

US EPA ARCHIVE DOCUMENT

Asbestos Mechanisms of Toxicity Workshop

Asbestos – a group of highly fibrous silicate minerals that readily separate into long, thin, strong fibers that have sufficient flexibility to be woven are heat resistant and chemically inert, are electrical insulators and therefore are suitable

(Gary et al., 1974)

Serpentine - chrysotile

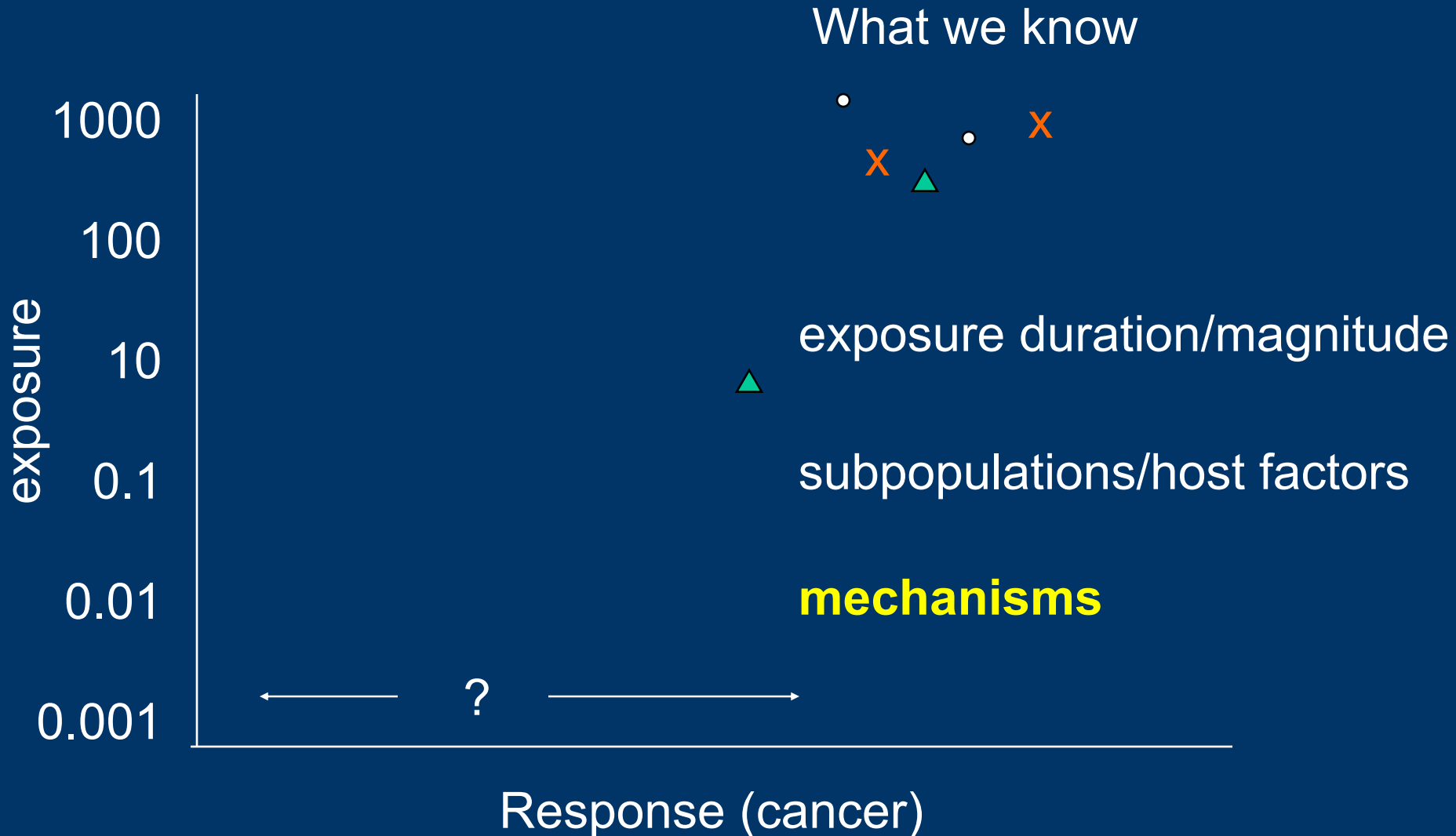
Amphibole - anthophyllite, tremolite, actinolite,
grunerite (amosite), riebeckite (crocidolite)

Asbestos Mechanisms of Toxicity Workshop

Challenges in evaluating asbestos fiber health risks

- Similarities/Differences in activity of amphiboles & chrysotile
- Importance of fiber length as a determinant of bioactivity
- Understanding exposure and relating it to dose
 - ❖ biopersistence, fiber durability
- Extrapolating outcomes at high occupational exposures to much lower environmental exposure

Issues in evaluating asbestos fiber health risks



Asbestos - Mechanisms of Toxicity

Hypothetical Mechanisms of Asbestos Toxicity

- **Fibers generate free radicals that damage cells & DNA**
- **Fibers stimulate proliferation of target cells**
- **Fibers produce a chronic inflammatory reaction
oxidants – cytokines – growth factors**
- **Fibers act to enhance activation and delivery
of chemical carcinogens**
- **Physical action of fibers interfere with mitosis**

Asbestos Mechanisms of Toxicity Workshop

- **Exposure- and dose-response relationships**

Drs. Churg, Lockey and McConnell

- **Mechanisms of fiber-induced lung & pleural disease**

Drs. Brody, Castranova, Kane and Hobbs

- **Molecular & biochemical mechanisms of toxicity**

Drs. Mossman, Hei and Fubini

Exposure and Dose-Response Relationships

What is the influence of:

fiber type

fiber dimensions (*diameter, length for fibers > 5 um and fibers < 5 um*)

exposure duration/magnitude

on the nature of the response to asbestos (cancer and non-cancer)/

Is there evidence that pleural plaques precede (predispose to) mesothelioma?

Mechanisms of Fiber-Inducing Lung and Pleural Disease

What are the key mechanisms underlying asbestos-induced development of interstitial lung disease and pleural lung disease?

Are they unique to asbestos fibers?

What role does fiber biopersistence play in the nature and magnitude of response to asbestos fibers

Do differences in biopersistence explain apparent differences in fiber-type toxicity

What factors influence development of pleural and lung disease resulting from asbestos exposure.

Molecular, Cellular and Biochemical Mechanisms of Asbestos Fiber Toxicity

How does the chemical/physical properties of asbestos influence its activity

- elemental composition
- surface characteristics
- fiber type, e.g., amphibole versus chrysotile; various amphiboles
- biopersistence

How do the following processes/factors contribute to adverse responses to asbestos

- cell activation and proliferation
- receptor-mediated toxicity
- cytotoxicity
- cell transformation
- effects on immune responses.

Molecular, Cellular and Biochemical Mechanisms of Asbestos Fiber Toxicity

What role do the direct genetic or genotoxic effects of fibers play in asbestos toxicity.

Based on mechanism of action is there evidence to support additive, synergistic or confounding effects from other exposures.