Asbestos: A Science-Based Examination of the Mode of Action of Asbestos and Related Mineral Fibers

DAY ONE -- Wednesday December 16, 2009

Pre-Workshop SESSION – Finalize documents by Original Teams

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30am – 9:00am</td>
<td>Registration (Team members, Planning Committee &amp; Reviewers ONLY)</td>
<td>Venetian Foyer</td>
</tr>
<tr>
<td>9:00am – 9:15am</td>
<td>Brief overview of morning activities</td>
<td>Venetian Room</td>
</tr>
<tr>
<td></td>
<td>Maureen Gwinn, USEPA</td>
<td></td>
</tr>
<tr>
<td>9:15am – 12:00pm</td>
<td>Original Expert panels plus reviewers meet separately to finalize White Papers and prepare for presentation of key findings. Prepare PowerPoint presentation (15min max)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary Toxicology</td>
<td>Zurich</td>
</tr>
<tr>
<td></td>
<td>Pleural Toxicology</td>
<td>Paris I</td>
</tr>
<tr>
<td></td>
<td>Non-pulmonary Toxicology</td>
<td>Executive Boardroom</td>
</tr>
<tr>
<td></td>
<td>Genetic Toxicology</td>
<td>Paris II</td>
</tr>
<tr>
<td></td>
<td>Susceptibility</td>
<td>Vienna B</td>
</tr>
<tr>
<td></td>
<td>Environmental Exposure</td>
<td>Brussels</td>
</tr>
</tbody>
</table>

The specific charge to the panels is to come to conclusions concerning:
The strength of the published data on asbestos and related mineral fibers as reviewed in the white papers. Thus the breakout groups will assess the strength of the data on each of the areas covered by the white papers in their specific areas: pulmonary endpoints, pleural endpoints, non-pulmonary endpoints, Role of Mutagenicity in fiber-induced carcinogenicity, main factors that impact susceptibility to fiber-induced health effects and extrapolation of environmental exposure levels (low-dose, sporadic, high-dose) to health effects. Focus will be on the strength of the data, critical examination of conflicting data, data gaps and needs.

Each panel will develop a report that will put all the data from their specific area into sections:

1. Based on existing evidence we are confident of the following....
2. We consider the following to be likely but require confirmation....
3. Research on asbestos and related mineral fibers suggests several broad themes which we believe should be pursued on future investigations. These include...
4. Overall conclusion

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:00 – 1:00pm</td>
<td>LUNCH</td>
<td>Shula’s 347</td>
</tr>
<tr>
<td>12:00 – 1:00pm</td>
<td>Public registration</td>
<td>Venetian Foyer</td>
</tr>
</tbody>
</table>
Public Workshop Begins

1:00pm – 1:05pm  Welcome  
*Venetian*  
*Claudia Thompson, NIEHS*

1:05pm – 1:20pm  Opening Remarks  
*Linda Birnbaum, Director, NIEHS*

1:20pm – 1:45pm  Workshop Background, Overview of Agenda and Planned Activities  
*Maureen Gwinn, USEPA and Claudia Thompson, NIEHS*

SESSION I – Presentation of Key Points from Original Teams

1:45pm – 3:45pm  Plenary Presentations of Key Findings  
*Venetian*

Based on a mechanism/MOA, can the range of fibers or specific components that contribute to adverse health effects be determined, keeping in mind the role of different fibers in various disease endpoints. A key consideration will be how to express the dose metric corresponding to different effect endpoints, e.g., fiber burden (mg or surface area) normalized to lung tissue volume. During this session the results of the writing team’s efforts will be discussed for the following six endpoints.

1:45pm – 2:05pm  Pulmonary Endpoints (cancer and noncancer)  
*Brooke Mossman, University of Vermont*

2:05pm – 2:25pm  Pleural Endpoints (cancer and noncancer)  
*Agnes Kane, Brown University*

2:25pm – 2:45pm  Non-Pulmonary Endpoints (cancer and noncancer)  
*Andrij Holian, University of Montana*

2:45pm – 3:05pm  Role of Mutagenicity in Fiber-Induced Carcinogenicity  
*Tom Hei, Columbia University*

3:05pm – 3:25pm  Main factors that impact susceptibility to fiber-induced health effects  
*Joseph Testa, Fox Chase Cancer Center*

3:25pm – 3:45pm  Extrapolation of Environmental Exposure levels (low-dose, sporadic, high-dose) to health Effects  
*Kent Pinkerton, University of California at Davis*

3:45pm – 4:00pm  BREAK

SESSION II – Overarching Questions

4:00pm – 4:15pm  Charge to breakout group tasks, overview of Overarching Questions
4:15pm – 6:00pm Four Concurrent Breakout Sessions

Group I                               Zurich
Group II                               Paris I
Group III                              Paris II
Group IV                               Vienna B

The breakout groups should examine the literature to come to conclusions on some overarching issues related to asbestos and related mineral fibers including:

Question 1. **Physicochemical characteristics**
What are the physico-chemical attributes (mineralogy, morphology, dimension) contributing to target organ deposition/clearance/response (durability, biopersistence and bioreactivity)? Are there qualitative and quantitative differences or similarities in dosimetry/toxicity and mode of action for different mineral fibers (pulmonary and pleural, cancer and non-cancer)?

Question 2. **Mode of Action (MOA; Defined as a chemical's influence on the molecular, cellular and physiological functions in producing tumors or toxicity)**
Do MOA/mechanisms findings from in vitro studies operate in vivo in laboratory animals? In humans at relevant exposure levels? What in vivo responses are not adequately explained by current understanding of the MOA or available in vitro findings?

Question 3. **Genotoxicity**
What is known about the direct and indirect mutagenicity of the various asbestos fiber types? What physicochemical attributes account for the differences/similarities in the genotoxic response to various fiber types? What role does this genotoxicity play in different clinical diseases? In vitro? Are there quantitative species differences?

Question 4. **Extrapolation to Humans**
What mechanistic studies in vivo or in vitro best bridge to current clinical outcome measures? Do we know what factors or mechanisms occur before inflammation following exposure to asbestos? What is the relationship between inflammation and fibrotic changes (e.g., on chest films or observed by other imaging) and mesothelioma? What data should be collected in epidemiological or other clinical surveys to enhance mechanistic understanding of the different dimensions of asbestos disease?

Question 5. **Susceptibility**
There is limited information on exposures in potentially susceptible populations (children, women, elderly, sick, etc). Would you expect there to be a dosimetry difference or susceptibility issue in any of these groups? If so, how best can this be determined?

The goal will be to reach a consensus on these questions/issues.

These questions will also be answered in the same framework as used for the white papers.

1. Based on existing evidence we are confident of the following....
2. We consider the following to be likely but require confirmation....
3. Research on asbestos and related mineral fibers suggests several broad themes which we believe should be pursued on future investigations. These include...
4. Rapid advances and critical recent advances
5. Summary of Overall conclusions

6:00pm - 6:15pm  CLOSE – discussion of next day tasks

7:00pm  DINNER

DAY TWO - Thursday December 17, 2009

Session II – Overarching Questions (continued)

8:00am – 8:15am  Discussion of the day’s agenda  

8:15am – 10:30am  Breakout groups, continuation of discussion of questions

10:30am – 10:45am  BREAK

10:45am – 11:30am  Finalize PowerPoint presentation for Discussion

Session III – Plenary Presentation of Overarching Questions

11:30am – 12:30pm  Presentation of Key Findings to Overarching Questions  

11:30am – 12:00pm  Group I

12:00pm – 12:30pm  Group II

12:30 – 1:30pm  LUNCH  

Session III – Plenary Presentation of Overarching Questions (CONTINUED)

1:30pm – 2:00pm  Group 3

2:00pm – 2:30pm  Group 4

2:30pm – 3:30pm  Group Discussion

3:30pm – 4:00pm  Summary presentation, next steps  

Maureen Gwinn and, Claudia Thompson

4:00pm  END WORKSHOP