Asbestos and Related Durable Fibers:

Too Ubiquitous, Too Persistent, Too Complex to Put Health Risks to Rest?

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Are health effects from exposures to microscopic durable fibers an old issue ?

- An extensive history of research, discussion and debate which focused on occupational exposures to a few types of asbestos fibers has not lead to an understanding of all risks.
- “Asbestos” is more of a slowly expanding pollutant problem than a re-emerging one.
- A hallmark complication for risk assessment is the very long lag time between exposure and effects.

Objectives for this presentation*:

- Provide overview of asbestos health risks.
- Give examples of EPA's experience with "asbestos-like" fibers.
- Describe why we need and how we can develop a relative potency model for assessing risks from complex mixtures of mineral fibers and new synthetic fibers.
- Comment on similarity of some synthetic nanofibers to asbestos.

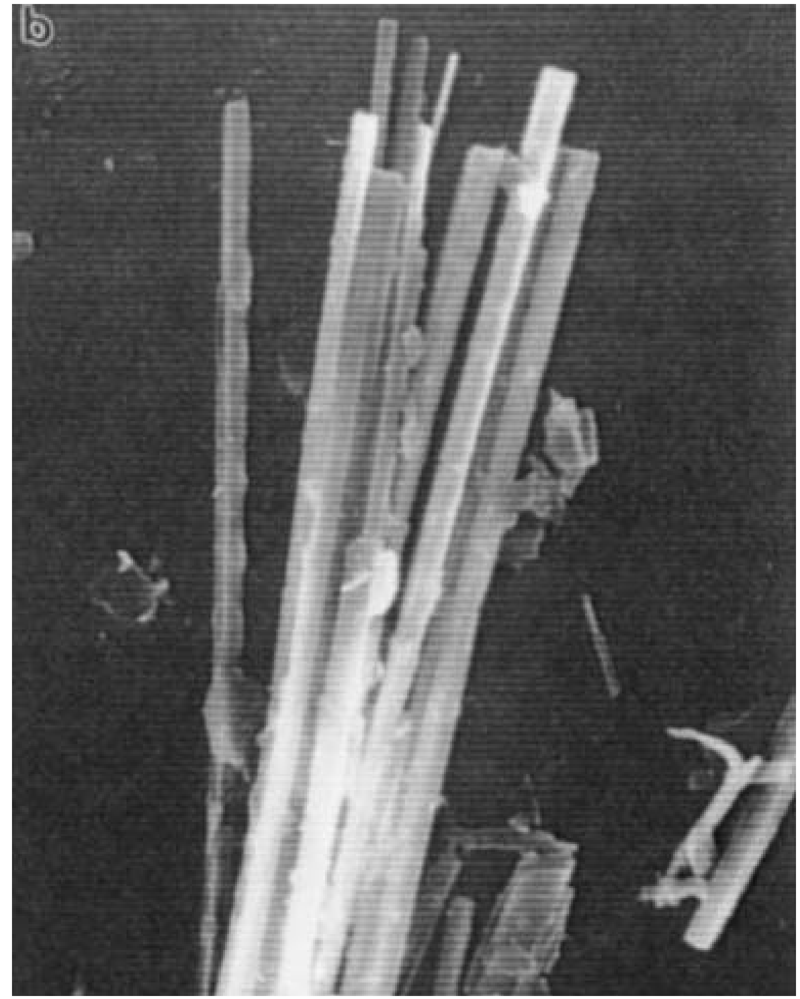
*The content of this presentation represents the experience and opinions of the author and not U.S. EPA procedures or policies.

Chrysotile asbestos cross-fiber vein

Amphibole crystals in taconite (iron ore) - ferroactinolite replacing hornblende

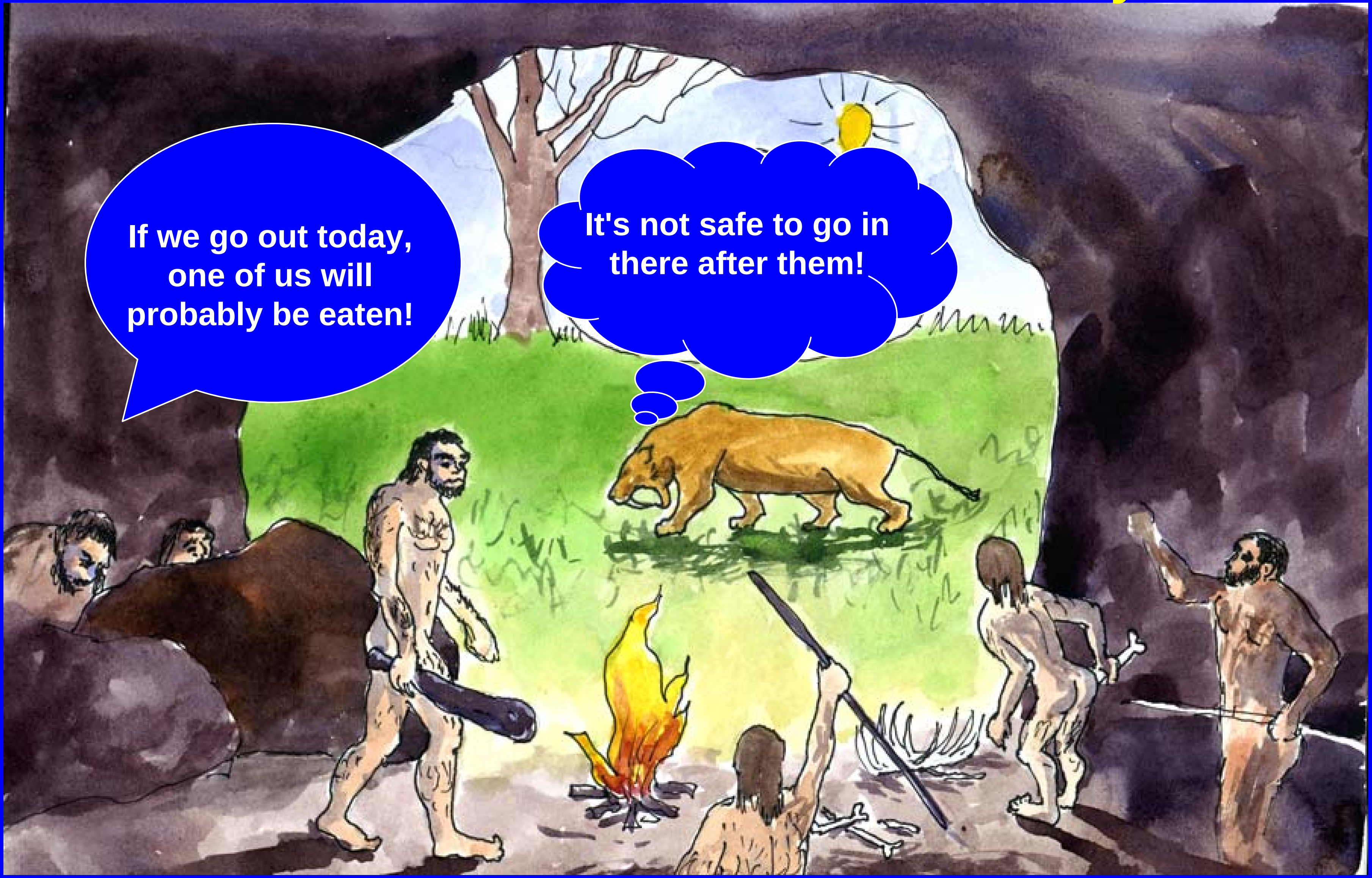
Asbestos fibers - TEM (high magnification)

bundles and fibrils of chrysotile asbestos fibers

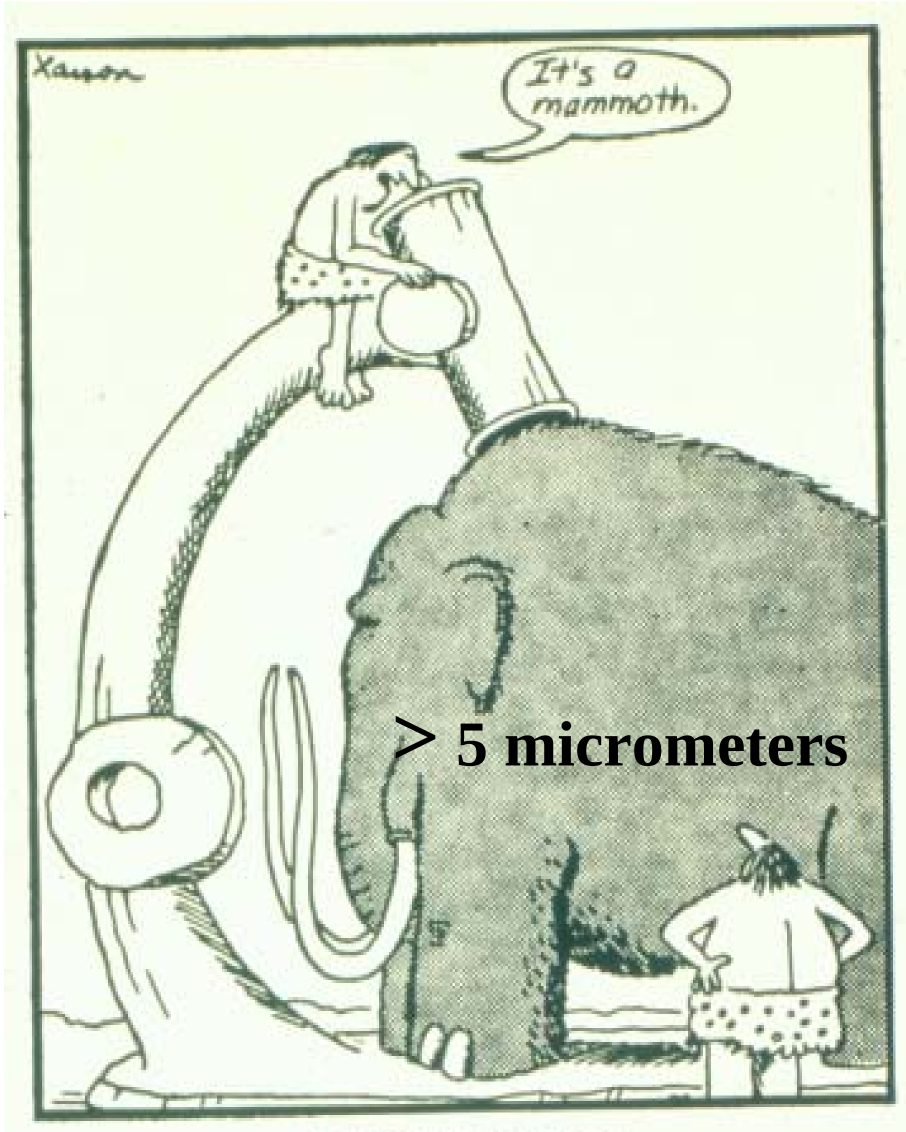


rodlike bundle of crocidolite asbestos fibers

Evolution of Risk Assessment: The Early Years



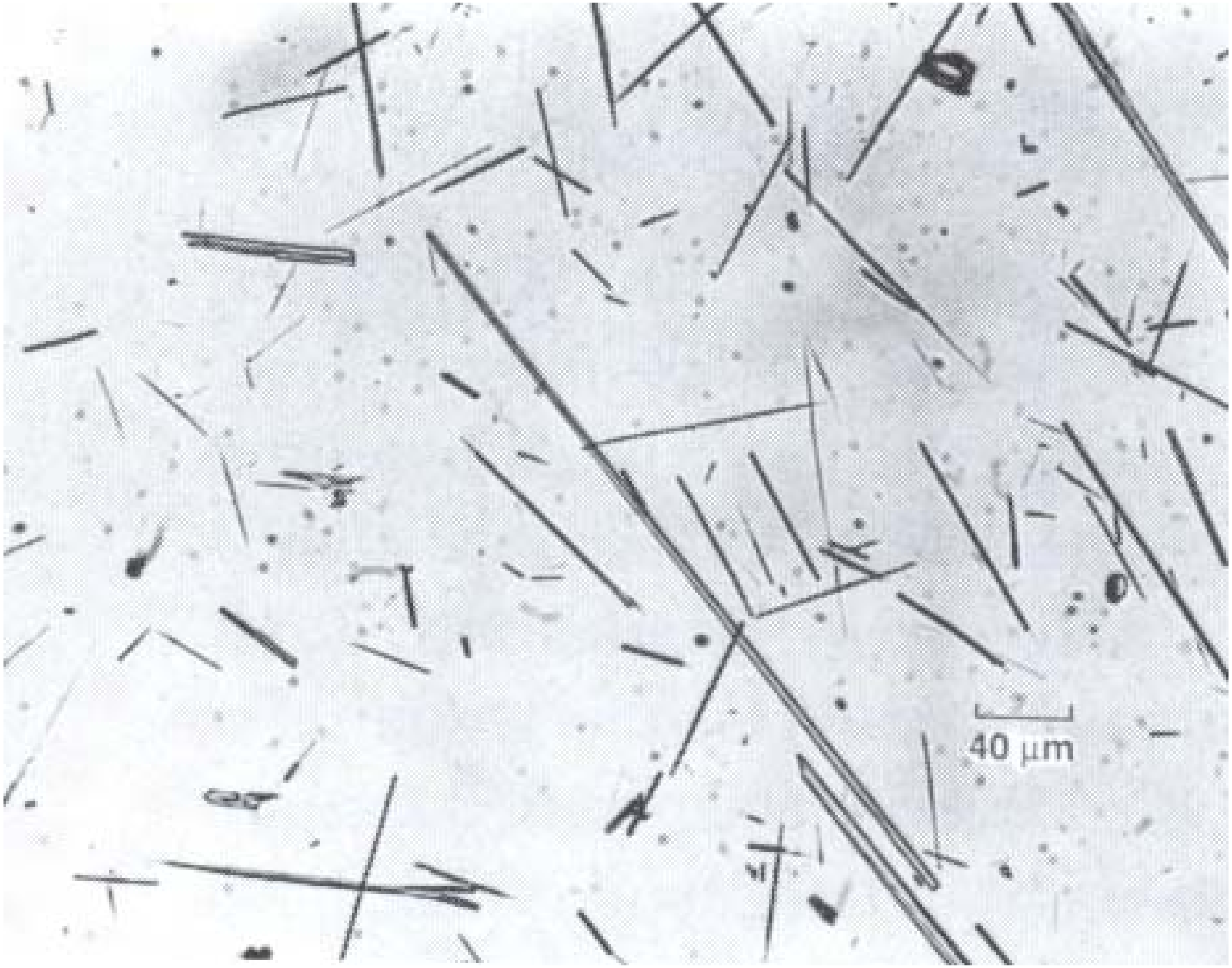
Tempus fugit



Early microscope

Transmission Electron Microscope (TEM)

Tremolite acicular “Cleavage Fragments” ?



Amphibole asbestos fibers have complex crystalline structures that may regulate size and shape changes in response to physical, chemical and biological processes.

Cleavage of asbestiform fibers can occur and the resulting fibers (cleavage fragments?) are unlikely to be less toxic than the original fibers.

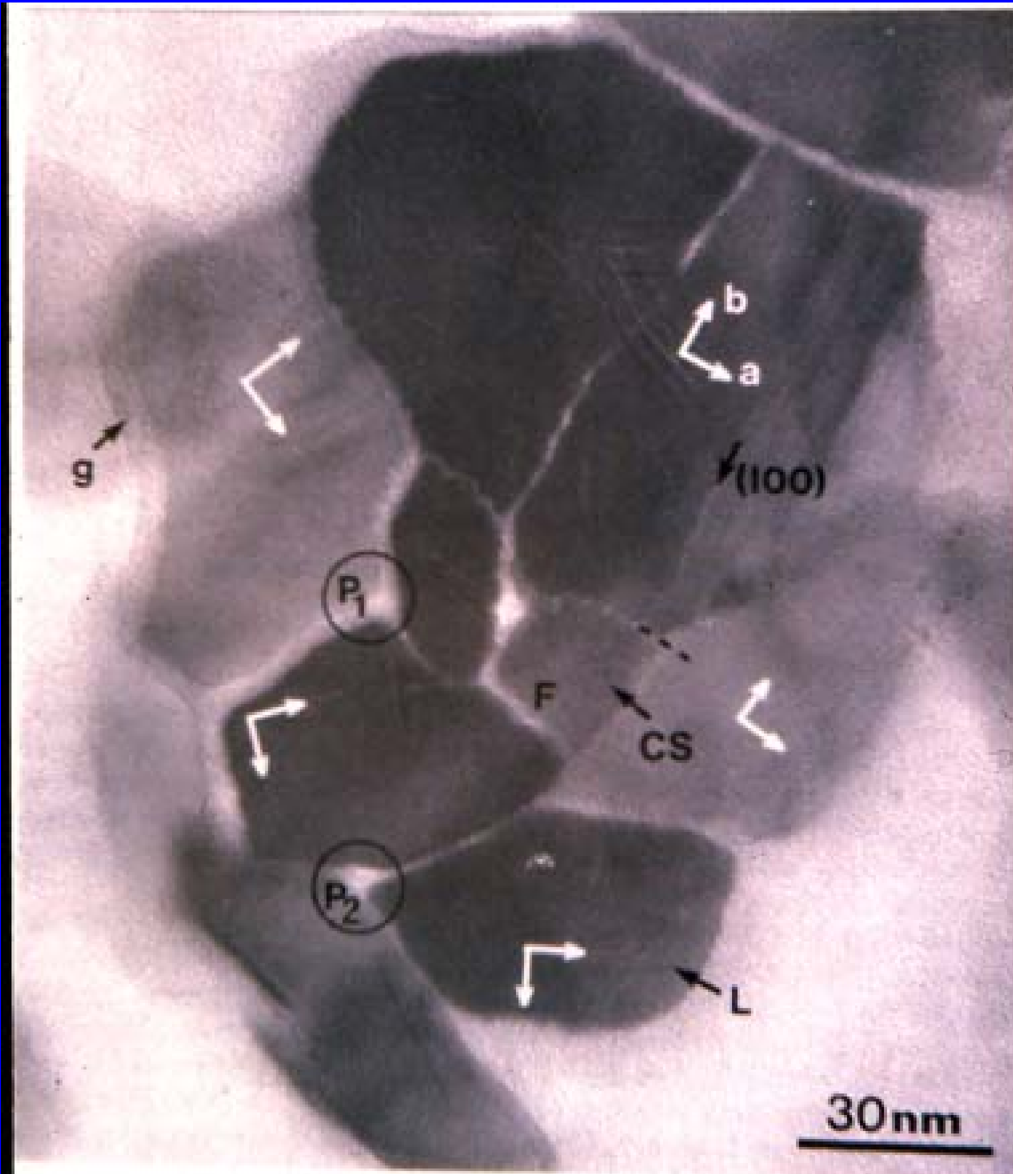
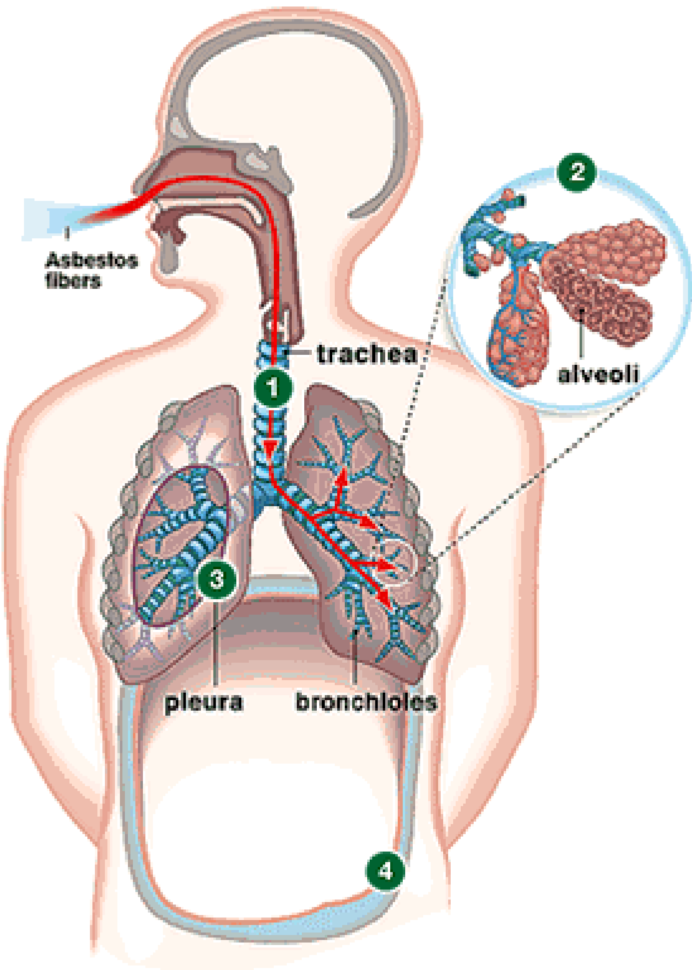
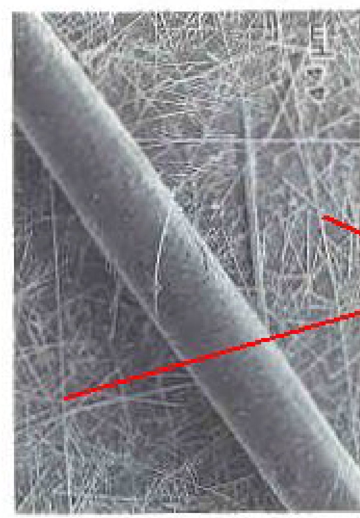


Fig. 2. Lattice image of a transverse section of a crocidolite fibre taken from human blood serum. This image was recorded with *hk*0 beams contributing to the image. See text for details.

Diseases Associated with Inhaled Asbestos

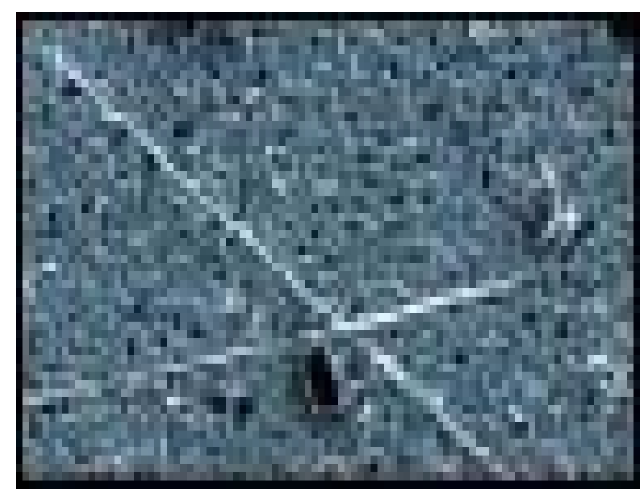




Amosite asbestos fibers seen under electron microscope appear as tiny, fine, straight images.

Human Hair

Tremolite

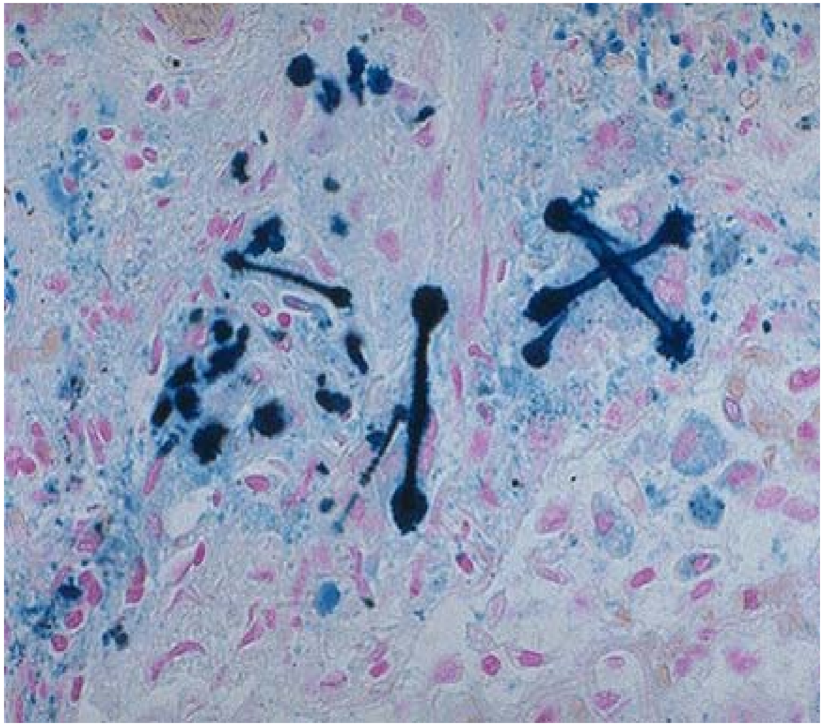


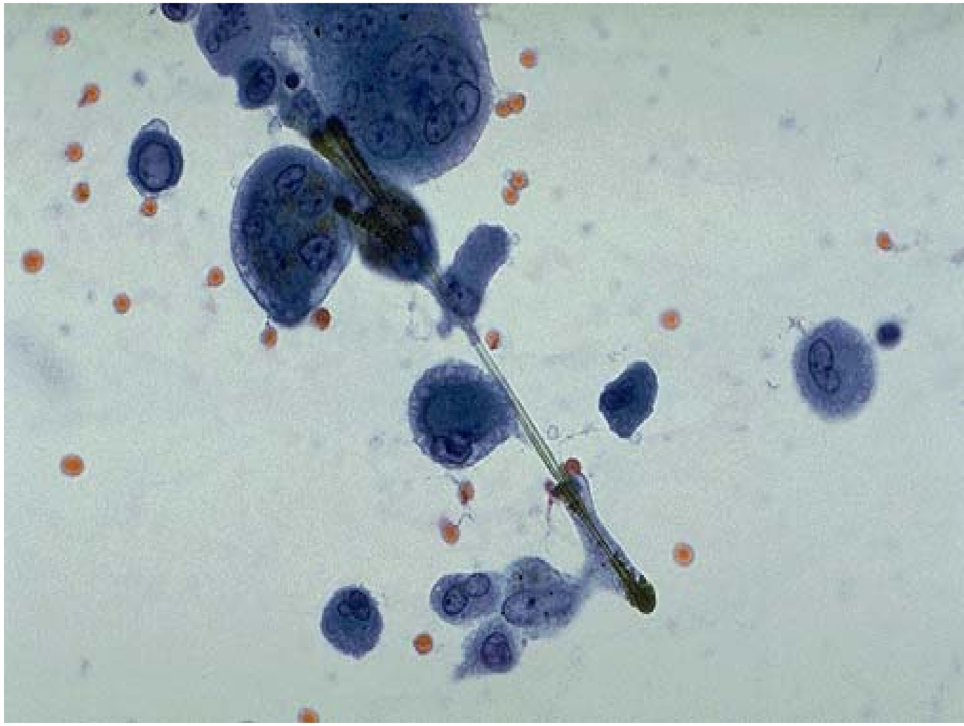
Phagocytosis of asbestos fibers

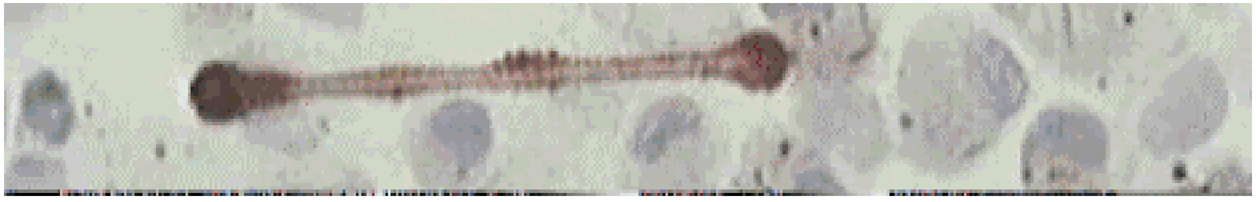
pulmonary alveolar macrophage cell attempting to engulf and ingest several long crocidolite asbestos fibers

incomplete ingestion of asbestos fibers can lead to extensive ‘selective release’ of proteolytic enzymes and ROS from the ‘frustrated’ PAMs

Ferrugenous bodies in lung tissues







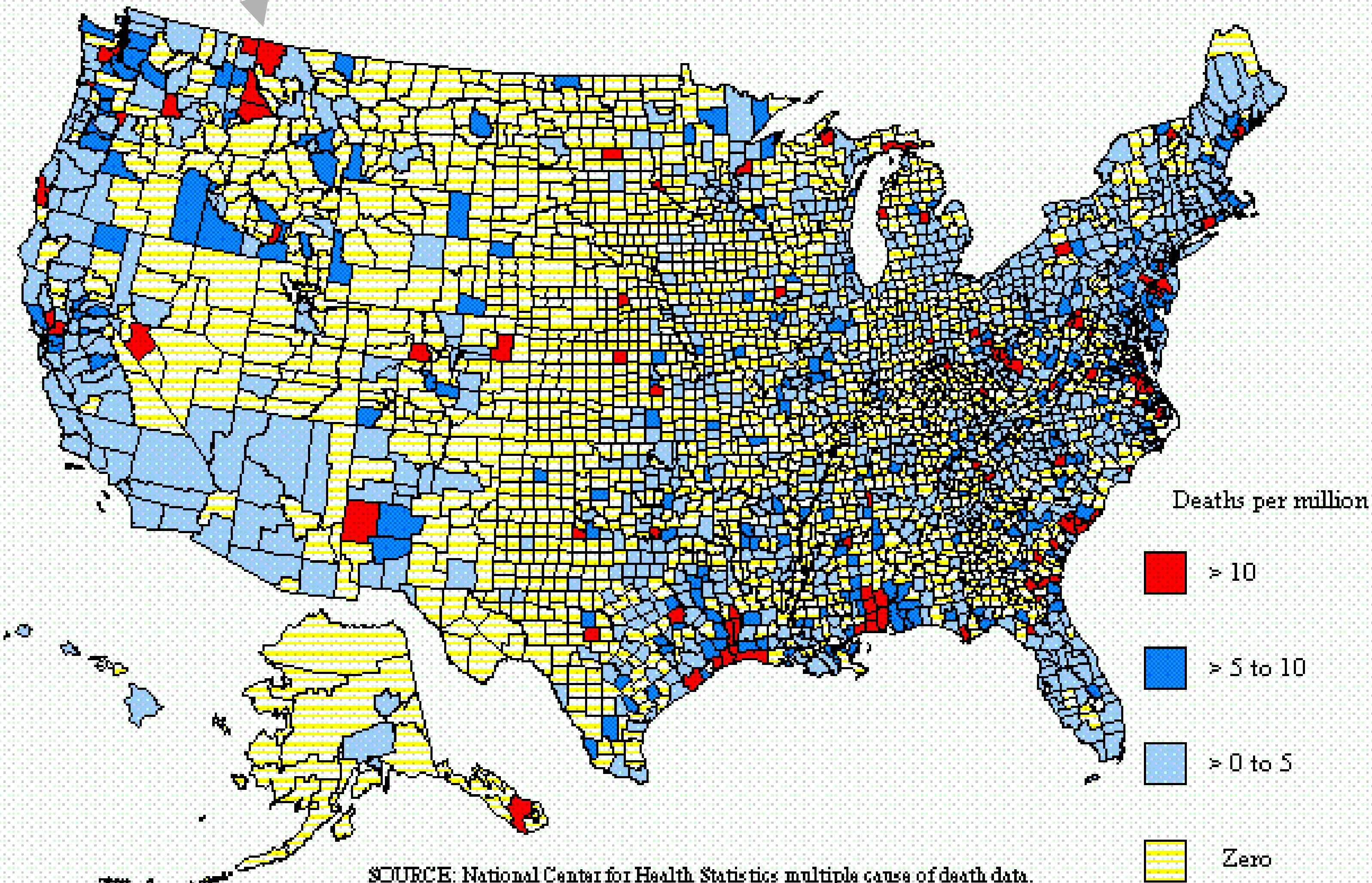
Mortality Rates (ATSDR, NIOSH)

Lincoln County: 60.1

40-60 times US Ave.

Figure 1-5. Asbestosis: Age-adjusted mortality rates by county,

U.S. residents age 15 and over, 1983-1992



SOURCE: National Center for Health Statistics multiple cause of death data.
Population estimates from U.S. Bureau of the Census.

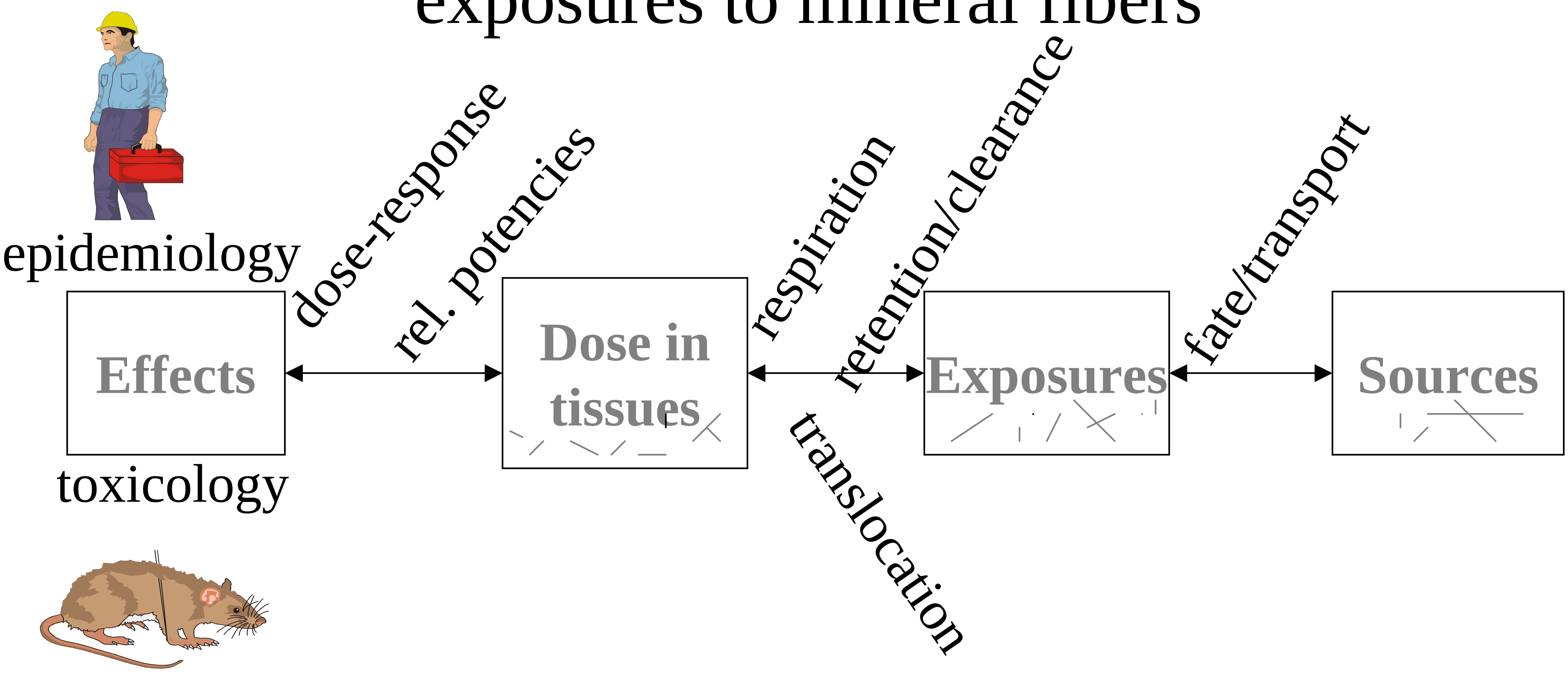
Loci of Cancers Associated with Asbestos Fiber Exposures

- Lung (smoking is a strong co-factor)
- Pleura - Mesothelioma
- Peritoneum - Mesothelioma
- Gastrointestinal tract
- Kidney

Times from low dose exposures to observations of disease are long: 30 - 40+ years lag time

Conceptual Model

for development of methods for prospective assessment of health risks associated with exposures to mineral fibers



Key question: what dose in tissues/lung should not be exceeded?

Temporal exposure issues - lifetime, short term, early life stages

Libby MT - old mine, new concerns

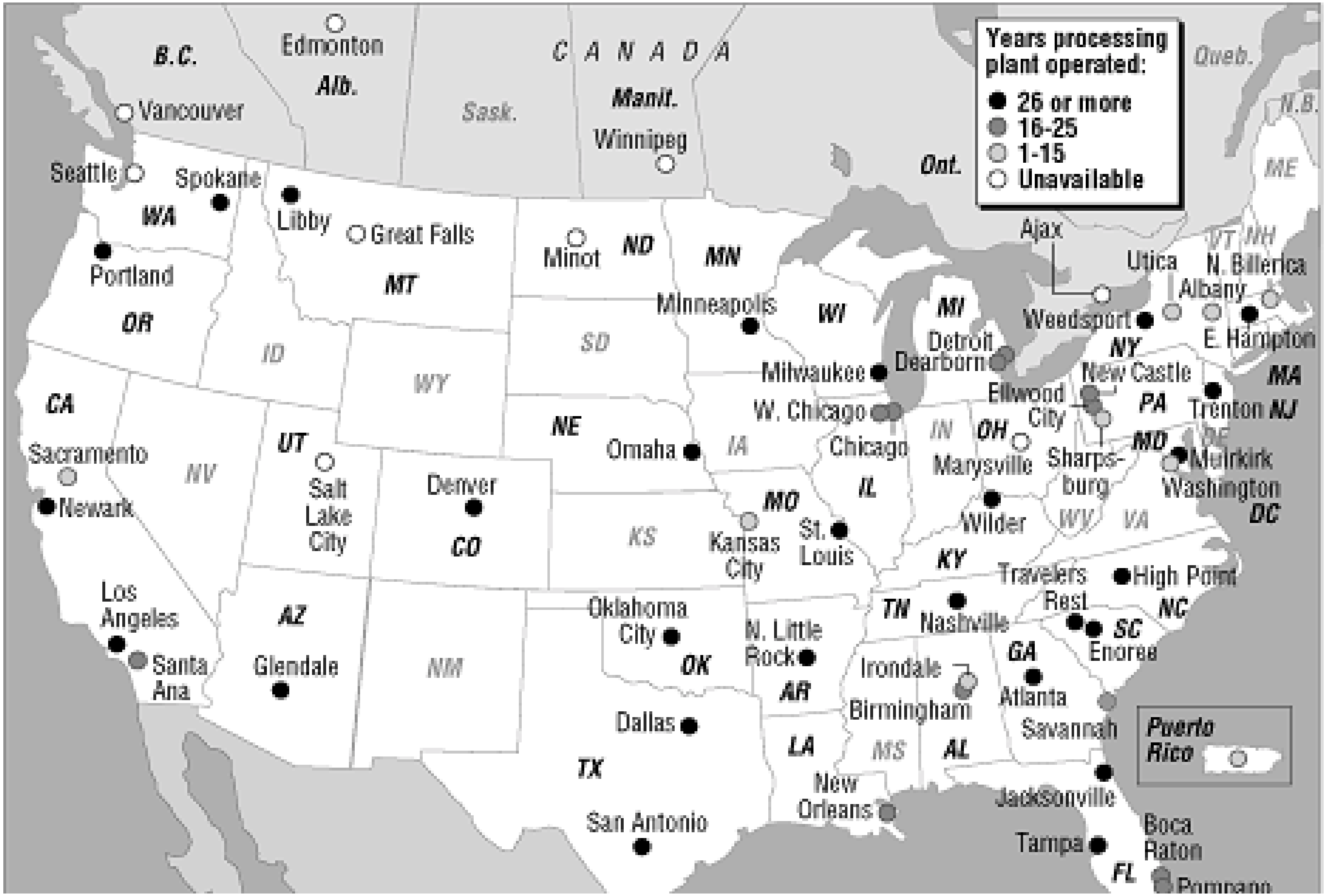
Zonolite Mine - Libby, MT

- Vermiculite mine started 1920’s
- About 6 miles from town
- Produced up to 80% of worlds vermiculite
  - Reportedly processed over 300,000 lbs/day
  - 5000 lbs/day of asbestos into the Libby Airshed
- WR Grace bought in 1963 & closed in 1990.

  - Products: construction aggregate, fireproof coatings, insulation, soil additive, fertilizer

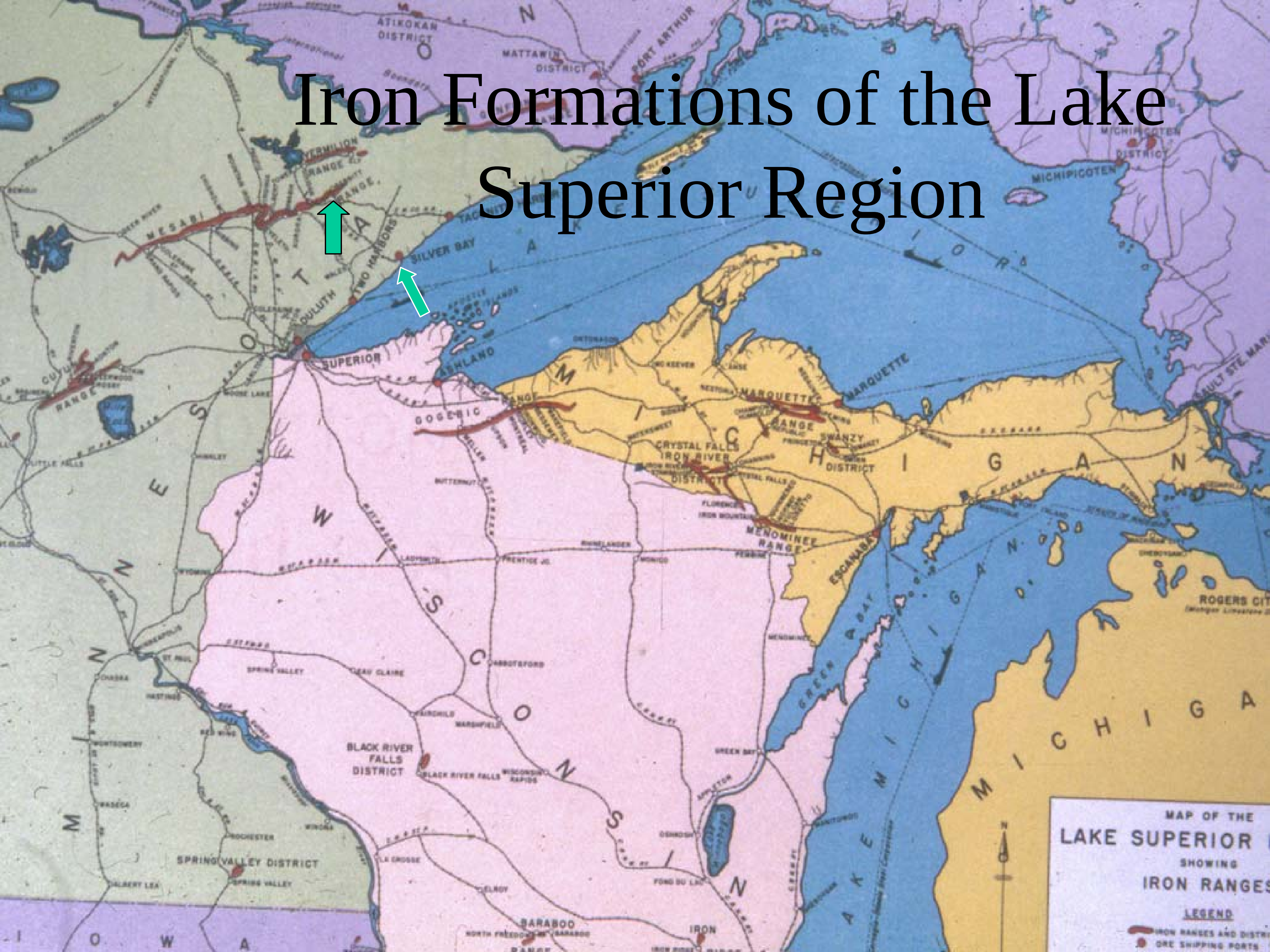
Plants that processed asbestos-tainted ore

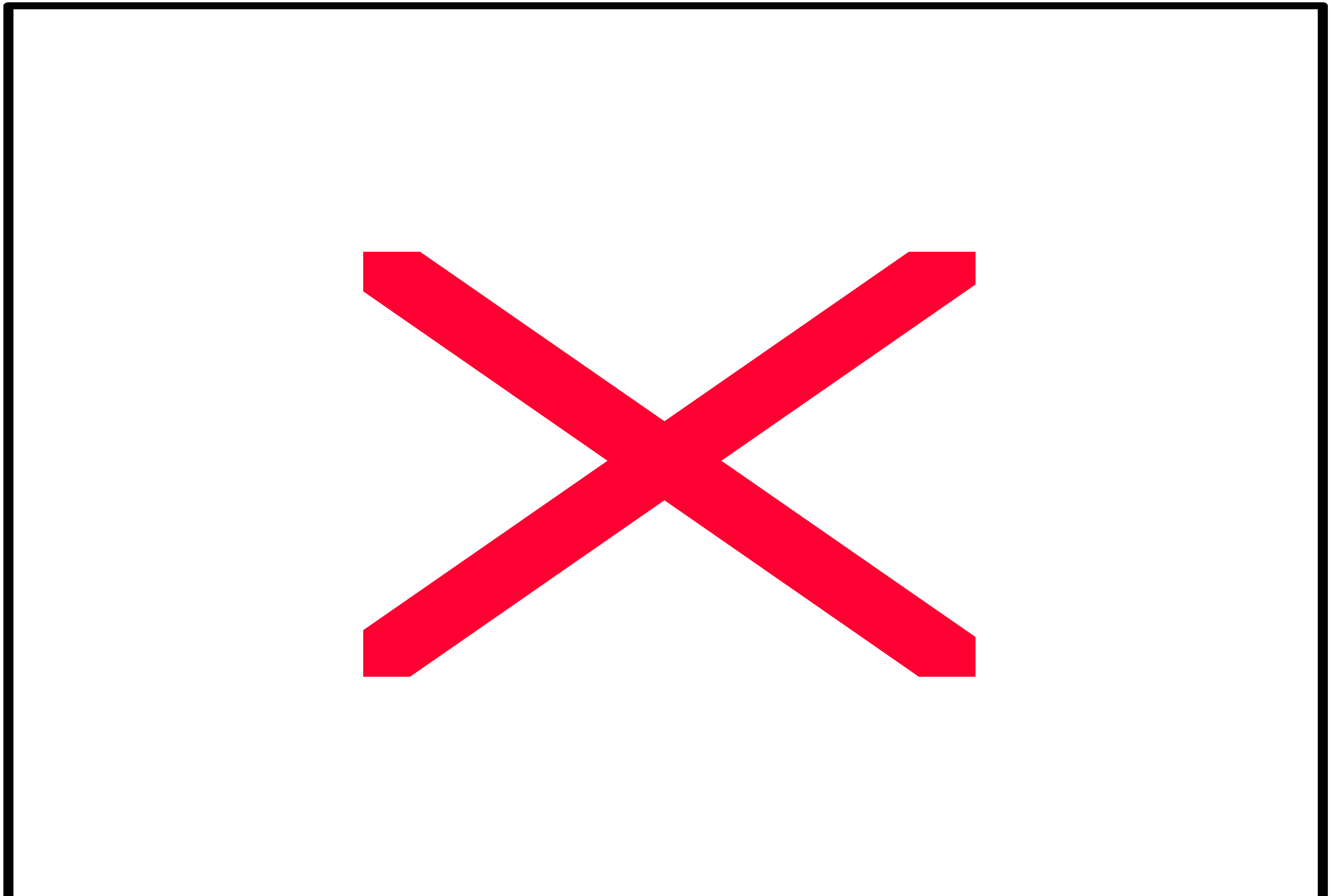
Millions of tons of the same asbestos-tainted vermiculite ore that sickened and killed hundreds in Libby, Mont., was shipped to plants in cities across the United States and Canada. The mine operated from 1924 to 1990. Some of the plants were owned or licensed by the mine's owners, the Zonolite Co., and after 1963, the W.R. Grace Co. Other plants were operated by firms that bought the ore. The ore was used in potting soil, insulation and other construction materials.



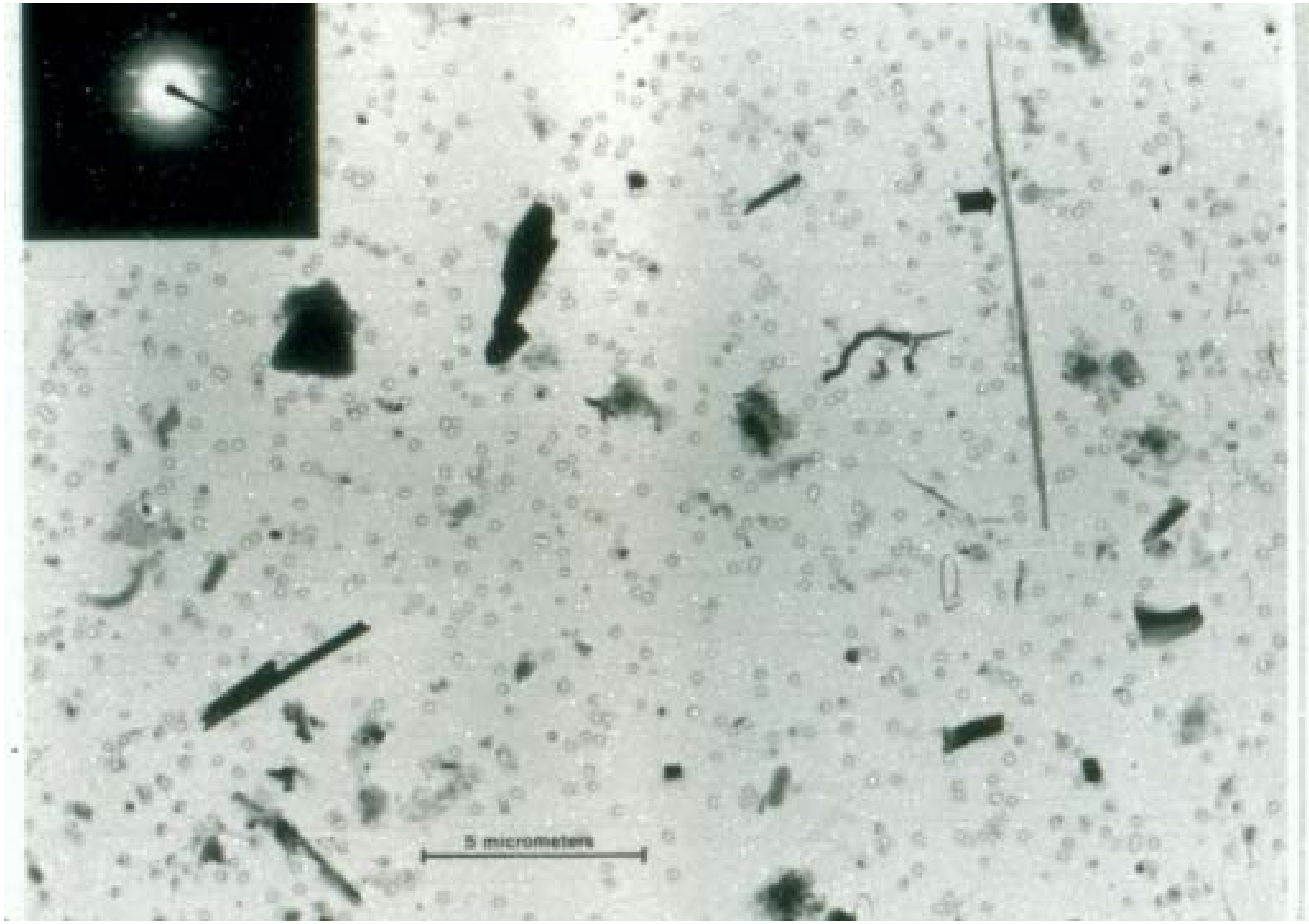
Over 300 Processing Plants Nationwide

Iron Formations of the Lake Superior Region

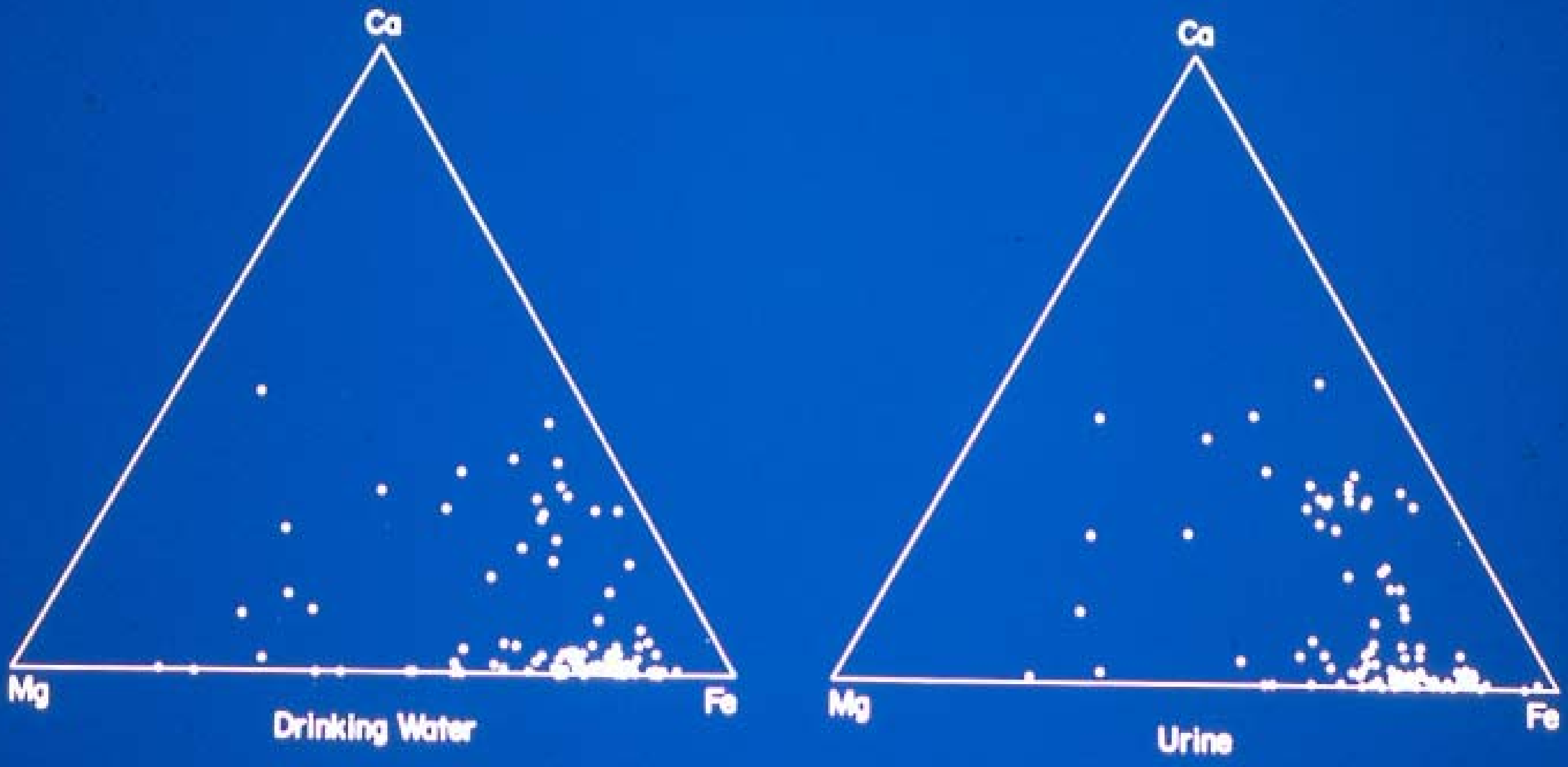




Transport of fine tailings particles caused turbidity in western Lake Superior



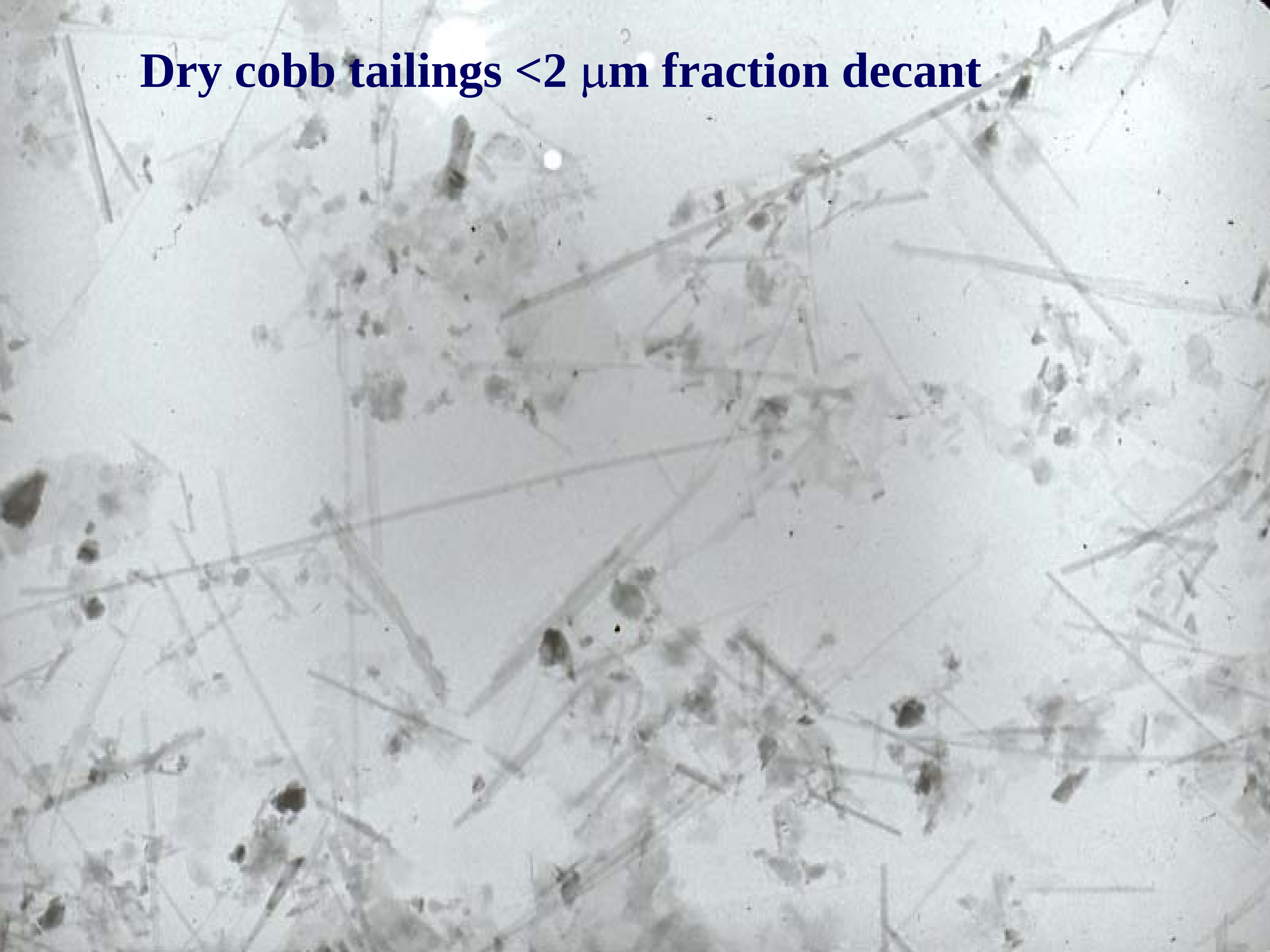
TEM view of particles in Duluth MN drinking water - 1973



Cook and Olson, *Science*, 1979


Dry cobb tailings <2 µm fraction

Dry cobb tailings <2 μm fraction decant

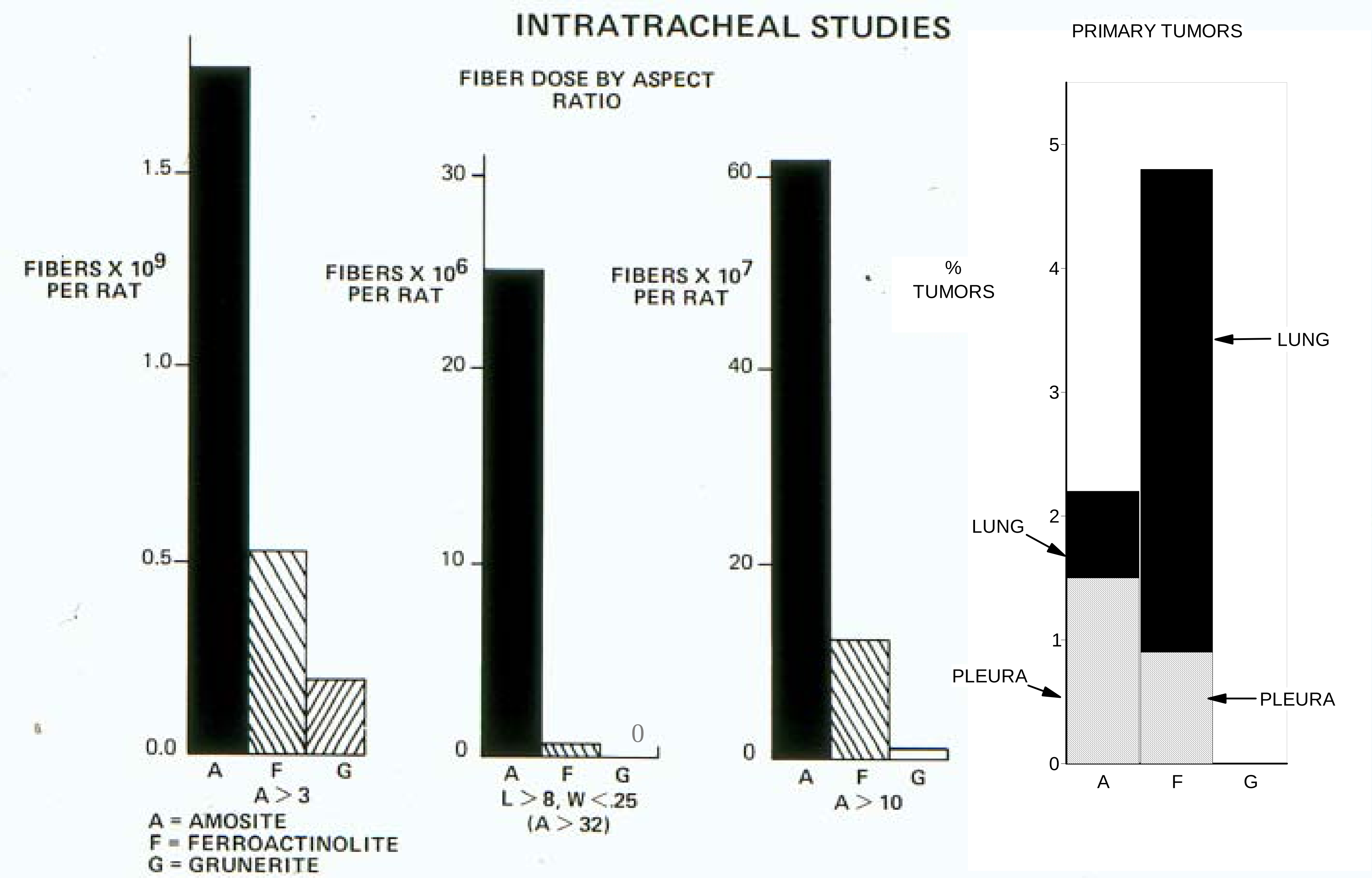


Background

- Concerns for risks associated with non-occupational exposures to mineral fibers (e.g. Reserve Mining Case), and interest in effects of synthetic fibers led to EPA research on effects associated with a wide variety of durable fibers during the period of 1978-1985.
- Determination of carcinogenic potencies relative to known asbestos materials was a major objective.
- The EPA laboratory at Duluth provided electron microscopic characterizations of samples used in biological tests, quantitative measurements of fiber doses in test animals, and determinations of dose-response relationships.

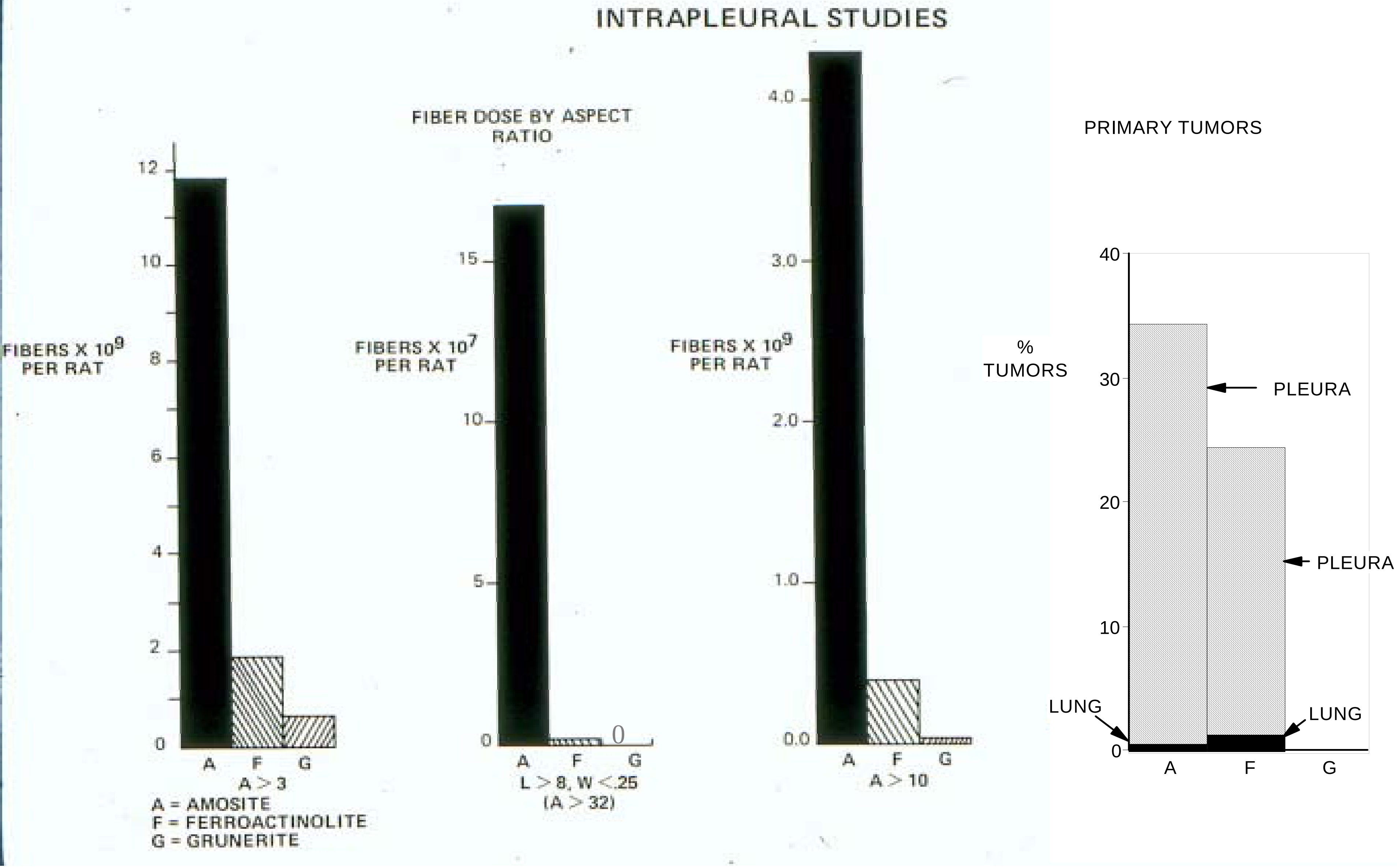
Intratracheal and Intrapleural Exposures of Fischer-344 Rats

- Primary objective was to determine relative potencies of different fiber types for carcinogenesis
- Studies included two samples of amphibole from taconite at Peter Mitchell Pit - ferroactinolite (fibrous) and grunerite (non-fibrous)
- Details of bioassays and effects provided in Coffin et al. *Toxicology Letters*, 1982
- Details of quantitative dose-response analysis provided in Cook et al. *Toxicology Letters*, 1982

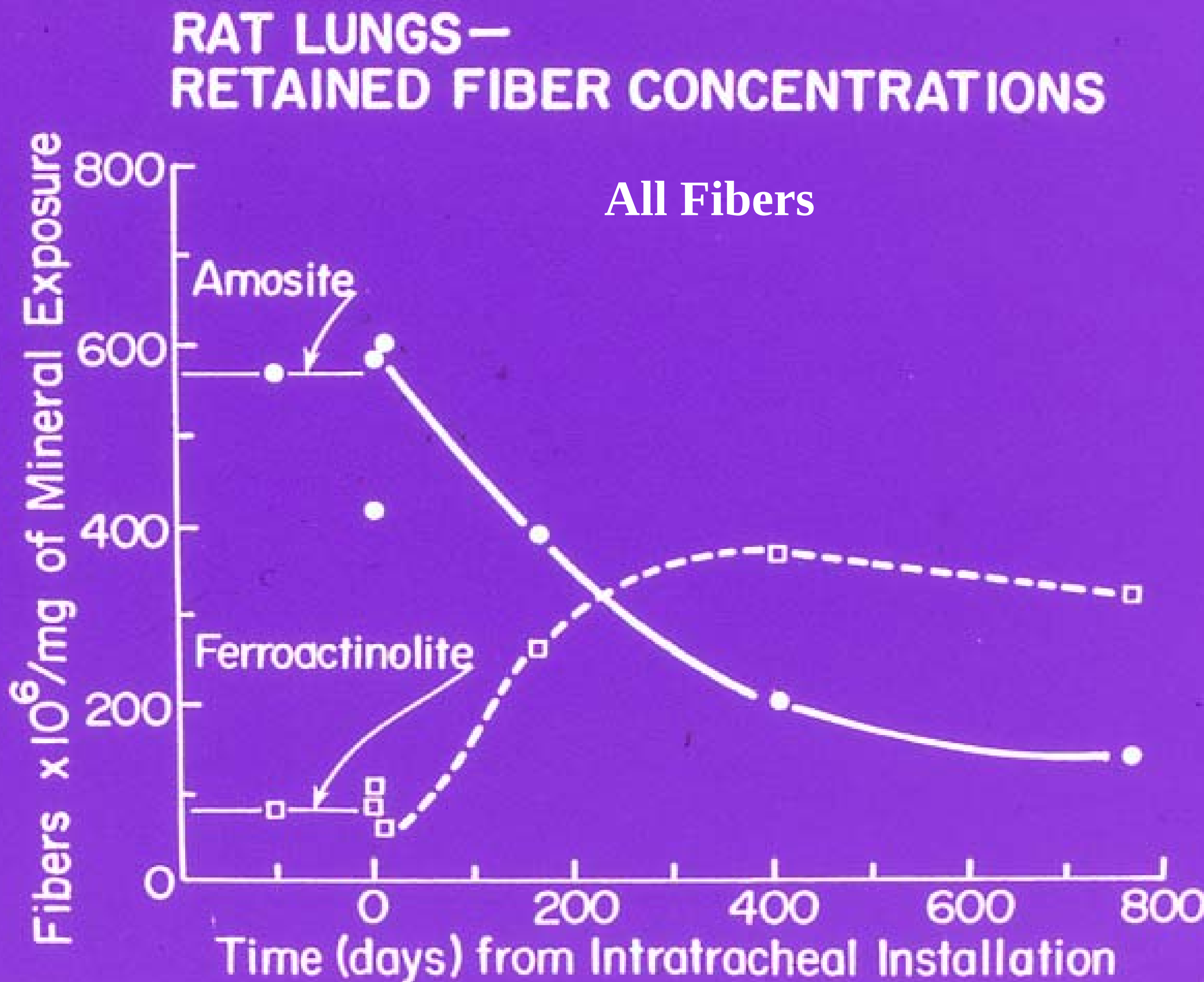


F/A ReP: 7.8 104 11.6

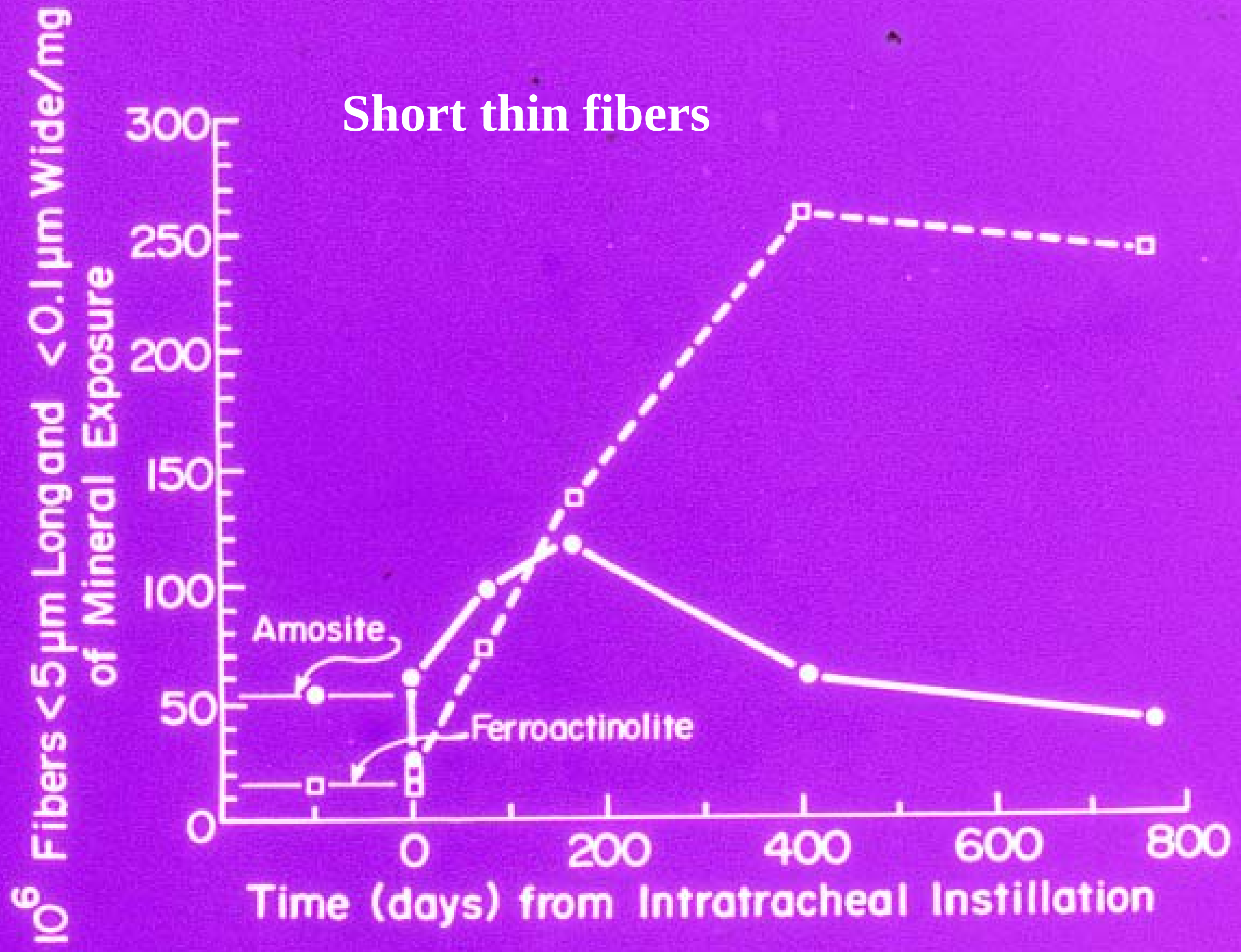
G/A ReP: <0.7 <200 <2.7



F/A ReP:	**4.7**	**62**	**11.6**
G/A ReP:	**<0.3**	**<70**	**<1.6**

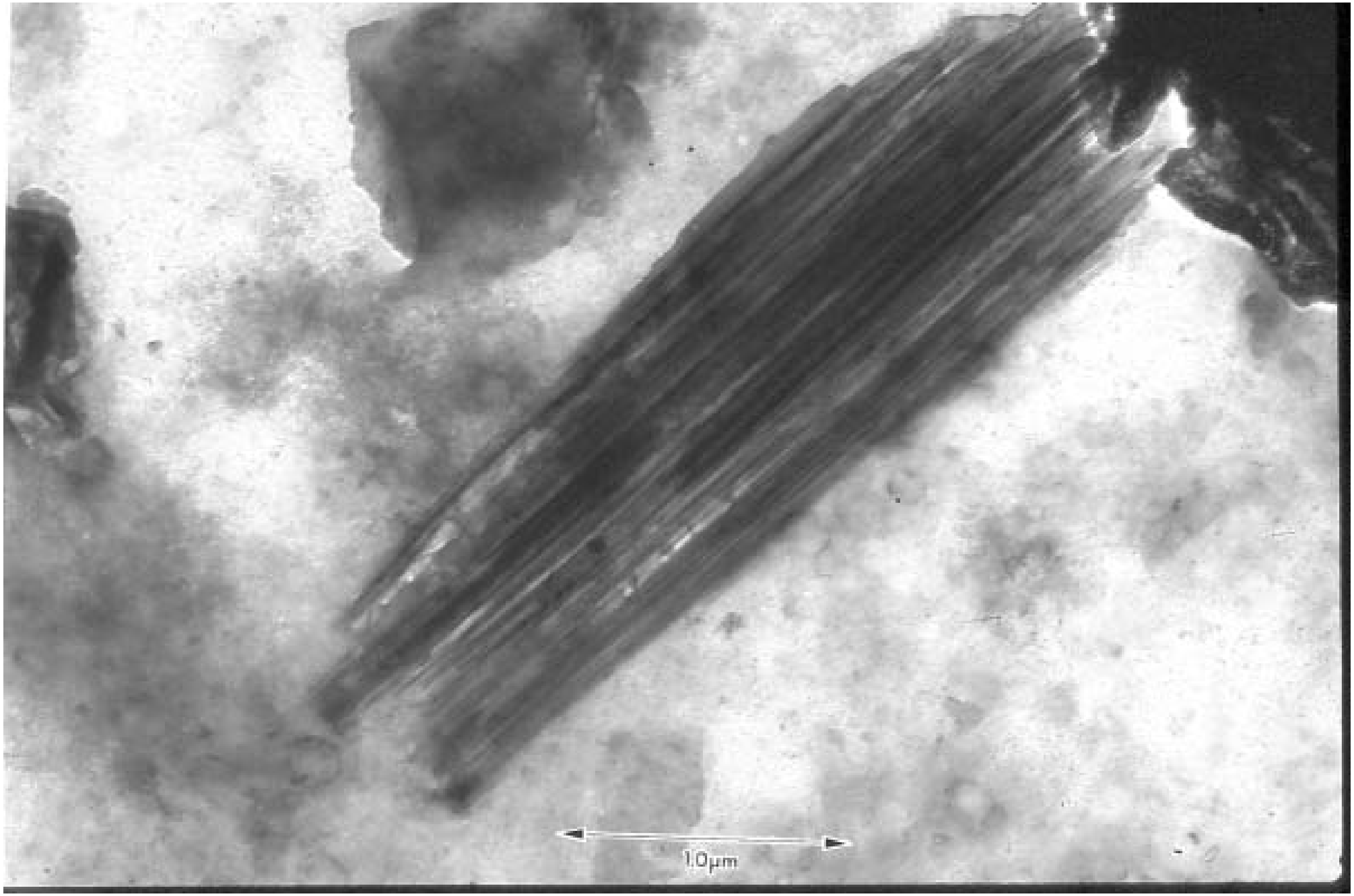

RAT LUNGS—
RETAINED FIBER CONCENTRATIONS
All Fibers
Amosite
Ferroactinolite
Fibers x 10⁶/mg of Mineral Exposure
800
600
400
200
0
0
200
400
600
800
Time (days) from Intratracheal Installation

Short thin fibers

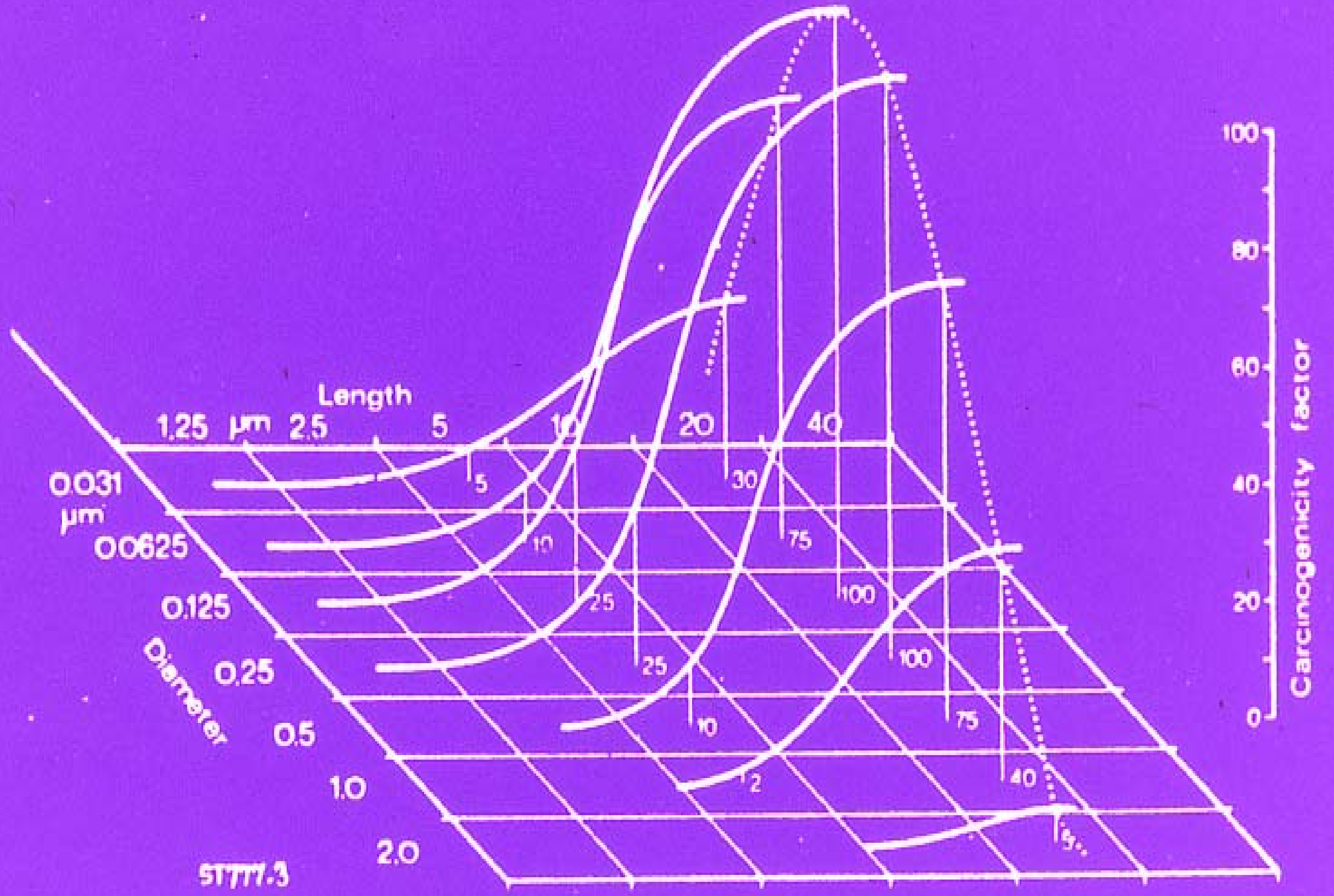


Eureka!

ferroactinolite fibers were dissolving and splitting longitudinally while residing in rat lung tissues over time.

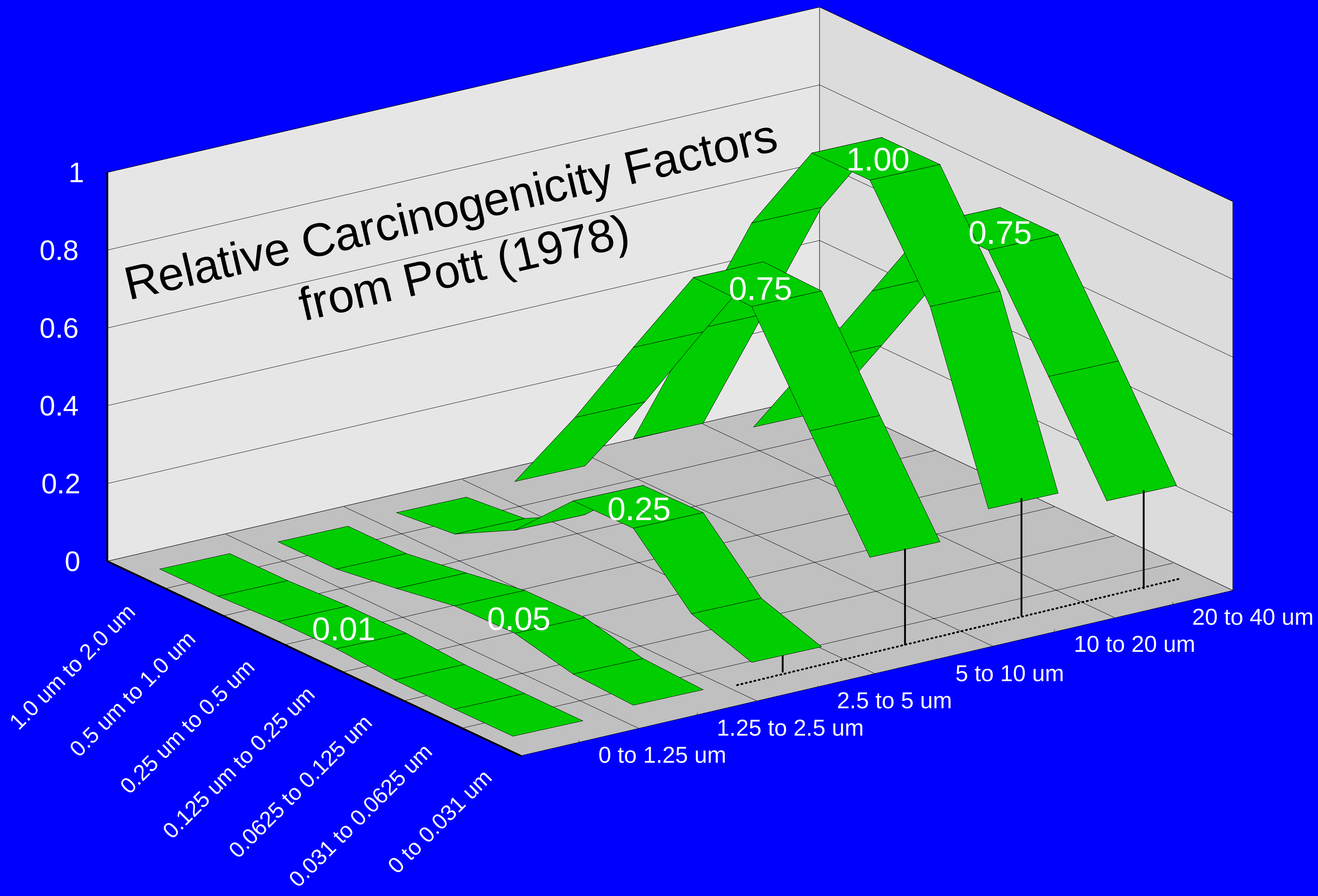


Anthophyllite in human lung



Conceptual Model for Carcinogenic Potency - Pott, 1978

(This three-dimensional model requires the fibre sizes of a sample to be divided into numerous categories. The size categories include three parameters: length, diameter and the length/diameter ratio)

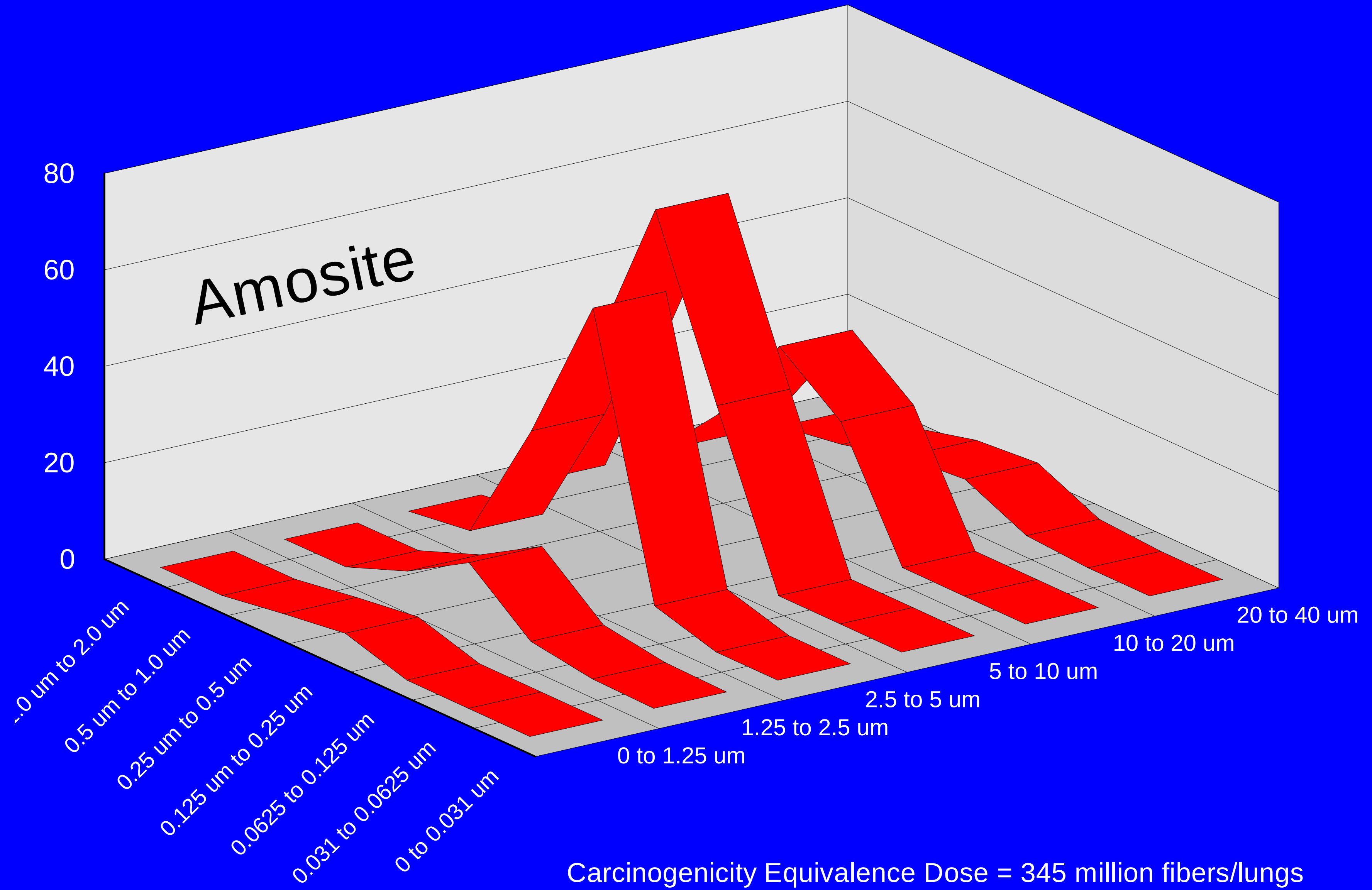


RCF = fraction of maximum potency/fiber

Carcinogenicity Equivalence Dose (CED)

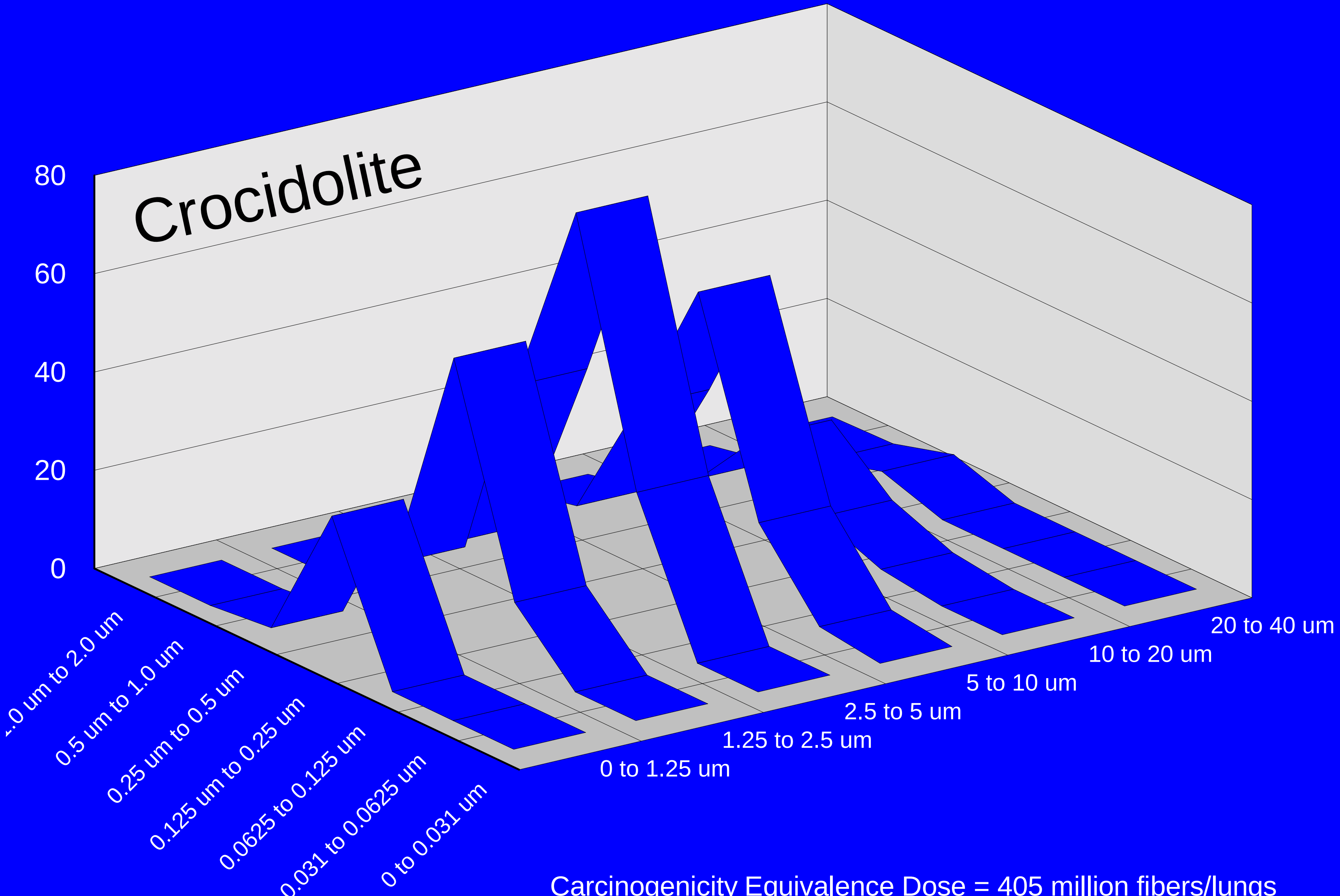
- A CED is the number of most potent fiber equivalents in the lung or pleura that results in a defined % of tumors.
- CED = $\Sigma(RCF_{i,j})(C_{i,j})$, where $C_{i,j}$ = # fibers/organ, RCF is the relative carcinogenicity factor (0 - 1), and i,j defines each of $i \times j$ length/width categories.
- The smaller the sample's CED, the greater the predicted potency for individual fibers.
- If amphiboles have equipotent fibers within specified size and shape ranges and the associated RCF values are reasonable, CEDs should be similar.

Rat Intratracheal Instillation



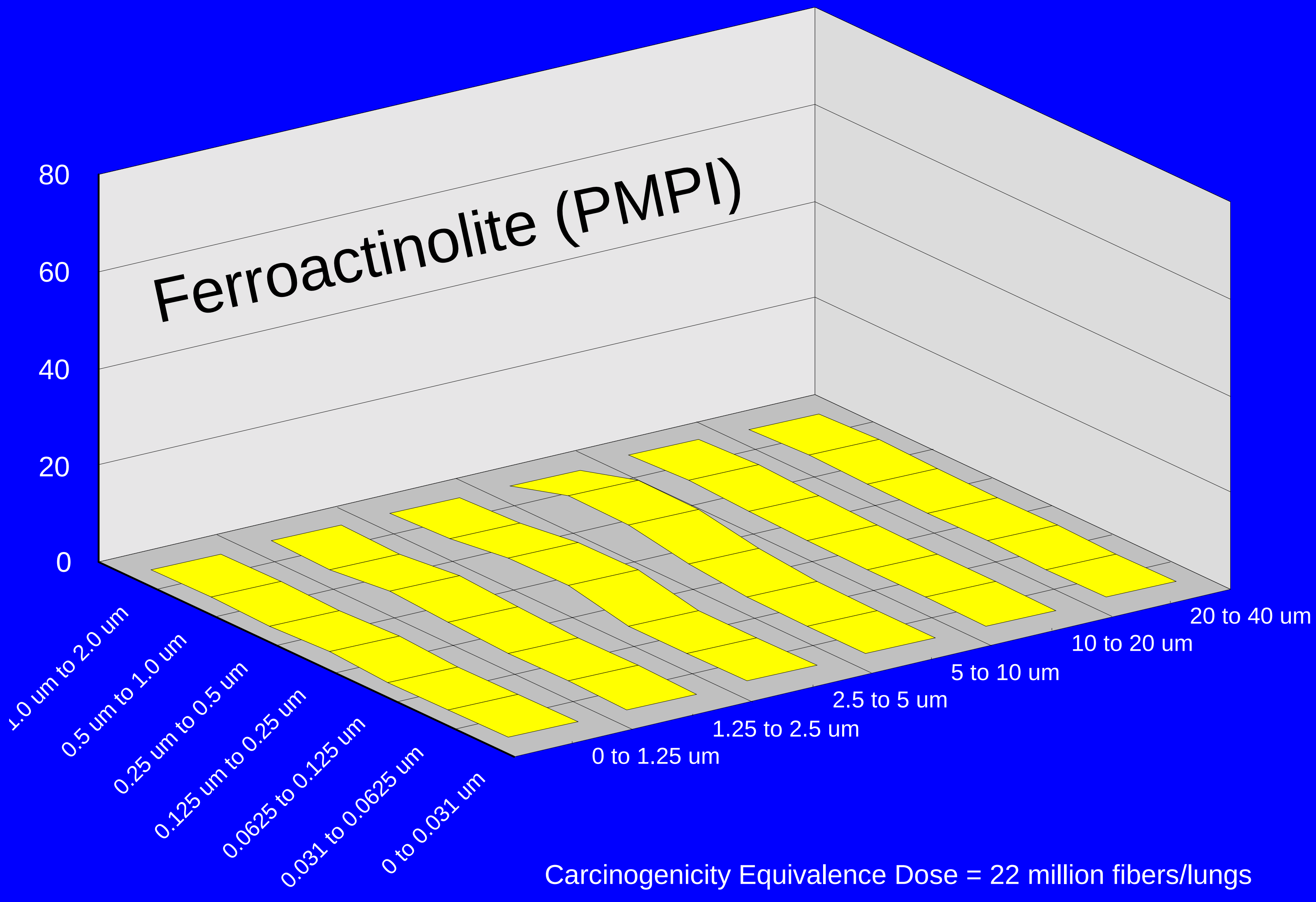
Carcinogenicity Equivalence Dose = 345 million fibers/lungs

Rat Intratracheal Instillation



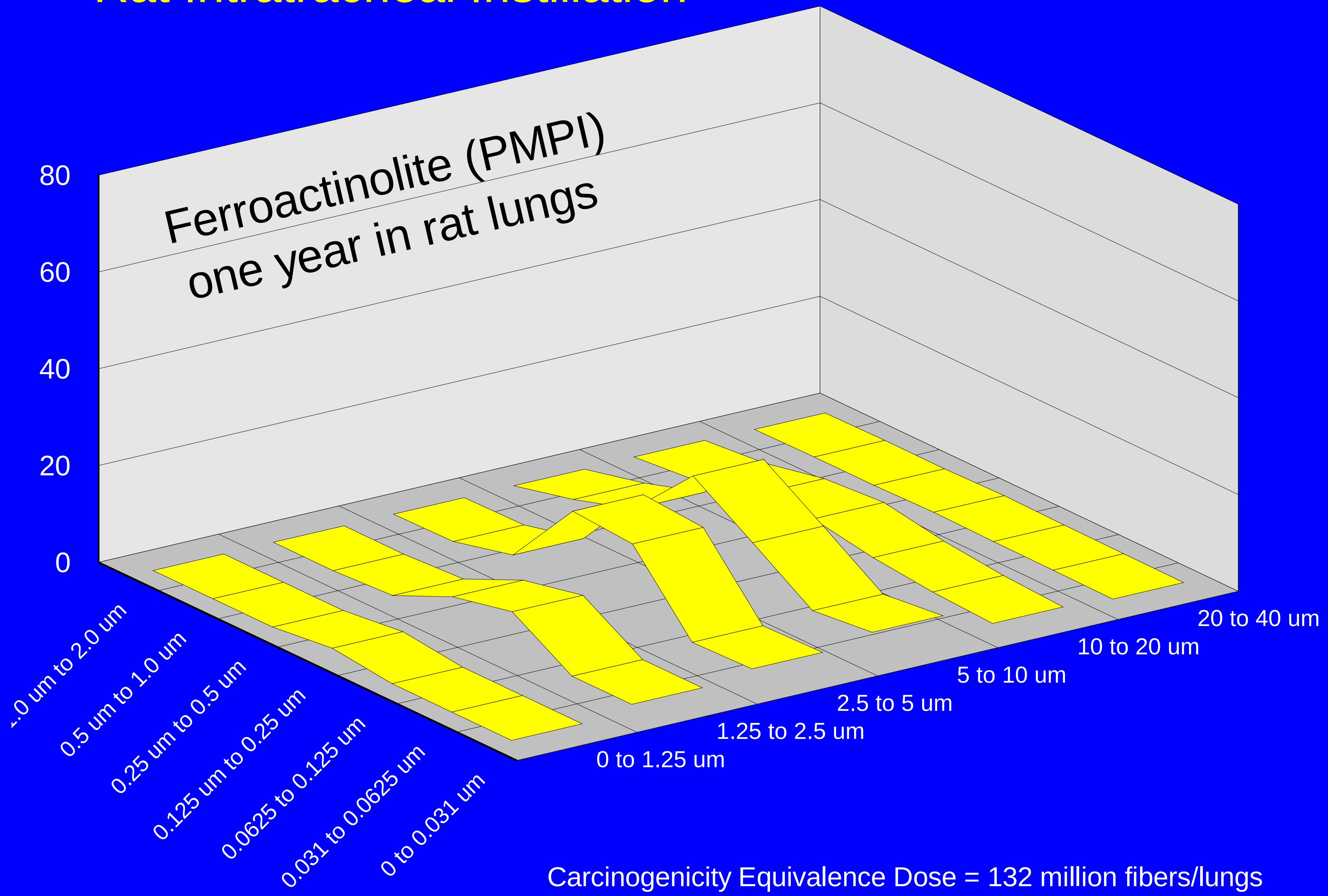
Carcinogenicity Equivalence Dose = 405 million fibers/lungs

Rat Intratracheal Instillation



Carcinogenicity Equivalence Dose = 22 million fibers/lungs

Rat Intratracheal Instillation



Carcinogenicity Equivalence Dose = 132 million fibers/lungs

Summary of fiber carcinogenicity equivalence doses (CEDs) from relative carcinogenicity factors (RCFs) based on Pott's hypothesis

Units for CEDs are millions of most potent fibers in lung per 5% tumors (IT) or in pleura per 30 % tumors (IP)

	amosite	crocidolite	ferroactinolite	ferroactinolite – one year	non-fibrous grunerite
Intratracheal	345	404	22	132	> ?
Intrapleural	1149	539	72	441	> ?

The greater the CED, the less potent the amphibole (if RCFs are accurate)

Proposal: greater RCFs for short and thin fibers than those proposed by Pott should be investigated and considered.

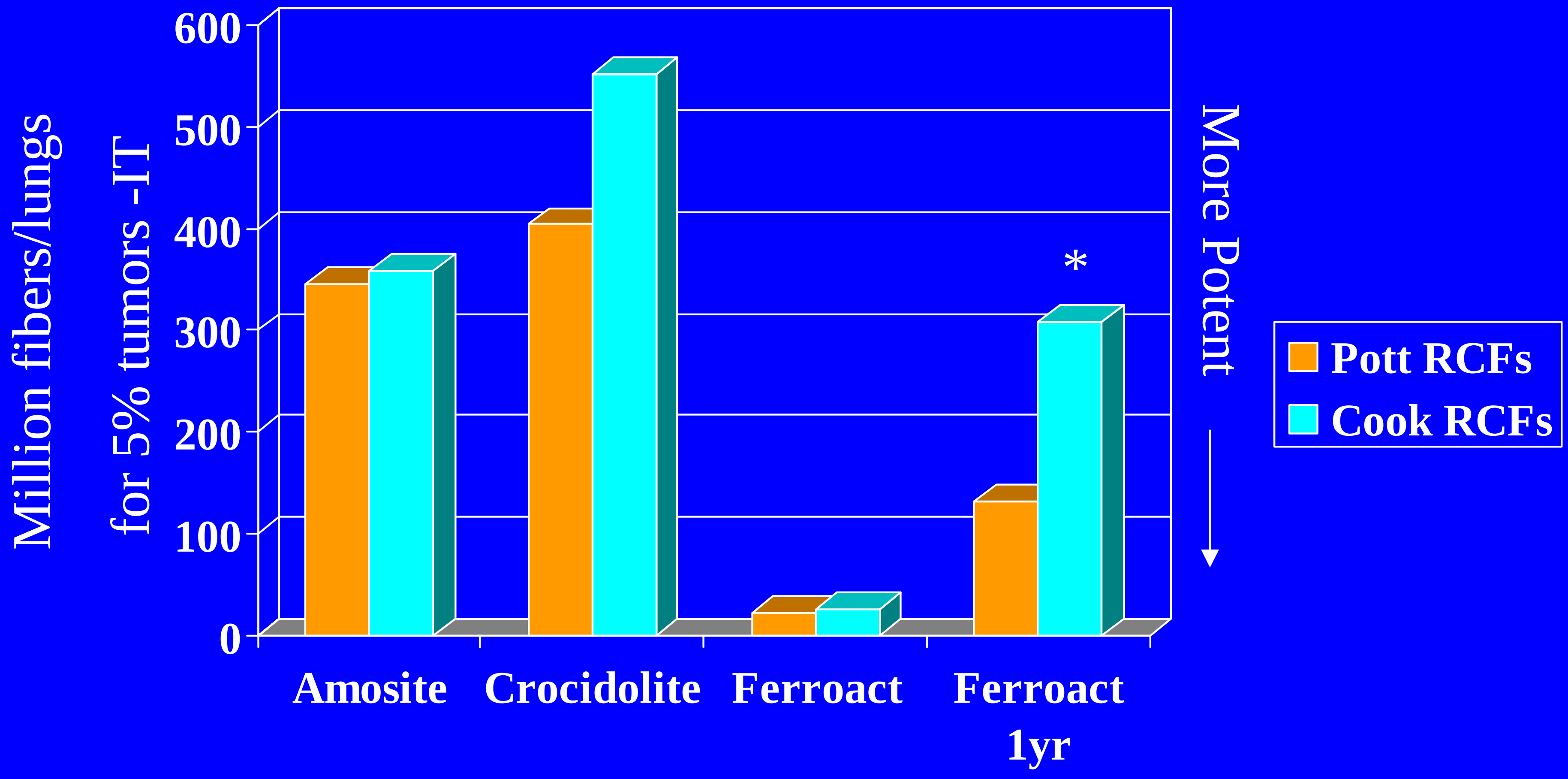
Conclusions

- Fiber splitting *in vivo* greatly enhanced the potency of ferroactinolite in rat studies.
- Short and thin amphibole fibers appear to affect toxicity. If not, long ferroactinolite fibers would have to be regarded as many times more potent than long amosite or crocidolite fibers.
- Because risk is a function of cumulative fiber dose, exposures should be measured on the basis of all fiber sizes with consideration of relative carcinogenicity and fibrogenicity of different size and shape categories.
- Similarly, exposure predictions should be based on all fiber sizes so that relative potencies can be included in risk assessments.

Adjust Relative Carcinogenicty Factors to Determine Optimum Values

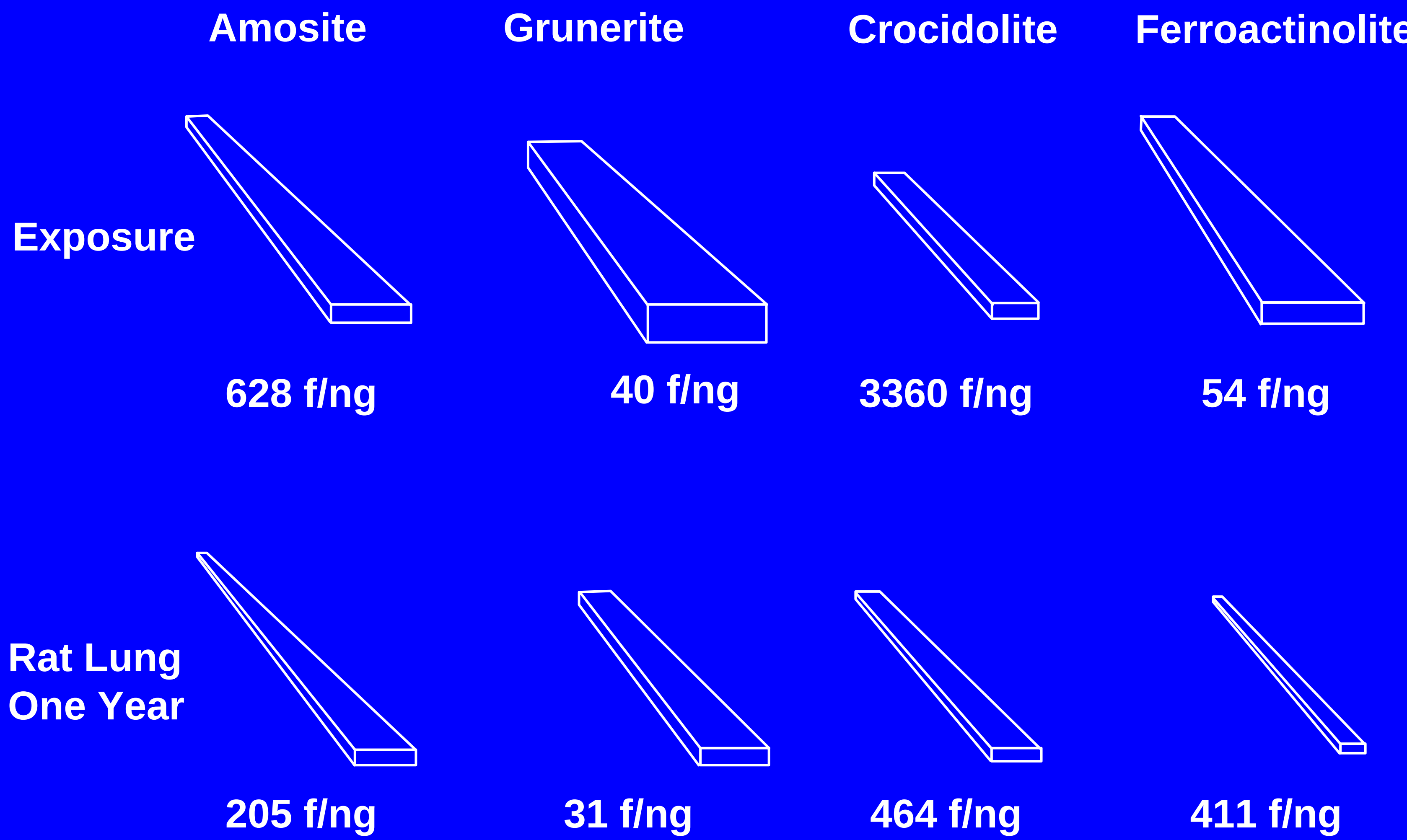
- Pott assumed short fibers have very low potencies and did not increase potency of very thin fibers.
- Cook suggests modest increase of RCFs for short, thin fibers.
- If all amphibole fibers have potencies primarily determined by fiber size and shape, carcinogenicity equivalence doses should be similar.

Carcinogenicity Equivalence Doses with Alternative RCFs

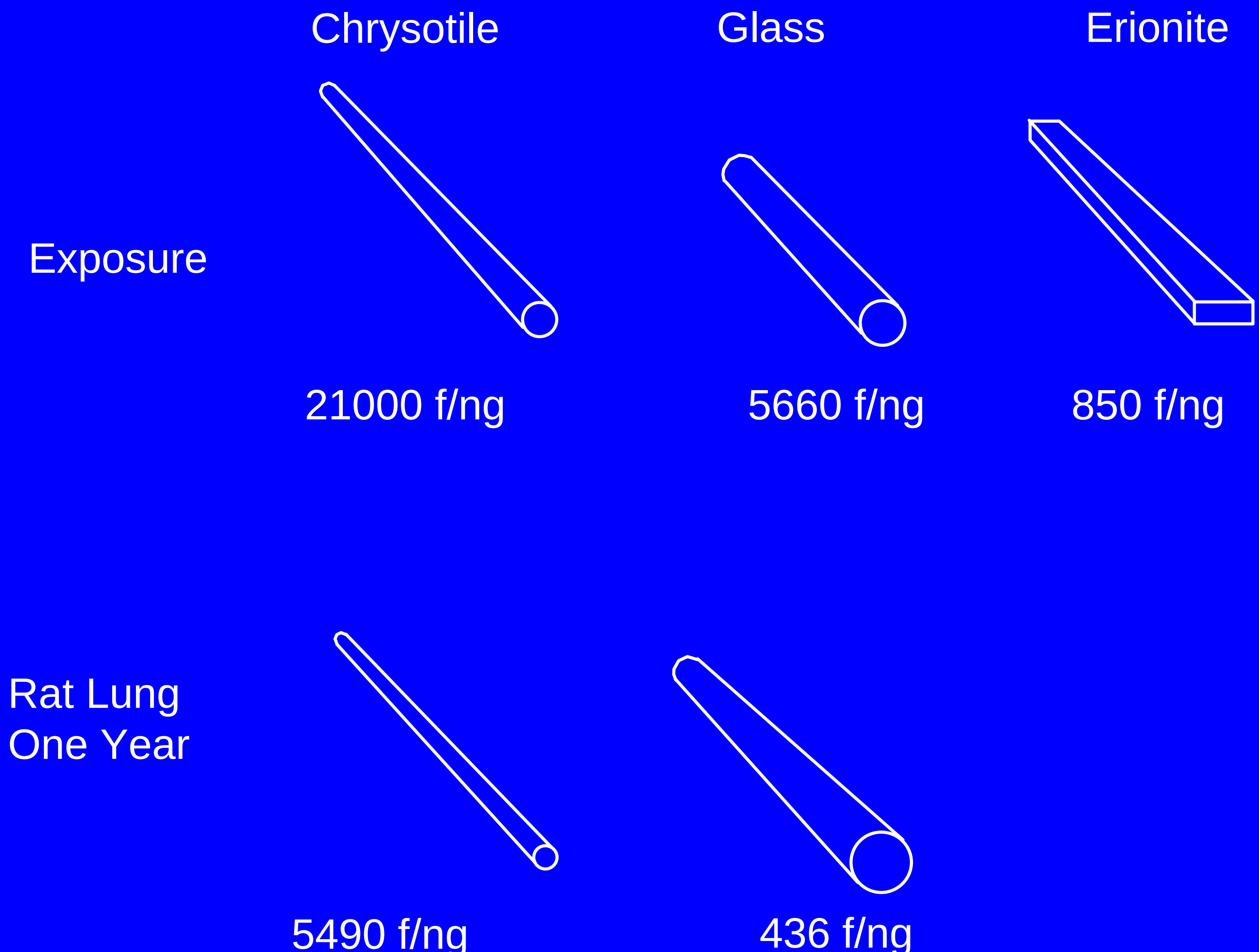


* For Cook RCFs, Amosite and Crocidolite CEDs at 1 year ☞ Ferroactinolite CED at 1 year.

Mean Shapes and Sizes of Fiber Types



Mean Shapes and Sizes of Fiber Types



Conclusions continued

- **Need to determine fiber residence time in lung for optimal expression of potency in rats and humans in order to better define and extrapolate dose-response relationships.**

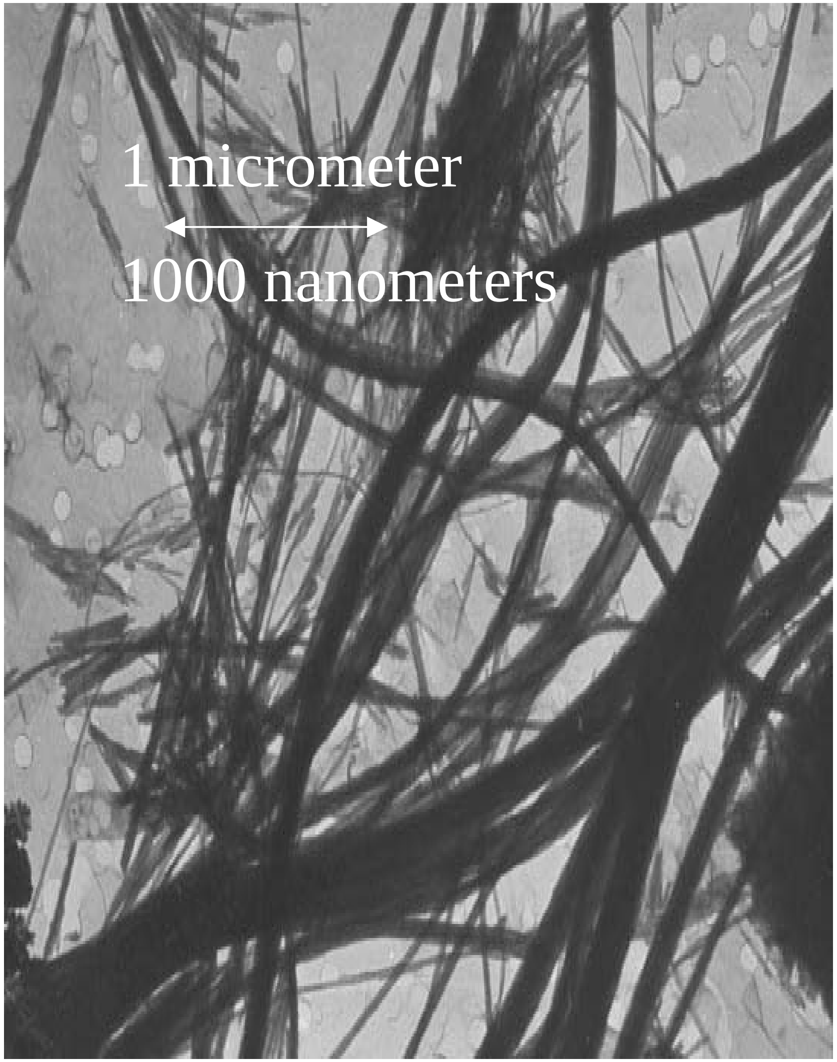
- **Quantitative TEM analyses may be used to calibrate PLM, XRD, and other analytical methods which can not directly measure all fibers in exposure assessments.**

Risk Assessment Limitations Perpetuated by Narrow Definitions of Hazardous Fibers

- No methodology for assessing risks from short fibers - need a relative potency model
- Weak links to mechanism of action data
- Unable to provide precise definition of undesirable synthetic fibers so that safe alternatives can be developed
- Human dose-response relationships are very uncertain and may be inaccurate

Properties of microscopic fibers that indicate potential for causing asbestos-like pathologies

- Size and shape that allows respiration, retention in lungs, and translocation to pleura
- Durable, persistent in tissues
- Reactive surfaces, ability to induce ROS
- High collective surface area
- Propensity to split into thin fibers *in vivo*



Chrysotile Asbestos

Asbestos ?

Carbon Nanofibers

L = 5-20 λm

W = 0.1-0.2 λm

$3,500/kg

Potential Applications of Carbon Nanofibers

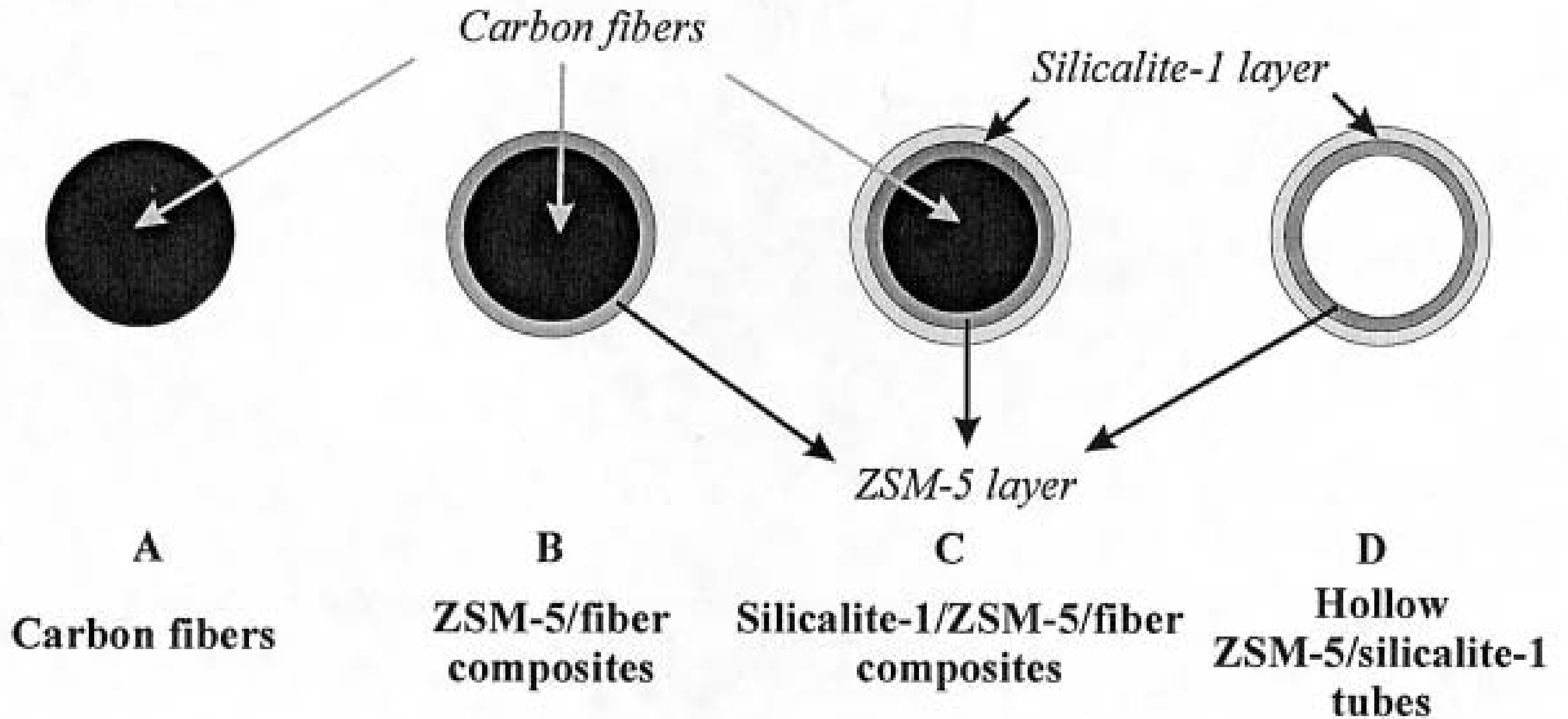
Additives in ploymers
Catalysts
Electron field emitters for
- cathode ray lighting elements
- flat panel display
- gas-discharge tubes in telecom networks

Electromagnetic-wave absorption and shielding
Energy conversion
Lithium-battery anodes
Hydrogen storage
Nanotube composites (by filling or coating);
Nanoprobes for
- STM, AFM, and EFM tips
- nanolithography
- nanoelectrodes
- drug delivery
- sensors

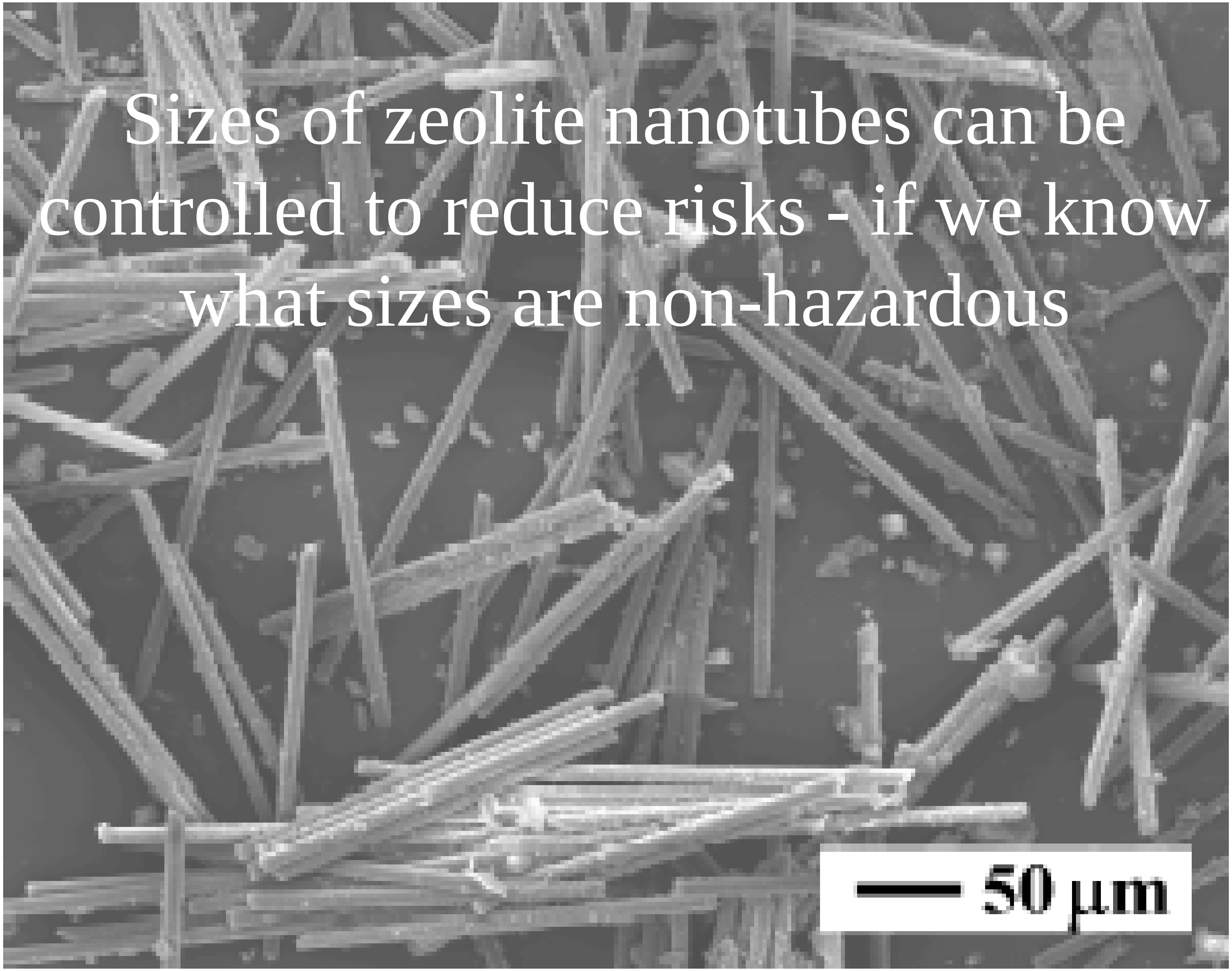
Reinforcements in composites
Supercapacitor

Zeolite tubes

Carbon nanofibers are used to produce zeolite nanotubes



Sizes of zeolite nanotubes can be controlled to reduce risks - if we know what sizes are non-hazardous



Effective environmental protection requires that each new generation advances the knowledge passed on by the previous generation