. RESPONSES TO EPA'S CHARGE QUESTIONS 8
3.1. GENERAL CHARGE QUESTIONS 8
3.1.1. Overall Clarity 8
3.1.2. Additional Literature 9
3.2. SPECIFIC CHARGE QUESTIONS 10
3.2.1. Mineralogy 10
3.2.2. Toxicokinetics 12
3.2.3. Noncancer Health Effects of Libby Amphibole Asbestos 14
3.2.4. Carcinogenicity of Libby Amphibole Asbestos 17
3.2.5. Inhalation Reference Concentration (RfC) 21
3.2.6. Inhalation Unit Risk (IUR) 31
4. LONG-TERM RESEARCH NEEDS 38
4.1. EPIDEMIOLOGY 38
4.2. MODE OF ACTION 38
4.3. FUTURE DEVELOPMENT OF A TEM METHOD FOR PCM EQUIVALENCY 38
REFERENCES 40
APPENDIX A: EPA'S CHARGE QUESTIONS A-1

ED_002435_00001461-00011

Abbreviations and Acronyms

AIC	Akaike Information Criteria
ADAF	age-dependent adjustment factor
ATS	American Thoracic Society
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	lower 95% confidence limit of the benchmark concentration
BMD	benchmark dose
BMDL	lower 95% confidence limit of the benchmark dose
BMR	benchmark response
BW	body weight
CHEEC	cumulative human equivalent exposure for continuous exposure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DPT	diffuse pleural thickening
EDS	energy dispersive spectroscopy
EPA	Environmental Protection Agency
FEV1	forced expiratory volume in one second
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ILO	International Labor Organization
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LAA	Libby Amphibole asbestos
LOAEL	Lowest Observed Adverse Effect Level
LPT	Localized Pleural Thickening
MCMC	Markov Chain Monte Carlo
MOA	mode of action
NAS	National Academy of Sciences
NCI	National Cancer Institute
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No Observed Adverse Effect Level
NRC	National Research Council
NTP	National Toxicology Program
OR	odds ratio
ORD	Office of Research and Development
PCM	phase contrast microscopy
PCME	phase contrast microscopy equivalent
POD	point of departure
RfC	reference concentration
ROS	reactive oxygen species
RR	relative risk
RTW	residence time-weighted
SAED	Selected Area Electron Diffraction
SEER	Surveillance, Epidemiology, and End Results
SEM	scanning electron microscopy

ED_002435_00001461-00012

SMR	standardized mortality ratio
SIR	standardized incidence ratio
TEM	transmission electron microscopy
Th1	T Helper Cell Type 1
Th2	T Helper Cell Type 2
TSFE	time since first exposure
UCL	Upper Confidence Limit
UF	uncertainty factor
UF_D	Database uncertainty factor
UF_H	Human inter-individual variability uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WDS	wavelength dispersive spectroscopy
XRD	X-ray diffraction

ED_002435_00001461-00013

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.

ED_002435_00001461-00014

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.

ED_002435_00001461-00016

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.

ED_002435_00001461-00017

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.

ED_002435_00001461-00018

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.

ED_002435_00001461-00019

2. INTRODUCTION

EPA's Office of Research and Development requested the Science Advisory Board (SAB) to review the *Draft IRIS Toxicological Review of Libby Amphibole Asbestos* (hereafter referred to as the draft document). The draft document is based on a comprehensive review of the available scientific literature on the health effects of Libby Amphibole asbestos (LAA), a term used to refer to the mixture of amphibole mineral fibers of varying elemental composition (e.g., winchite, richerite and tremolite) that have been identified in the Rainy Creek complex near Libby, Montana. The draft document provides the scientific and quantitative basis for toxicity values that will be entered into EPA's online Integrated Risk Information System (IRIS) database. Specifically, this draft IRIS assessment provides an overview of sources of exposure to LAA, and characterizes the hazard posed by exposure to LAA for carcinogenicity and noncancer health effects based on the available scientific evidence. The assessment includes the derivation of a chronic inhalation reference concentration (RfC) and an inhalation unit risk (IUR) that can be combined with exposure information in a risk assessment to estimate noncancer hazard and carcinogenic risk, respectively, in humans. The assessment does not address oral exposure to LAA.

In response to the agency's request, the SAB convened an expert panel (the Libby Amphibole Asbestos Review Panel) to conduct the review. The SAB panel discussed its responses to the EPA's charge questions during a February 6-8, 2012 face-to-face meeting and on public teleconferences on May 1, May 8, and July 25, 2012. The SAB Panel's draft report was discussed and approved with clarifying edits by the chartered SAB on a public teleconference on September 25, 2012. Oral and written public comments were considered throughout the advisory process. The SAB Panel and the chartered SAB considered and discussed these comments as part of the process of developing this report.

EPA's charge questions consist of two general charge questions on the organization, presentation, and clarity of the draft document, as well as specific charge questions that focus on: mineralogy and toxicokinetics, hazard assessment of non-cancer and cancer health effects, exposure-response assessment for derivation of an RfC for non-cancer endpoints, cancer weight of evidence classification, mode of action of LAA carcinogenicity, and exposure-response assessment for derivation of an IUR for LAA (see Appendix A). The Executive Summary highlights the SAB's major findings and recommendations. The SAB's full responses to the EPA charge questions are detailed in Section 3 and brief recommendations on long-term research needs are provided in Section 4.

ED_002435_00001461-00020

3. RESPONSES TO EPA'S CHARGE QUESTIONS

3.1. General Charge Questions

3.1.1. Overall Clarity

Question 1. Is the Toxicological Review logical, clear, and concise? Has EPA clearly, and in sufficient detail, presented and synthesized the scientific evidence for health hazards from Libby Amphibole asbestos?

In general, the SAB finds the toxicological review to be well-written, logical and appropriately referenced relative to the health hazards and exposure response of Libby Amphibole asbestos (LAA). However, the SAB has identified sections where extraneous and repetitive materials could be deleted. Examples include the following:

- For Section 3, since the focus of the draft document is on Libby amphibole fibers, it would be better to limit the literature reviews and discussions to those dealing with the family of amphibole asbestos fibers. Chrysotile asbestos fibers are very different from amphibole fibers in terms of their airborne concentration measurement errors and uncertainties, much lower biopersistence, faster clearance, and different translocation pathways.
- There are a large number of studies discussed in Section 4— nine community studies (4.1.4) and two case reports (4.1.5)—that offered no detailed exposure information and cannot be used in the risk assessment.
- Discussions that offer little or no new insights into the toxicology of asbestos should be briefly summarized.
- Some sections are repetitive (e.g., Section 5.4.4 and 5.4.5).

Regarding clarity and sufficient detail in the presentation and synthesis of the scientific evidence for health hazards from LAA, the SAB finds the scientific evidence for health effects of LAA to be reasonably well presented. However, the SAB has identified areas where the draft document could be clarified and some aspects of the EPA's analysis that require more explanation and justification, as provided in the responses to specific questions in subsequent sections. In addition, the SAB has comments on the following areas:

Relevance of Other Literature Related to Amphiboles

- The toxicological review does not make clear the relevance of the extensive literature on the health effects of other amphibole fibers. There are numerous publications on the mode of action of other amphiboles, inhalation studies in rodents, and epidemiological studies of populations exposed to amphiboles environmentally. Literature on epidemiological studies of other amphiboles is particularly useful for model selection for dose-response assessment of LAA due to the small size of the Libby subcohort used in exposure-response modeling.

Early Lifestage Susceptibility

- There is inconsistency in the tone of the conclusions in Section 4.7.1.1 (Lifestage Susceptibility) and in Section 6.3.3 (Applications to Early Lifetime and Partial Lifetime Environmental Exposure Scenarios for IUR) to either support or refute early lifestage susceptibility. The SAB recognizes that no firm conclusion can be drawn about differential risk of adverse health effects after early life stage exposure to LAA compared to exposure during adulthood, due to the limited

ED_002435_00001461-00021

and inconclusive studies on other forms of asbestos. However, the available limited evidence pointing to excess risk for exposures during childhood needs to be considered when considering a margin of safety.

Recommendations

- An overall summary set of tables or figures describing the major cohorts (Libby workers, community, Marysville plant), the types/timelines of exposure, and the studies associated with each would help orient the readers of the document.
- The draft document would benefit from greater usage of graphs and figures to highlight conclusions.
- The section on susceptible populations could be better organized and more succinctly summarized. The section should especially focus on childhood asbestos exposure, the asbestos susceptibility issue most relevant to this EPA document, as this is the topic where there is at least some (albeit limited) data.
- The draft document could be enhanced with quantitative comparison of the environmental exposures that have taken place in other geographic regions of the world (i.e., the Anatolia region of Turkey and Greece) (Sichletidis et al., 2006; Constantopoulos, 2008; Gogou et al., 2009; Carbone et al., 2011; Metintas et al., 2008, 2010, 2012) with the Libby, Montana, community with regard to airborne tremolite. This comparison should include numbers of fibers and fiber size distribution in relation to health effects.
- A table comparing these results with the results from the earlier 1988 EPA analysis (USEPA, 1988) on asbestos would be helpful.

3.1.2. Additional Literature

Question 2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of Libby Amphibole asbestos.

The SAB has identified additional studies to be considered in the assessment:

Adgate, JL; Cho, SJ; Alexander, BH; Ramachandran, G; Raleigh, KK; Johnson, J; Messing, RB; Williams, AL; Kelly, J; Pratt, GC. (2011). Modeling community asbestos exposure near a vermiculite processing facility: Impact of human activities on cumulative exposure. *J Expo Sci Environ Epidemiol* 21: 529-535.

Alexander, BH; Raleigh, KK; Johnson, J; Mandel, JH; Adgate, JL; Ramachandran, G; Messing, RB; Eshenaur, T; Williams, A. (2012). Radiographic evidence of nonoccupational asbestos exposure from processing Libby vermiculite in Minneapolis, Minnesota. *Environ Health Perspect* 120: 44-49.

Antao,VC; Larson,TC; Horton, DK.(2012). Libby vermiculite exposure and risk of developing asbestos-related lung and pleural diseases. *Curr. Opin. Pulmonary Med.* 18:161-167, PMID: 22139761.

Berman, DW (2011). Apples to apples: The origin and magnitude of differences in asbestos cancer risk estimates derived using varying protocols. *Risk Analysis* 31: 1308-1326.

Cyphert,JM; Padilla-Carlin, DJ; Schladweiler, MC; Shannahan, JH; Nyska, A; Kodavanti, UP; Gavett, SH. (2012). Long-term response of rats to single intratracheal exposure of libby amphibole or amosite. *J Toxicol Environ Health* A 75: 183-200. http://dx.doi.org/10.1080/15287394.2012.641203.

ED_002435_00001461-00022

Marchand, LS; St-Hilaire,S; Putnams, EA., et al.(2012). Mesothelial cell and anti-nuclear autoantibodies associated with pleural abnormalities in an asbestos exposed population of Libby MT. *Toxicology Letters* 208: 168-173.

Shannahan, JH; Nyska, A; Cesta, M; Schladweiler, MC; Vallant, BD; Ward, WO; Ghio, AJ; Gavett, SH; Kodavanti, UP. (2012). Subchronic pulmonary pathology, iron overload, and transcriptional activity after libby amphibole exposure in rat models of cardiovascular disease. *Environ Health Perspect* 120: 85-91.

Shannahan, JH; Ghio, AJ; Schladweiler, MC; Richards, JH; Andrews, D; Gavett, SH; Kodavanti, UP. (2012).Transcriptional activation of inflammasome components by Libby amphibole and the role of iron. *Inhalation Toxicology* 24:60-69, PMID: 22168577

Webber, JS; Blake, DJ; Ward, TS; Pfau, JC. (2008). Separation and Characterization of Respirable Amphibole Fibers from Libby, Montana. *Inhal. Toxicol.* 20: 733 - 740.

Zeka A; Gore R; Kriebel D (2011). The two-stage clonal expansion model in occupational cancer epidemiology: results from three cohort studies. *Occupational and Environmental Medicine* 68: 618-24.

3.2. Specific Charge Questions

3.2.1. Mineralogy

Question 1a. Please comment on whether the presentation of the available data on the mineralogy of Libby Amphibole asbestos is clear, concise and accurate.

Section 2, Geology and Mineralogy of Libby Amphibole Asbestos, provides a discussion of the mineralogical and geological aspects of Libby Amphibole. In general, the SAB finds that this section provides an important foundation for understanding the nature of Libby Amphibole asbestos (LAA) as related to evaluation of potential exposures. There are places where the clarity and accuracy of the section can be improved, and these are detailed below.

There is a mismatch between the mineralogical detail embodied in the definition of mineral species and the detail available relative to specific exposures in Libby. Specifically, mineral species define a very specific structure (e.g., amphibole) and a specific composition or range of compositions (e.g., winchite or tremolite). Given that these factors affect a mineral's physical and chemical behavior, they may in principle be factors to consider for potential hazard. The SAB recognizes that this level of detail is not typically available for toxicity studies to allow its application to the evaluation of LAA *per se*. In general, however, the observed unique aspects of amphibole asbestos support the evaluation of LAA through comparison with other amphiboles based on particle morphology and amphibole designation. Nevertheless, the SAB encourages a rigorous and accurate description of LAA in Section 2, perhaps while noting the potential ambiguities in the use of mineral-species names in other studies.

ED_002435_00001461-00023

Comments on the subsections follow:

- Discussions of mineralogy and morphology in Sections 2.2.1.1 and 2.2.1.2 are good, with appropriate discrimination between methods/definitions that are applied to mineral field samples collected from the site versus terms/definitions that are applied to environmental samples collected via air monitoring (line 16 of page 2-9 and lines 4 and 5 of page 2-10).

- Section 2.1 is generally sufficient for providing a background on historical aspects of the mining operations in Libby, Montana.

- Section 2.2 needs modification. This section should lay a foundation for understanding the nature of Libby Amphibole (e.g., mineralogical characteristics such as composition and morphology), information on how the material may vary spatially and temporally (with respect to mining operations), and other factors that may impact exposures. The section does contain much relevant information. There are parts of the section that are incorrect and misleading; recommendations to address these issues include:

  - *Consistent use of terminology associated with particle morphology.* The section mixes a number of terms that address particle morphology, and these are critically important in assessing potential exposures and subsequent impacts. As an example, "fibers (e.g., acicular…)" implies fibrous and acicular are the same, when in conventional usage they are different (e.g., see Veblen and Wyllie, 1993). A tight use of terms that are defined up front should be followed in the EPA document even when a lax use of terms may exist in the literature cited. A partial attempt is provided in Section 2.2.1.2, but it could be expanded and carefully vetted with respect to accepted terminology. The four most important terms to lay out clearly are fibrous, acicular, prismatic and asbestiform. If the report's intent is to note differences in these terms, they should be discussed; if the conclusion is that there are poorly defined distinctions, that topic also should be discussed. One specific example of inaccurate usage is the term "prismatic," which by definition is "prism"-shaped (meaning parallel sides; it is incorrectly used in multiple places).

  - *Double-check all mineral formulae.* There are numerous incorrect compositions in the report; although some of these may be typographic errors (which, of course, should be fixed), some may be incorrectly reported. An example of one incorrect formula is that attributed to vermiculite, which is listed incorrectly as: $[(Mg,Fe,A)_3(Al,Si)_2O_{10}(OH)_2 \cdot 4H_2O]$.

  - *Double check that all mineral-species definitions used are accepted mineralogical standards.* Mineral species are fundamental terms that describe a material with a specific structure and a specific composition or range of compositions; both factors are primary determinants of a material's properties. Indeed, at the heart of this report is the definition of likely exposures to (and risks from) inhaled particles and other fibers based on the use of mineral-species names. The problems in this category are probably most widespread in Section 2.2.1.1, which details amphibole mineralogy (which is central to the report). For example, anthophyllite is not a Libby amphibole.

- The SAB appreciates the discussions that highlighted the complexity and variability of LAA in the context of compositional solid solutions, emphasizing that even the use of mineral-species names for LAA may mislead readers to believe that LAA is represented by a few discrete materials as opposed to a mixture of materials with varying compositions. Overall, the

mineralogy section could benefit from some technical editing. It presents some irrelevant material (e.g., section 2.2.1, which is a general description of silicate mineral hierarchy), omits some critical information (e.g., section 2.2.1.1 does not provide the mineralogical definitions of key minerals like winchite or richterite), and presents some erroneous and irrelevant characterizations (e.g., some of the vermiculite-mineralogy descriptions in section 2.2.2).

- The report provides a good summary of available information on the LAA. One specific observation that could be added is one reported by Sanchez et al. (2008), namely that they observed no correlation between morphology (fibrous vs. prismatic) and major-/minor-element chemistry. Webber et al. (2008) similarly concluded that there was no correlation between mineral species and fiber width for respirable fibers. In other words, this is consistent with the implication that the large set of compositional data from Meeker et al. (2003) shown in the report reflects the range of compositions associated with inhaled-fiber exposures.

- Discussion on page 2-10 glosses over a serious shortcoming of phase contrast microscopy (PCM); namely, its inability to detect fibers narrower than ~0.25 μm. These thin fibers are among the most biologically potent according to the Stanton-Pott hypothesis. The fact that only a third of the Transmission Electron Microscopy (TEM)-visible Libby fibers were PCM-visible is buried in McDonald et al. (1986). Furthermore, Text Box 2-2 does not adequately contrast the capability of EM versus PCM. EM's capability to yield elemental composition via Energy Dispersive Spectroscopy (EDS) and Wavelength Dispersive X-ray Spectroscopy (WDS) provides information to identify different asbestos types. PCM, in contrast, cannot even determine if the fiber is mineral. Furthermore, the Selected Area Electron Diffraction (SAED) capability of TEM allows determination of crystalline structure, e.g., amphibole versus serpentine. Finally, Box 2-2 incorrectly states that scanning electron microscopy (SEM) "produces three-dimensional (3-D) images". Rather, SEM produces 2-D images that reveal surface structure of particles.

- The electron microscopy section on page 2-11 could be clarified. SEM and TEM provide higher resolution to allow better particle morphological analysis. Electron diffraction allows mineralogical assessment. Energy dispersive X-ray analysis allows elemental composition determination, which can corroborate the mineralogical determination. X-ray diffraction (XRD) mentioned in this section is useful for bulk sample mineralogy measurements.

3.2.2. Toxicokinetics

Question 1b. In the absence of toxicokinetic information specific to Libby Amphibole asbestos, the draft assessment contains a general summary description of fiber toxicokinetics. Please comment on whether this overview of general fiber toxicokinetics is clear, concise and accurate.

The discussion of general fiber toxicokinetics is not clear, nor concise, especially since it fails to distinguish between chrysotile and amphibole fibers. Furthermore, it is inaccurate in many places, as noted below.

- In view of the fact that the focus of the document is on Libby Amphibole fibers, it would be better to limit most of the literature reviews and discussions to those dealing with the various kinds of amphibole asbestos fibers. Chrysotile asbestos fibers, which are not a significant complication in exposures to Libby vermiculite, are very different from amphibole fibers in terms of their: (a) airborne concentration measurement errors and uncertainties (HEI-AR, 1991);

(b) much lower biopersistence (Bernstein et al., 2004; 2005a; 2005b); (c) clearance and translocation pathways and rates (Bernstein et al., 2004; 2005a; 2005b).

- There are some misstatements on fiber deposition and dosimetry in the document.
  - The authors should draw on more authoritative and comprehensive reviews in the literature (e.g., Lippmann, 2009; Mossman et al., 2011). One misstatement in the draft is that impaction is affected by fiber length. Another is that interception is affected by aspect ratio. The document should cite the work by Sussman et al. (1991a; 1991b) that demonstrates that interception of amphibole (crocidolite) fibers is only demonstrably in excess when fiber lengths are >10 μm. Also, the report should cite the work of Brody and colleagues (Brody et al., 1981; Brody and Roe, 1983; Warheit and Hartsky, 1990) on chrysotile fiber deposition in the alveolar region in rodents. In terms of deposition sites, there should be no significant difference between chrysotile and amphibole fibers.
  - Another misstatement is that mucociliary clearance is complete within minutes or hours rather than the true time frame of hours to a few days (Albert et al., 1969). The authors also need to acknowledge that particles depositing in the alveolar region can reach the tracheobronchial tree in two ways: (a) on surface fluids drawn onto the mucociliary escalator by surface tension, and (b) by passing through lymphatic channels that empty onto the mucociliary escalator at bronchial bifurcations. The report also should acknowledge that macrophage-related clearance of fibers is only applicable to short fibers that can be fully phagocytosed. Nearly all of the references to chrysotile in the discussion of translocation should be deleted. The Libby asbestos fibers are essentially all amphibole fibers, and there is very little commonality among serpentine and amphibole fibers in terms of translocation or long-term retention.
  - There are also toxicokinetic misstatements in Section 4.2 describing cancer bioassays in animals. The section should cite the inhalation study of Davis et al. (1985) with fibrous tremolite, which is very similar to Libby amphibole. Also, this section should discuss the tremolite inhalation study of Bernstein et al. (2003, 2005) that is cited in Table 4-16, as well as the more recent study by Bernstein et al. (2011) that demonstrated pleural translocation in rats using non-invasive means following airborne amosite asbestos exposure. The study examined animals for up to one year following a short one-week exposure to amphibole and characterized the size of fibers that were present in parietal pleura. Non-cancer inflammatory pleural changes were demonstrated associated with fiber translocation. This paper shows rapid translocation of fibers to the pleura (at least of rodents) and it should be referenced for completeness on toxicokinetic issues. Furthermore, the results of the various studies cited in Section 4.2 are almost all very difficult to interpret with respect to the toxic effects that were, or were not, reported, since no information was provided in Tables 4.15 and 4.16 on the key dosimetric factor of fiber dimensions. There were comprehensive summaries of available information on fiber dimensions of materials administered in the bioassays in Appendix D, including numbers of long fibers, but Section 4.2.5 is deficient as a summary of animal studies for LAA and tremolite because it does not discuss how the content of long fibers in the administered materials had an influence on the effects observed.

ED_002435_00001461-00026

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.

ED_002435_00001461-00027

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.

ED_002435_00001461-00028

3.2.3.2. Use of Animal and Mechanistic Studies

Question 3. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in the draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the RfC. Please comment on whether the laboratory animal and mechanistic information presented is used appropriately in the draft assessment.

The EPA draft document discusses the different types of minerals present in LAA and it is uncertain how the various components relate to adverse health effects. LAA contains ~6% tremolite and there is clear evidence from human and animal studies that tremolite causes adverse health effects in humans and experimental animals. However, since LAA also contains winchite (84%) and richterite (~11%), it would be prudent to determine whether these mineral forms contribute to the adverse health effects of LAA or whether there are interactive effects of winchite or richterite that modify the toxicity of tremolite. The SAB recommends that this issue be highlighted since it is well-known that tremolite is highly fibrogenic and causes malignant mesothelioma (MM). However, the contribution of winchite or richterite to adverse health effects is apparently unknown.

In general, the listing of the laboratory animal studies in Tables 4-15 and 4-16 and the underlying data summary in Appendix D are appropriate and complete. However, Tables 4-15 and 4-16, and the summary data in Appendix D do not include the distributions of fiber lengths, and Section 4.2.5 is therefore deficient as a summary of animal studies for LAA and tremolite, in terms of not discussing how the content of long fibers in the administered materials had an influence on the effects observed. The report text in Section 4.2.5 also is deficient in not discussing how the contents of long fibers in the administered materials had an influence on the effects observed. Therefore, the issue of the influence of fiber dimensions, and especially of fiber length, needs to be strengthened. The LAA fiber dimensions, listed in Table D-5 (page D-6) should be moved to the main text in Section 4.4, Mechanistic Data and Other Studies in Support Of the Mode of Action. A recent paper by Berman (2011), which was not cited in the draft report, suggests that cancer risk coefficients for various amphiboles are more consistent when fiber length was taken into consideration. Berman (2011) also suggests that the health risks presented by amphibole are greater than those of chrysotile.

Laboratory animal studies utilizing various stocks and strains of mice and rats as well as hamsters, by 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 with the LAA mixture with this route of fiber administration in experimental animals. However, there has been intratracheal instillation of LAA in short-term studies with mice and rats that resulted in airway inflammatory change consistent with earlier changes seen in tremolite-exposed animals. The lack of any inhalation data in rats or mice is an important issue, since the deposition of particles and fibers cannot be adequately addressed using intratracheal instillation of a bolus of fibers delivered in aqueous suspension. For example, the development of pleural lesions may be quite different when comparing fibrogenic or carcinogenic fibers or other particles by inhalation versus instillation. Since inhalation studies have been conducted with tremolite fibers (e.g., Bernstein et al., 2005) and the fact that 6% of LAA are tremolite, the potency of inhaled LAA from epidemiology studies should be compared to that of tremolite fibers in rodents. This relative potency of LAA could add new information for refining the RfC for LAA. Additional parameters in better defining the RfC can be found in Section 3.2.5.1.

In vitro assay systems utilizing both primary cells and established human and mammalian cell lines have been used to provide mechanistic insights on the potential mode of action of LAA. These limited *in vitro* studies have demonstrated the importance of fiber-cell interactions, the ability of LAA to induce reactive radical species, inflammatory gene expression, and micronuclei, a marker of genomic instability. Unfortunately, with the exception of the latter, most of these endpoints are non-specific and can be demonstrated with any particles including glass fibers in short-term assays. Similarly, Section 4.4.1 (page 4-63) mentions increases in Th1 and Th2 cytokines that are not specific to the effects of LAA or other types of asbestos, but rather generalized mediators of non-allergic or allergic inflammatory responses. Likewise, pro-inflammatory cytokines (e.g., interleukin-8), enzymes (e.g., cyclooxygenase-2) and oxidative stress markers (e.g., heme oxygenase) are biomarkers of a wide variety of cellular stress and inflammation responses that will probably not shed much light on the mechanisms of LAA-induced disease. 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 reported/ examined with LAA.

3.2.4. Carcinogenicity of Libby Amphibole Asbestos

3.2.4.1. Weight of Evidence Characterization

Question 1. Under EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005; www.epa.gov/iris/backgrd.html), the draft IRIS assessment characterizes Libby Amphibole asbestos as "carcinogenic to humans" by the inhalation route of exposure. Please comment on whether the cancer weight of evidence characterization is scientifically supported and clearly described.

Human epidemiological data supersede animal and other laboratory studies in the identification of a human carcinogen/toxicant. For LAA, the SAB agrees with the EPA that, while there are no concrete laboratory studies that unequivocally demonstrate carcinogenicity of the fiber mix, there are strong epidemiological data that support the notion that LAA fiber is closely linked to cancer incidence and mortality in humans under occupational settings. The occupational studies appeared most persuasive at showing dose-related increased risks of lung cancer and mesothelioma among workers exposed by inhalation. However, the number of mesothelioma cases is small. The case series in the community, while supportive, do not provide the same level of evidence for an association or for the strength of the association. Nonetheless, the epidemiologic evidence from the occupational studies does support the choice of descriptor "carcinogenic to humans by the inhalation route" for LAA under the conditions of exposure in those studies.

On the other hand, the only solid evidence that the LAA is carcinogenic to animals is in hamsters injected intraperitoneally with a single 25-mg dose of the fiber mix, which is not a physiologically relevant route of exposure in humans. Although inflammation of the lung has been demonstrated using both mice and rats exposed to LAA by intra-tracheal instillation, these short-term studies failed to demonstrate any cancer induction. The SAB, however, concurs with the EPA report that these findings—which include altered gene expression, collagen induction, and inflammation—are consistent with the early-stage disease process induced by other amphibole fibers. As such, the EPA has derived additional supporting evidence for the carcinogenic potential of LAA from studies with tremolite fibers. Although the SAB recognizes that these studies provide circumstantial, supporting evidence of the carcinogenic potential of LAA in light of its ~6% tremolite by composition, the

ED_002435_00001461-00030

limited data base on LAA *per se* cannot provide a well defined mode of action for either lung cancer or mesothelioma induction, as will be discussed in the following section.

3.2.4.2. Mode of Carcinogenic Action

Question 2. Due to the limitations of the data available, the draft assessment concludes that there is insufficient information to identify the mode of carcinogenic action of Libby Amphibole asbestos. Please comment on whether this determination is appropriate and clearly described. Note that in the absence of information to establish a mode of action, a linear low dose extrapolation is recommended by the Guidelines for Carcinogen Risk Assessment (U.S., EPA, 2005; Section 3.3). If it is judged that a mode of action can be established for Libby Amphibole asbestos, please identify the mode of action and its scientific support (i.e., studies that support the key events, and specific data available to inform the shape of the exposure-response curve at low doses).

A formal mode of action analysis in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) has not been conducted in the draft assessment. The mechanisms by which amphibole fibers produce malignancy and fibrosis are complex and likely to be multifactorial in nature. The induction of reactive radical species through persistent interaction of fibers with target cells, the involvement of chronic inflammatory response, the activation of certain oncogenes and inactivation of yet-to-be-identified suppressor gene(s), have been proposed as possible mechanisms. In addition, various *in vitro* and *in vivo* studies have shown that fiber dimensions, surface properties, shape and crystallinity, chemical composition, physical durability, and exposure route, duration, and dose are important determinants of the biological potency of fibers.

With the LAA, neither the fairly limited amount of research conducted using *in vivo* as well as *in vitro* assays that are described in the review, nor the more extensive body of published work on other asbestiform minerals, which is also summarized, lead to clear conclusions as to a single mode of carcinogenic action. The SAB agrees with the EPA conclusion that the laboratory-based weight of evidence for the mode of action of LAA is weak. Given the limited data base available in the literature and some limited support from data on carcinogenesis by other amphiboles, the EPA's conclusion that there is insufficient information to identify the mode of carcinogenic action of LAA may be justified. However, there are extensive data suggesting multiple mechanisms of carcinogenic action of other amphibole asbestos fibers (IARC, 2012). The SAB finds that, given the available information, the default linear extrapolation at low doses may be appropriate.

Recommendation:

- A formal mode of action analysis for LAA should be conducted in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005).

3.2.4.3. Selection of Critical Study and Endpoint

Question 3. An occupational cohort of workers from Libby, MT exposed to Libby Amphibole asbestos (i.e., the Libby worker cohort) was selected as the basis for the derivation of the inhalation unit risk (IUR). 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 IUR, please identify this study and provide scientific support for this choice.

The selection of the Libby cohort is scientifically supported and clearly described. It appears to be the best cohort available for cancer outcomes. This cohort has been thoroughly studied previously, had

ED_002435_00001461-00031

detailed work histories with a job exposure matrix available, had elevated asbestos exposure, had a wide range of measurements of asbestos exposure (covering a range of two orders of magnitude), was large, and had cancer mortality data available. Limitations of this cohort include the possible environmental exposures to asbestos and limited smoking information available, especially given that smoking is an important risk factor for lung cancer (but not for mesothelioma) and also may have a synergistic effect with asbestos exposure. Also, outcomes are based on death certificates, which could undercount incidences of relevant endpoints.

Libby Amphibole asbestos is the only possible source of the asbestos measured in the air samples (i.e., there are no other sources of asbestos at the mine and associated facilities). It should be noted, however, that this study population may not be representative of the larger population, since most of its members are white males, exposed as adults, and it contains a higher proportion of cigarette smokers than the larger population. If a residential study is ever completed that includes a larger proportion of women, other races, and those exposed as children, the derivation of the IUR should be revisited. Additionally, it is noted that the endpoints are based on cancer mortality noted on death certificates. While this could lead to an undercounting of actual cases of lung cancer, it seems less likely that lung cancer in a heavily asbestos-exposed population would either be missed on a death certificate or would significantly undercount incidence more so than in the comparison population. Mesothelioma cases might not have been fully accounted for using death certificates, as mesothelioma did not have a distinct classification (International Classification of Diseases, or ICD) code prior to ICD-10, implemented in 1999. However, death certificates were manually reviewed, as noted, and possible under-ascertainment of mesothelioma cases was addressed in the modeling.

Use of the subcohort post-1959 seems reasonable due to the lack of exposure information for many of the workers in earlier years. Out of 991 workers hired before 1960, 811 had at least one job with an unknown job assignment and of these 706 had all department and job assignments listed as unknown. It would seem highly problematic to include workers with limited or no job information in the model. However, at least some information existed for the remaining 285 workers.

The EPA should strengthen the analysis to calculate an overall Standardized Mortality Ratio (SMR) for the Libby worker full- and sub- cohorts for lung cancer, using both Montana and U.S. data for comparison. The later cohort also had lower levels of exposure to asbestos, which would be closer to the lower levels found in the environment.

Question 4. Mortality from lung tumors and mesothelioma in the Libby worker cohort was selected to serve as the basis for the derivation of the IUR. Please comment on whether this selection is scientifically supported and clearly described. If a different health endpoint is recommended for deriving the IUR, please identify this endpoint and provide scientific support for this choice.

Lung cancer and mesothelioma are entirely appropriate endpoints for derivation of the IUR. They are scientifically supported and clearly described. Mesothelioma is caused by asbestos exposure. While it is possible to consider an alternative model focused on mesothelioma alone to derive the IUR, the number of deaths from mesotheliomas is small and this would likely understate the overall cancer risk.

Since determining the cancer outcome from mortality rather than incidence data may have resulted in an undercount of both cancer outcomes, the discussion would benefit from more detail on how the use of incidence data could impact the derived IUR. In addition, the mesothelioma outcome may be underrepresented because the cohort has been followed for 25 to 46 years, and lag times from exposure

to detectable disease onset range from 15 to greater than 60 years. Mesothelioma also may have been underreported on death certificates. Under-represented outcomes could lead to an underestimated IUR. While there is sufficient information for derivation of the IUR, revisiting derivation of the IUR after additional follow-up is warranted. Additional follow-up of both the occupationally and environmentally exposed populations should be encouraged.

The report mentions laryngeal (n = 2) and ovarian (n = 0) cancer deaths in the text. The number of deaths from these two cancer types should be included in Table 5-6. The International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence in humans that some types of asbestos were causally associated with cancer of the larynx and the ovary as cited in the publication by Straif et al. (2009). However, no ovarian cancer deaths and only 2 laryngeal cancer deaths were observed in the Libby worker cohort.

Recommendation:

- Tables 5-6 and 5-8 are mis-titled, since the tables include the number of deaths from mesothelioma and lung cancer as well as demographic and exposure data. The titles should either be changed and additional causes of death included in the tables or new tables should be created that focus on the causes of death. Provision of data on other major categories of mortality, including numbers of COPD, cardiovascular, colorectal cancer and other cancer deaths, could provide useful information on the representativeness of the mortality experience of these cohorts.

3.2.4.4. Use of Laboratory Animal and Mechanistic Studies

Question 5. The database of laboratory animal and mechanistic studies of Libby Amphibole asbestos is summarized in this draft assessment (see Section 4.2 and 4.3, details in Appendix D) to inform the mechanisms of the biological response to Libby Amphibole asbestos and support the epidemiology studies used for derivation of the IUR. Please comment on the use of laboratory animal and mechanistic information in the draft assessment.

The SAB agrees, with some exceptions, that the database of laboratory animal and mechanistic studies pertaining to LAA is appropriately presented for support of the analysis of the human effects observed. These studies are informative in identifying similar mechanism and progression of pathological changes in animals as are seen in humans, and help in establishing that similar pathological endpoints are seen with other amphibole fibers. Although the mechanistic studies fall short of delineating a complete mode of action, they are useful in identifying some common themes and potential key mechanisms in asbestos toxicity and will undoubtedly be valuable in guiding future research on this topic.

It is generally accepted that the toxicity and carcinogenicity of mineral and synthetic vitreous fibers are governed by fiber dimensions, *in vivo* durability, and dose, and that all long amphibole fibers are very durable *in vivo*. Thus, the differences in biological potency among the various amphibole fiber types are due primarily to their differences in dimensions, especially in their fiber length distributions (Berman, 2011). The SAB noted that the text in Sections 4.2 and 4.3, and the tables cited therein, are deficient in not citing all that is known about the dimensions of the administered fibers.

ED_002435_00001461-00033

Recommendations:

- Section 4.2 should start with a discussion of the relevance of routes of exposure, and then should proceed to discuss inhalation data, followed by a discussion of data from other, less relevant routes of exposure.
- Areas of needed improvement in the report include: (1) a discussion on known determinants of fiber toxicity; and (2) the differences in fiber size distributions between LAA and other known amphiboles.
- Section 4.6.2.2 should be modified to reflect that there are insufficient data to determine if a mutagenic mode of action for LAA is supported.

3.2.5. Inhalation Reference Concentration (RfC)

3.2.5.1. Estimates of Human Exposure Concentration

Question 1. Exposures to Libby Amphibole asbestos for workers in the Marysville, OH facility were reconstructed based on industrial hygiene data collected in the facility from 1972 to 1994. Exposures from 1957 to 1971 were estimated based on extrapolation from the available industrial hygiene data. The information used for the exposure reconstruction was based on employee interviews, court and company records, and the expert judgment of the researchers. Is the methodology used for the exposure reconstruction reported in Appendix F and the subsequent development of exposure estimates used in the analyses scientifically supported and clearly described?

The approach described in the Appendix F of the EPA document is detailed and specific. The strengths and weaknesses of the approach are clearly laid out. Large uncertainties are associated with the *unmeasured* pre-1972 exposures: subjectivity of workers' estimating relative concentrations, and unsupported weighting of Libby/South Carolina fiber concentrations. Hence the report appropriately eliminates this set of estimates and adheres to only measured exposures for its derivation of RfC.

The development of cumulative exposure estimates for the workers in a retrospective study has as its goal the estimation of the area under the curve of the plot of each individual worker's annual exposure concentration vs. time (calendar year), producing a summary metric of cumulative fibers/cc-years. In Appendix F of the EPA document, the authors report using the natural-log-transformed exposure data to calculate the geometric mean for the job groups for use in developing the cumulative exposure metric. This approach could introduce bias by decreasing the significance of the highest exposures if the sampling data represent a random sample of the true underlying distribution of exposures. However, most company industrial hygienists historically have focused sampling on evaluating compliance using a methodology that targets the worst case or "most exposed" workers (NIOSH, 1977; Mulhausen and Damiano, 1998). In such a case, use of the mean of the unlogged data, or preferably the minimum variance unbiased estimator (MVUE) of the mean (Attfield and Hewett, 1992), would overestimate the most likely exposure of the average worker. The EPA should 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, and consider whether a sensitivity analysis using the MVUE of the mean is warranted in the development of the cumulative exposure metric.

There should be a table summarizing the changes in proportion of each type of vermiculite used (South Carolina, Libby and African) at the Marysville plant throughout the time frame represented by the cohort. This section should explicitly discuss the fact that Libby vermiculite usage ended in 1980, and

that the fiber counts used in the cumulative exposure calculation for the production workers, though small, are generally 1.5 to 6.3 times higher than background. These fibers are presumably from combinations of African/Virginia/South Carolina vermiculite that were used from 1980 to 2000. Likewise, the description of the calculation of the cumulative human equivalent exposure concentration (CHEEC) in Section 5.2.3.1 would benefit by addition of a version of the material on page F-19 to clarify the correction factors and breathing rate adjustments made due to extended work hours during some seasons. The approach used has the typical drawbacks of oversimplification of breathing rate (one size fits all) but is consistent with previous EPA approaches.

The SAB recommends that the EPA consider sensitivity analyses of additional exposure metrics such as: no exposure since 1980 in any cohort members (based on end date of processing of Libby vermiculite), and alternative weighting schemes [particularly ones weighting earlier life exposures more heavily given the importance of time since first exposure, e.g., residence time weighting (RTW)]. These sections also could be enhanced by showing relationships between the exposure metrics, such as by scatter plots of unlagged CHEEC vs. other measures (separately by cohort) and by adding more explanation about the effects of lagging.

Recommendations:

- Re-evaluate the raw exposure data and review pertinent sampling documentation to bolster the use of the geometric mean to represent the job group exposure. Consider whether a sensitivity analysis using the MVUE of the mean is warranted in the development of the cumulative exposure metric.
- Add a table summarizing the changes in proportion of each type of vermiculite used at the Marysville plant over time. Clarify the correction factors and breathing rate adjustments made due to extended work hours.
- Consider sensitivity analyses of additional exposure metrics, particularly those weighting earlier life exposures more heavily.

3.2.5.2. Exposure-Response Modeling

Question 2. Exposure-response modeling was conducted using the incidence of localized pleural thickening in workers and cumulative exposure to estimate the point of departure (POD) for derivation of the RfC. EPA's estimate of the POD is based upon a Michaelis-Menten model applied to the subcohort of workers examined in 2002-2005 and first exposed to Libby Amphibole asbestos in 1972 (when measurements of fiber levels in the workplace began) or later with cumulative exposure as the explanatory variable. Is the selection of the model scientifically justified and clearly described? Has the modeling and the choice of a benchmark response (BMR) for the POD of 10% extra risk of localized pleural thickening been clearly described and appropriately conducted according to EPA's Draft Benchmark Dose Technical Guidance (U.S. EPA, 2000b)?

This response focuses on the primary analysis of the Marysville subcohort. Additional comments on the analysis of this cohort can be found in response to Question 4 in Section 3.2.5.4. The SAB found that the various exposure-response models that were examined were reasonably well described. However, the SAB recommends a clearer description of how the "best" model was chosen. It appears that EPA fits a series of quantal response models, retained models with adequate fit according to the Hosmer-Lemeshow test (presumably based on $p > 0.1$, but, if so this should be stated). Then, among the retained models, the authors selected the model with the lowest Akaike Information Criteria (AIC). From a

statistical standpoint, this methodology can be justified. However, it is not clear how well aligned it is with the guidance for selection of the POD in the updated version of EPA's *Benchmark Dose Technical Guidance* (USEPA, 2012). Thus the SAB recommends the EPA revise the approach to be better aligned with the *Benchmark Dose Technical Guidance* document.

Consistent with the tone of the *Benchmark Dose Technical Guidance* (USEPA, 2012), the SAB recommends that a thoughtful approach to model selection be used, including consideration of biological/epidemiological plausibility, and desirable model features, combined with careful examination of the data, model fit, and application of the AIC. The SAB highlights the following points:

- Model fit (visual comparison of model predictions to data and/or local smoother estimates from data) in the region of the benchmark response rate (BMR) should play a role in model selection.

- The fitted Michaelis-Menten model has an upper plateau of 60% LPT incidence, while a study of highly exposed asbestos insulation workers reported a prevalence of 85% (Lilis et al., 1991a). The Marysville cohort does not support precise estimation of the plateau. Thus, EPA should consider fixing the plateau at a level justified by the literature.

- Other exposure metrics besides the simple cumulative exposure, such as time weighting of exposures, should be considered. The dichotomous Hill model is attractive because it allows estimation of an exposure parameter (b in Table 5-4), allowing the exposure effect to scale as covariates are added, the exposure metric changed, or the plateau fixed.

The authors explain that their choice of a 10% Extra Risk (ER) as the BMR is in line with the EPA's *Benchmark Dose Technical Guidance*. However, that rate is generally considered to apply specifically to the analysis of quantal datasets from animal studies, which is the context in which it was developed. In the EPA's *Benchmark Dose Technical Guidance*, it is mentioned that a BMR of 1% ER is typically used for human quantal response data because epidemiologic data often have greater sensitivities than bioassay data. The authors should explain what features of the dataset or outcome variable led them to choose a BMR that is considerably greater than the norm for epidemiologic data.

Recommendations:

- Consider model features and balance plausibility, localized fit, and EPA's 2012 *Benchmark Dose Technical Guidance* (USEPA, 2012) when choosing the best model and explain decisions in more detail.
- In conjunction with updating and better justifying the primary analysis, evaluate the impact of different time weightings of the exposure metric.
- Either lower the BMR to be more consistent with common practice for epidemiological data or provide more justification for the 10% BMR used to calculate the POD.

ED_002435_00001461-00036

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

ED_002435_00001461-00037

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.

<u>Non-exposure-related covariates</u>: 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.

ED_002435_00001461-00038

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.

ED_002435_00001461-00039

- 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.

ED_002435_00001461-00040

3.2.5.5. Conversion from Cumulative Occupational Exposure to Lifetime Exposure

Question 5. The modeled POD estimate is based on cumulative exposure estimates for the worker cohort examined. For the derivation of the RfC, this cumulative exposure is prorated over the period of environmental exposure (lifetime or shorter duration chronic exposure when appropriate). The RfC is provided in units of continuous air concentration. Is the basis of this conversion clearly explained and scientifically justified?

The SAB agrees that the conversion is clearly explained and follows standard practice. However, the SAB recommends a revision to use the full 70-year lifetime in the conversion rather than 60 (70 minus the lag of 10 used for exposure in the POD derivation). Given that the cumulative exposure metric (concentration in fiber/cc x years of exposure) is arbitrarily related to the prevalence data, lagging does not have real meaning as it would in an incidence data analysis since the time of disease onset is not known. Using a divisor of 60 instead of 70 in deriving the RfC is less protective.

Recommendations:

- Use the full 70-year lifetime when converting cumulative to continuous exposure; i.e., do not correct for the lag of 10 for a 10-year lagged exposure.
- The SAB recommends EPA indicate more clearly in Section 5.2.3.1. that "year" is in the numerator in the exposure metric "fibers/cc-year", and to describe more clearly how cumulative exposure is derived.

3.2.5.6. Selection of Uncertainty Factors

Question 6. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. Are the UFs appropriate based on A Review of the Reference Dose and Reference Concentration Processes (U.S. EPA, 2002; Section 4.4.5) and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support. Specifically, please comment on the rationale for the selection of the database uncertainty factor (UF_D) of 10 applied in the derivation of the RfC. The database uncertainty factor accounts for the lack of data on effects other than in the respiratory system, including other effects observed in community and laboratory animal studies (cardiovascular disease and autoimmune effects) that have not been well-studied (See Section 5.2.3 of the Toxicological Review); and lack of health data assessed at later time points. Is the rationale for the UF_D appropriate and clearly described? Please provide the rationale if a change in the UF_D is proposed.

Uncertainty factors were selected in accordance with the usual procedures laid out in EPA risk assessment guidelines. A value of 10 was selected for UF_H (human inter-individual variability) and UF_D (database uncertainty), with a value of 1 for all others.

Use of a UF_H of at least 10 is standard in considering health protective levels based on effects in the workforce, which is generally healthier and less diverse than the general population. In fact, publications are available that discuss whether a factor of 10 is sufficient to cover all sensitive sub-populations, especially children (Hattis et al., 1999; Miller et al, 2002; Scheuplein et al., 2002; Dourson et al., 2002; OEHHA, 2008). Some treatment of the question of inter-individual variability is offered in the later summary of conclusions (Section 6 of the EPA document). There is no specific evidence on the relative sensitivity of children to the non-cancer effects of Libby asbestos, although some indications with other amphiboles suggest the possibility of enhanced effects following exposure at younger ages (Haque et al., 1996; 1998; Isaacs and Martonen, 2005; Bennett et al., 2008). Overall, it seems unlikely

that a departure from the default guideline value of UF_H =10 could be justified within the existing guidelines, but concerns remain for the impact on susceptible subpopulations, especially women and children.

EPA explains and justifies the selection of a UF_D of 10 based on the limited number of studies of exposure to Libby asbestos (Libby workers, ATSDR community study and Marysville workers) and the lack of evaluation of potentially more sensitive alternative endpoints. The SAB finds that this uncertainty factor would not be reduced even if improved exposure estimates allowed consideration of the full cohorts (or a larger fraction thereof).

However, some additional data have recently been published for the community surrounding a Minnesota expansion plant (Adgate et al., 2011; Alexander et al., 2012). Although there appears to be a rationale for at least an initial consideration of LAA as a unique material (to provide an unbiased comparison with other amphiboles), this SAB review has identified very substantial grounds for considering this material as having composition, physical properties, and biological effects that are very similar to those seen for other amphiboles. The most relevant comparison would be to tremolite, since Libby Amphibole is ~6% tremolite, an amphibole that is known to cause cancer and non-cancer effects in human populations. However, it is uncertain how other components of Libby Amphibole (richerite and winchite) interact as a mixture with tremolite to modify toxicity. This consideration of data on other amphiboles is particularly pertinent to discussions of the mode of action, as well as the exposure-response relationships, for Libby Amphibole. In light of this similarity it appears reasonable, and indeed necessary, to at least debate the question of whether the available data on non-cancer health effects of amphiboles are sufficient to mitigate the acknowledged data shortage for Libby Amphibole itself. Therefore, the SAB considers that additional data (e.g., the Minnesota cohort and data on other amphiboles) might support a lower value, such as 3, for UF_D.

On the other hand, there are substantial remaining uncertainties that are not addressed by these additional data, including those raised by consideration of the severity of the endpoint and the selection of the BMR (see below). This uncertainty should also be revisited by EPA in its judgement of an uncertainty factor of 1-fold for a LOAEL-to-NOAEL uncertainty factor (UF_L). It can also be argued that a subchronic-to-chronic uncertainty factor (UF_S) higher than 1 should be used, given that the mean and maximum exposure duration in this study are both well below the lifetime exposure of interest. This uncertainty should also be revisited for EPA in its judgement of an uncertainty factor of 1-fold for UF_S.

It may be appropriate for EPA to select a value of 10 for UF_D, or a similar uncertainty spread across several factors, but EPA needs to re-evaluate selection of this factor explicitly once all the additional information has been incorporated in the discussion.

There is a concern that the BMR of 10%, which was chosen for a severe endpoint, is not reflected by the choice of a UF_L of 1. The SAB finds that it is appropriate for EPA to consider either a lower BMR, or the application of a larger UF_L for this endpoint. An argument could be made that some allowance has been made for this concern in the choice of the UF_D, but it is debatable whether this is sufficient, given the other matters to which that UF is also assigned. In any case, UF_D is not the appropriate place to consider this uncertainty. At the very least, this question deserves more consideration and analysis that it receives in the draft assessment report.

ED_002435_00001461-00042

Recommendations:

- Review additional data, in particular the exposure-response relationship for non-cancer endpoints in the Minneapolis community cohort.
- Determine whether this new analysis supports the existing analysis based on the Marysville data, and if so whether this warrants reduction of the value of UF_D since the limited data basis for the original analysis has been expanded.
- Reassess the selection of the BMR to reflect the severity of the chosen endpoint in the Marysville cohort and the precision available in the data. Whether or not the chosen BMR is changed, present this analysis in the document rather than simply asserting that a "default" value for the BMR was chosen. Similar consideration should be applied to the Minneapolis cohort to provide a valid comparison. This consideration needs to be linked to discussion of the selection of a value for UF_L as noted below.
- Review additional sources of uncertainty:
  - Timescale of cohort coverage, normally addressed by UF_S if this is a significant concern rather than including this as a component of UF_D which already has several major issues to account for.
  - Additional uncertainty resulting from target population diversity (including women and children, specific sub-populations of concern not represented in the cohort), and endpoint severity.
- Consider adjusting UF_D, UF_S or UF_L if necessary to accurately reflect the overall uncertainties in these categories: provide specific justification for the choices made rather than claiming unsupported use of default values.

3.2.5.7. Characterization of Uncertainties

Question 7. Please comment on whether the document adequately describes the uncertainties and limitations in the methodology used to derive the RfC and whether this information is presented in a transparent manner.

In the report there are two sections on uncertainty for the RfC: an application of uncertainty factors following standard EPA practice (Section 5.2.4), and a discussion of the uncertainties in the overall methodology and approach (Section 5.3). This response focuses on the latter. Overall the SAB found the discussion to be thorough, detailed and logical. The document can be improved by harmonizing the full set of uncertainty discussions, including both the discussion of RfC uncertainty and the related discussion of the IUR uncertainty (see the SAB response to question 5 under Section 3.2.6.5 below). In addition, the RfC uncertainty assessment can be strengthened. A key consideration of any assessment is whether the estimated RfC is adequately protective of public health. 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 [e.g., cause of death for the deceased non-participants in Rohs et al. (2008) and the Minneapolis exfoliation community cohort (Alexander et al., 2012)].

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. In sensitivity analyses, consider alternative exposure metrics (prioritizing residence time weighted metrics and excluding exposures after 1980), methods to fine-tune the RfC estimate from the subcohort (particularly fixing rather than estimating the plateau, allow the slope parameter to be estimated, use a lifetime of 70 regardless of the exposure metric), and added sensitivity analyses in the full cohort using suggestions from the SAB.

ED_002435_00001461-00043

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.

ED_002435_00001461-00044

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.

ED_002435_00001461-00045

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?

ED_002435_00001461-00046

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.

ED_002435_00001461-00047

- 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.

ED_002435_00001461-00048

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:

ED_002435_00001461-00049

> …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 — 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.

ED_002435_00001461-00050

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.

ED_002435_00001461-00051

ED_002435_00001461-00052

REFERENCES

Albert, RE; Lippmann, M; Briscoe, W. (1969). The characteristics of bronchial clearance in humans and the effects of cigarette smoking. *Arch. Environ. Health* 18:738-755.

Amandus, HE; Wheeler, R. (1987). The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. *Mortality. Am J Indian Med* 11:15-26.

ATS (2004). Diagnosis and initial management of nonmalignant disease of asbestos. *American J Respiratory Critical Care Med* 170: 691-715.

ATSDR (2000). Health consultation: mortality from asbestosis in Libby, Montana. Atlanta, GA.

ATSDR (2001). Year 2000 medical testing of individuals potentially exposed to asbestiform minerals associated with vermiculite in Libby, Montana: A report to the community. Atlanta, GA.

Ates,G; Yildiz, T; Akyildiz, L; Topcu, F; Erturk, B. (2010). Environmental asbestos-related pleural plaque in southeast of Turkey. *Arch Environ Occup Health*. 65(1):34-7.

Attfield, MD; Hewett, P. (1992). Exact expressions for the bias and variance of estimators of the mean of a lognormal distribution. *Am Ind Hyg Assoc* J 53:432-435.

Below, JE; Cox, NJ; Fukagawa, NK.; Hirvonen, A.; Testa, JR. (2011). Factors that impact susceptibility to fiber-induced health effects. *J Toxicol Environ Health, Part B* 14:246-266.

Bennett, WD; Zemean, KL; Jarabek, AM (2008). Nasal contribution to breathing and fine particle deposition in children versus adults. *J Toxicol Environ Health A* 71:227-237.

Berman, DW. (2011). Apples to apples: The origin and magnitude of differences in asbestos cancer risk estimates derived using varying protocols. *Risk Analysis* 31:1308-1326.

Bernstein, DM; Chevalier, J; Smith, P. (2003). Comparison of Calidria chrysotile asbestos to pure tremolite: Inhalation biopersistence and histopathology following short-term exposure. *Inhalation Toxicology* 15:1387-1419.

Bernstein, DM; Rogers, R; Smith, P. (2004). The biopersistence of Brazilian chrysotile asbestos following inhalation. *Inhal. Toxicol*. 16:745-761.

Bernstein, DM; Chevalier, J; Smith, P. (2005a). Comparison of calidria chrysotile asbestos to pure tremolite: final results of inhalation biopersistence and histopathology examination following short-term exposure. *Inhal. Toxicol*. 17:427-449.

Bernstein, D; Rogers, R; Smith, P. (2005b). The biopersistence of Canadian chrysotile asbestos following inhalation: final results through 1 year after cessation of exposure. *Inhalation Toxicology* 17:11-14.

Bernstein, DM; Rogers, RA; Sepulveda, R; Donaldson, K; Schuler, D; Gaering, S; Kunzendorf, P; Chevalier, J; Holm, SE. (2011). Quantification of the pathological response and fate in the lung and pleura of chrysotile in combination with fine particles compared to amosite-asbestos following short-term inhalation exposure. *Inhalation Toxicology* 23(7):372-391.

Berry, G; Lewinsohn, HC. (1979). Dose-response relationships for asbestos-related disease: implications for hygiene standards. Part 1: morbidity. *Annals New York Academy of Sciences* 330:185-194.

Berry, G; Gilson, JC; Holmes, S; Lewinsohn, HC; Roach, SA. (1979). Asbestosis: a study of dose-response relationships in an asbestos textile factory. *British J of Industrial Medicine* 36: 98-112.

Bourbeau, J; Ernst, P; Chrome, J; Armstrong, B; Becklake, MR. (1990). The relationship between respiratory impairment and asbestos-related pleural abnormality in an active work force. *Am Rev Respir Dis* 142:837-842.

Broaddus, VC; Everitt, JI; Black, B; Kane, AB. (2011). Non-neoplastic and neoplastic pleural endpoints following fiber exposure. *J Toxicol Environ Health, Part B* 14:153-178.

Brody, AR; Roe, MW. (1983). Deposition pattern of inorganic particles at the alveolar level in the lungs of rats and mice. *Am. Rev. Respir. Dis.* 128:724-729.

Brody, AR; Hill, LH; Adkins, B Jr; O'Connor, RW. (1981). Chrysotile asbestos inhalation in rats: deposition pattern and reaction of alveolar epithelium and pulmonary macrophages. *Am. Rev. Respir. Dis.* 123:670-679.

Brody, AR; Liu, JY; Brass, D; Corti, M. (1997). Analyzing the genes and peptide growth factors expressed in lung cells in vivo consequent to asbestos exposure and in vitro. *Environ Health Perspect.* 105 Suppl 5:1165-71

Carbone, M; Baris, YI; Bertino, P; Brass, B; Comertpay, S; Dogan, AU; Gaudino, G; Jube, S; Kanodia, S; Partridge, CR; Pass, HI; Rivera, ZS; Steele, I; Tuncer, M; Way, S; Yang, H; Miller, A. (2011). Erionite exposure in North Dakota and Turkish villages with mesothelioma. *Proc Natl Acad Sci U S A.* 108(33):13618-23. Epub 2011 Jul 25.

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* 66:985-991.

Constantopoulos, SH. (2008). Environmental mesothelioma associated with tremolite asbestos: lessons from the experiences of Turkey, Greece, Corsica, New Caledonia and Cyprus. *Regul Toxicol Pharmacol.52*(1 Suppl):S110-5. Epub 2007 Nov 13.

Davis, JMG; Addison, J; Bolton, RE; Donaldson, K; Jones, AD; Miller, BG. (1985) Inhalation studies on the effects of tremolite and brucite dust in rats. *Carcinogenesis* 6:667-674.

ED_002435_00001461-00054

Dourson, ML; Charnley, G; Scheuplein, R. (2002). Differential sensitivity of children and adults to chemical toxicity: II. Risk and Regulation. *Regulatory Toxicology and Pharmacology* 35:448-467.

Fréchet, M. (1935). Généralisations du théorème des probabilités totales. *Fundamenta Mathematica* 25: 379-387.

Gaylor, D; Ryan, L; Krewski, D; Zhu, Y (1998). Procedures for calculating benchmark doses for health risk assessment. *Regulatory Toxicology and Pharmacology* 28:150-164.

Gogou, E; Kerenidi, T; Chamos, V; Zintzaras, E; Gourgoulianis, KI. (2009). Mesothelioma mortality in Greece from 1983 to 2003. *Int J Clin Pract.*63:944-948. Epub 2007 Jun 15.

Haque, AK; Vrazel, DM. (1998). Transplacental transfer of asbestos in pregnant mice. *Bull Environ Contam Toxicol* 60:620-625.

Haque, AK; Vrazel, DM; Burau, KD; Cooper, SP; Downs, T. (1996). Is there transplacental transfer of asbestos? A study of 40 stillborn infants. *Pediatr Pathol Lab Med* 16:877-892.

Hattis, D; Banati, P; Goble, R. (1999). Distributions of individual susceptibility among humans for toxic effects. How much protection does the traditional tenfold factor provide for what fraction of which kinds of chemicals and effects? *Ann N Y Acad Sci* 895: 286-316.

HEI-AR, (1991). Asbestos in Public and Commercial Buildings: A Literature Review and Synthesis of Current Knowledge. Health Effects Institute-Asbestos Research, Cambridge, MA. http://pubs.healtheffects.org/view.php?id=13

Hjortsberg, U; Orbaek, P; Arborellius, M; Ranstam, J; Welinder, H (1988). Railroad workers with pleural plaques. I. Spirometric and nitrogen washout investigation on smoking and nonsmoking asbestos-exposed workers. *American J. of Industrial Medicine* 14: 649-656.

IARC (International Agency for Research on Cancer). (2012). Asbestos (Chrysotile, Amosite, Crocidolite, Tremolite, Actinolite, and Anthophyllite, in *A Review of Human Carcinogens: Arsenic, Metals, Fibres, and Dusts,* IARC Monographs - 100C, pg 219-309.

Isaacs, KK; Martonen, TB. (2005). Particle deposition in children's lungs: Theory and experiment. *J Aerosol Med* 18:337-353.

Jarvolm, B; Sanden, A. (1986). Pleural plaques and respiratory function. *American J. Industrial Medicine* 10:419-426.

Kamp, DW; Weitzman, SA. (1999). The molecular basis of asbestos induced lung injury. *Thorax* 54(7):638-52.

Klein, JP; Moeschberger, ML. (2003). *Survival Analysis: Techniques for Censored and Truncated Data.* New York: Springer.

ED_002435_00001461-00055

Kopylev, L; Sullivan, PA; Vinikoor, LC; Bateson, TF. (2011). Monte Carlo analysis of impact of underscertainment of mesothelioma cases on underestimation of risk. *The Open Epidemiology Journal* 4:45-53.

Küchenhoff, H; Bender, R; Langner, I. (2007) Effect of Berkson measurement error on parameter estimates in Cox regression models. *Lifetime Data Analysis* 13(2):261–72.

Larson, TC; Antao, VC; Bove, FJ; Cusack, C. (2012). Association Between Cumulative Fiber Exposure and Respiratory Outcomes Among Libby Vermiculite Workers. *J Occup Environ Med* 54:56-63.

Leake, BE; Woolley, AR; Arps, CES; Birch, WD; Gilbert, MC; Grice, JD; Hawthorne, FC; Kato, A; Kisch, HJ; Krivovichev, VG; Linthout, K; Laird, J; Mandarino, JMaresch, WV; Nickel, EH; Rock, NMS; Schumacher, JC; Smith, DC; Shephenson, NCN; Ungaretti, L; Whittake, EJW; Youzhi, G. (1997). Nomenclature of amphiboles: Report of the Subcommittee on Amphiboles of the International Mineralogical Association Commission on New Minerals and Mineral Names. *Mineral Mag* 61:295-321.

Lilis, R; Miller, A; Godbold, J; Chan, E; Selikoff, IJ. (1991a). Radiographic abnormalities in asbestos insulators: effects of duration from onset of exposure and smoking: relationships of dyspnea with parenchymal and pleural fibrosis. *Am J Ind Med* 20:1-15.

Lilis, R; Miller, A; Godbold, J; Chan, E; Selikoff, IJ. (1991b). Pulmonary function and pleural fibrosis: quantitative relationships with an integrative index of pleural abnormalities. *Am J Ind Med* 29: 145-161.

Lippmann, M. (2009). Asbestos and other mineral fibers. In: M. Lippmann, Ed., *Environmental Toxicants: Human Exposures and Their Health Effects, 3rd Ed.*, John Wiley, New York, NY, pp. 395-458.

Lockey, JE; Brooks, SM; Jarabek, AM; Khoury, PR; McKay, RT; Carson, A; Morrison, JA; Wiot, JF; Spitz, HB. (1984). Pulmonary changes after exposure to vermiculite contaminated with fibrous tremolite. *Am Rev Respir Dis* 129:952-958.

Manski, CF. (2003). *Partial Identification of Probability Distributions.* Springer, New York.

McDonald, JC; McDonald,AD; Armstrong, B; Sebastien, P (1986). Cohort study of mortality of vermiculite miners exposed to tremolite. *Occup Environ Medical* 43:436-444.

McDonald, JC; Harris, J; Armstrong, B. (2004). Mortality in a cohort of vermiculite miners exposed to fibrous amphibole in Libby, Montana. *Occup Environ Med* 61:363-366.

Meeker, GP; Bern, AM; Brownfield, IK; Lowers, HA; Sutley, SJ; Hoefen, TM; Vance, JS. (2003) The composition and morphology of amphiboles from the Rainy Creek Complex, near Libby, Montana. *American Mineralogist* 88:1955-1969.

Metintas, M; Metintas, S; Ak G, Erginel S; Alatas F; Kurt E; Ucgun I; Yildirim H.(2008). Epidemiology of pleural mesothelioma in a population with non-occupational asbestos exposure. *Respirology* 13(1):117-21.

ED_002435_00001461-00056

Metintas, M; Hillerdal, G; Metintas, S; Dumortier, P. (2010) Endemic malignant mesothelioma: exposure to erionite is more important than genetic factors. *Arch Environ Occup Health.* 65(2):86-93.

Metintas, S; Metintas, M; Ak ,G; Kalyoncu C. (2012). Environmental asbestos exposure in rural Turkey and risk of lung cancer. *Int J Environ Health Res.* Feb 2. [Epub ahead of print]

Miller, A. (2002) Pleural plaques and lung function. *Am J Respir Crit Care Med.* 165(2):305-6.

Miller, A; Lilis, R; Godbold, J; Chan, E; Selikoff, IJ. (1992). Relationship of pulmonary function to radiographic interstitial fibrosis in 2,611 long term asbestos insulators: an assessment of the International Labour Organization profusion score. *Am Rev Respir Dis* 145:263-270.

Miller, MD; Marty, MA; Arcus, A; Brown, J; Morry, D; Sandy, M. (2002). Differences between children and adults: Implications for risk assessment at California EPA. *Int J Toxicol* 21(5):403-418.

Mossman, BT; Lounsbury, KM; Reddy, SP. (2006). Oxidants and signaling by mitogen-activated protein kinases in lung epithelium. *Am J Respir Cell Mol Biol.* 34(6):666-9.

Mossman, BT; Lippmann, M; Hesterberg, TW; Kelsey, KT; Barchowsky, A; Bonner, JC. (2011). Pulmonary endpoints (lung carcinomas and asbestosis) following inhalation exposure to asbestos. *J Toxicol Environ Health, Critical Reviews, Part B* 14:76-121.

Mulhausen, J; Damiano, J. (1998) *A Strategy for Assessing and Managing Occupational Exposures. 2nd edition*, AIHA Press.

Neri, M; Ugolini, D; Dianzani, I; Gemignani, F; Landi, S; Cesario, A; Magnani, C; Mutti, L; Puntoni, R; Bonassi, S. (2008) Genetic susceptibility to malignant pleural mesothelioma and other asbestos-associated diseases. *Mutation Research* 659:126-136.

NIOSH (1977). Leidel, Bush & Lynch Occupational Exposure Sampling Strategy Manual. NIOSH 77-173 CDC.

Nguyen, HT; Kreinovich, V; Wu, B.; Xiang, G. (2012) *Computing Statistics under Interval and Fuzzy Uncertainty*. Springer, Berlin.

NRC (1994). *Science and Judgement in Risk Assessment*. Washington, DC: National Academy Press [Chapter 11, Appendix I-1, Appendix I-2] http://www.nap.edu/catalog.php?recird_id=2125

OEHHA (2008). Air Toxics Hot Spots Risk Assessment Guidelines Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Available online at: http://www.oehha.ca.gov

Ohlson, G; Rydman, T; Sundell, L; Bodin L; Hogstedt, C. (1984). Decreased lung function in long-term asbestos cement workers: a cross-sectional study. *American J Industrial Medicine* 14:649-656.

ED_002435_00001461-00057