Influence of Fiber Type, Size, and Number in Human Disease: Conclusions from Fiber Burden Analysis

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Techniques, Advantages, and Limitations of Fiber Burden Analysis

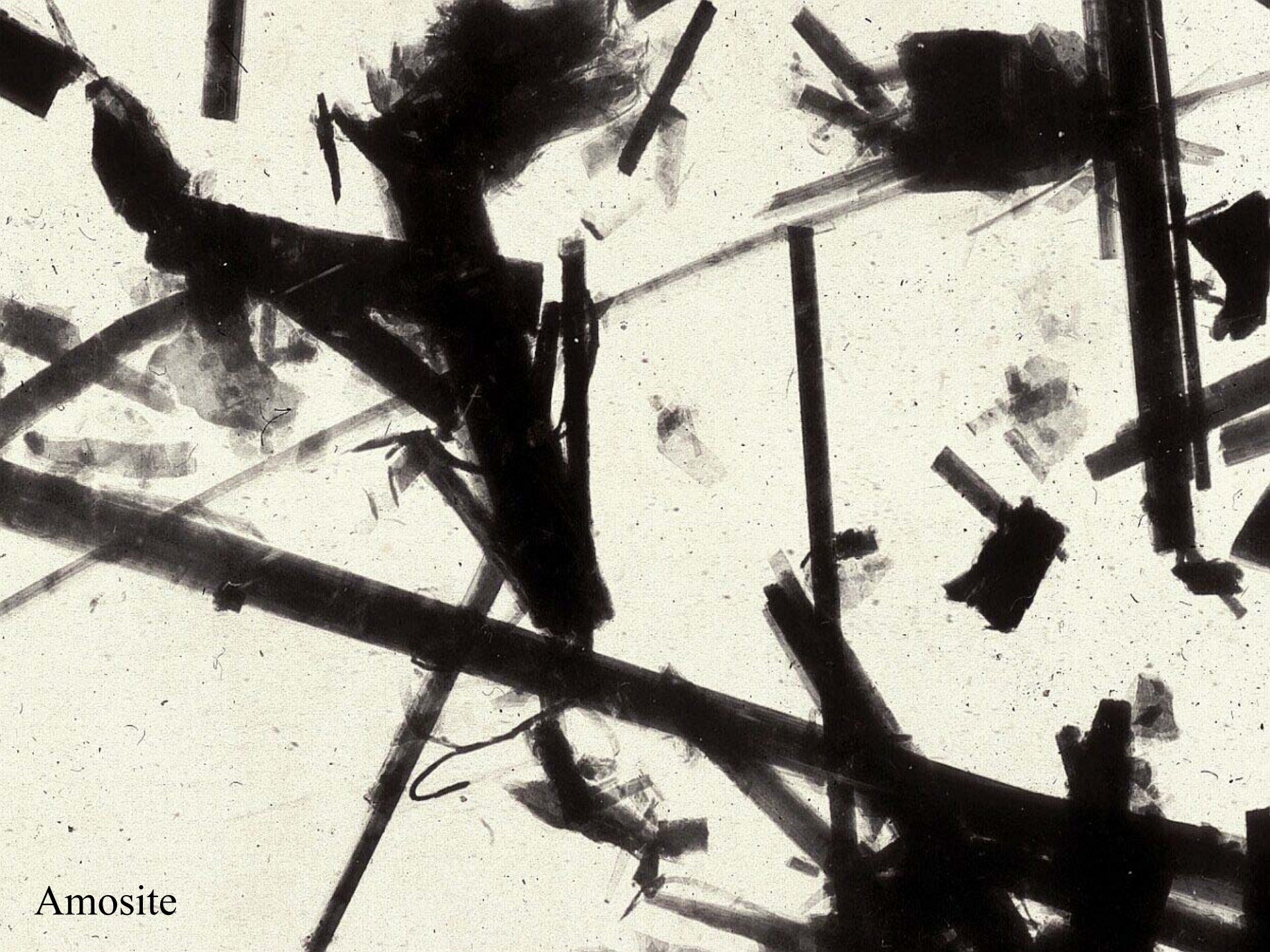
Chrysotile

Non-
Commercial

Amphiboles

Commercial

Amphiboles

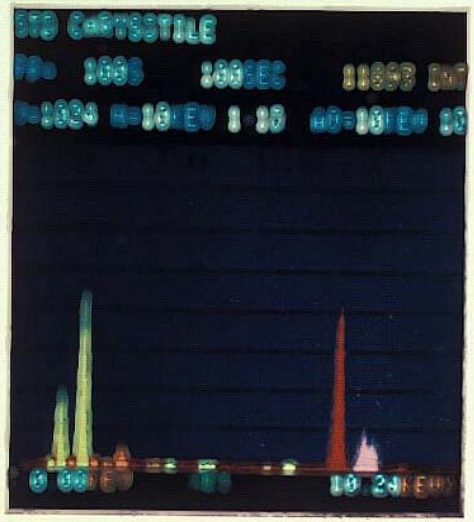


Amosite

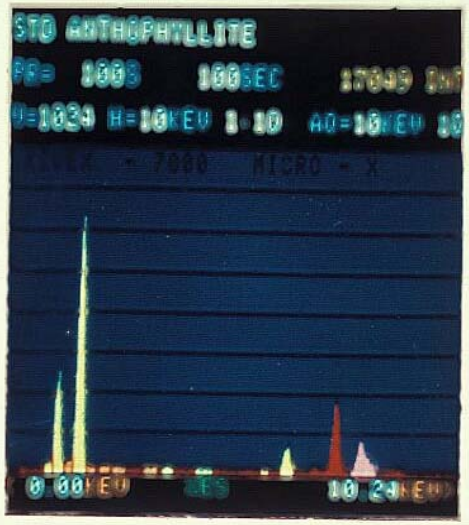

Chrysotile

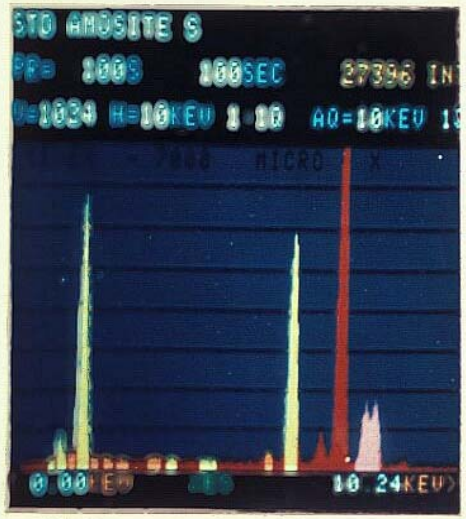
Energy Dispersive X-Ray Spectra

Chrysotile

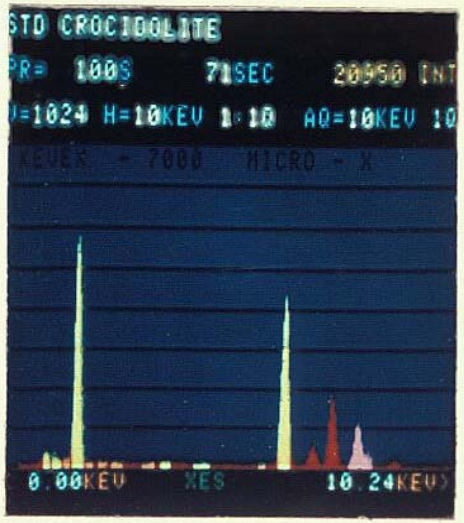


Anthophyllite





Amosite



Crocidolite

Fiber Burden Analysis: Definition

- Evaluation of the mineral (asbestos) content of lung or other tissue
- Term is usually applied to tissue digests examined by light or electron microscopy
- In principal can be applied to simply counting asbestos bodies in tissue sections (insensitive) or lung digests

Utility of Fiber Burden Analysis

- Only direct source of information about lung fiber content/exposures
- Detects occult (amphibole) exposures
- Supports/contradicts epidemiologic data
- Can be used to confirm/deny predictions from animal models
- Can be used to validate deposition/clearance models

Limitations of Fiber Burden Analysis

- Usually samples only 1 time point and that is typically after exposure has ceased
- Underestimates chrysotile exposures
- Geographic variations in intrapulmonary fiber burden may be important
- Marked lab to lab variation in absolute numbers/fiber sizes obtained

Fiber Burden Analysis: Instrumentation

- Transmission EM: Detects fibers of all sizes. Analytical instrument allows fairly exact identifications
- Scanning EM: Will miss small fibers, especially chrysotile. Analytical instrument allows fairly exact identification
- Phase contrast microscopy: Only detects relatively large fibers with no guarantee as to identity of fiber
- Counting asbestos bodies: In most settings is a measure of commercial amphibole exposure
- *Different methods give different results!*

Relationship of Amosite Fiber Burden and Disease from 2 Different Labs

Disease	Churg Lab[1]	Roggli Lab[2]
Asbestosis	10,000,000	253,000
Pleural plaques	1,400,000	8,140
Exposed, no disease	700,000	3,490
General population	0	<600

- [1]Geometric mean values, 144 cases, all fibers >0.5μm by TEM
- [2] Median values from 234 cases, all fibers >5μm by SEM

How to Interpret Fiber Burden Data

- Absolute numbers of fibers/sizes of fibers cannot be compared from lab to lab
- There is no set number of fibers that indicates above background exposure
- Data must be interpreted by examining the relationship of fiber burden and disease generated by each lab - this approach generates consistent results

Fibers in the General Population

Massive serpentine

Safeway Parking Lot

Old US Mint- Market St, San Francisco

Counties with reported occurrence of amphibole and chrysotile asbestos

Figure 1. Asbestos occurrences in the United States.

Fibers in the General Population
Mean Values /Gm Dry Lung

- Vancouver >0.5μ[1]
- Chrysotile: 300,000
- Tremolite: 400,000
- Amos/Croc 1,000

- Montreal >5.0μ[2]
- Chrysotile: 62,000
- Tremolite: 14,000
- Amos/Croc: 10,000

- [1] Churg et al 1986
- [2] Case et al 1988

Fibers in the General Population-Sizes

Size:	<5μ	5-10μ	>10μ	>20μ
Chrysotile:	94%	5%	1%	0
Tremolite	92%	8%	0	0

Mean Length and Aspect Ratio

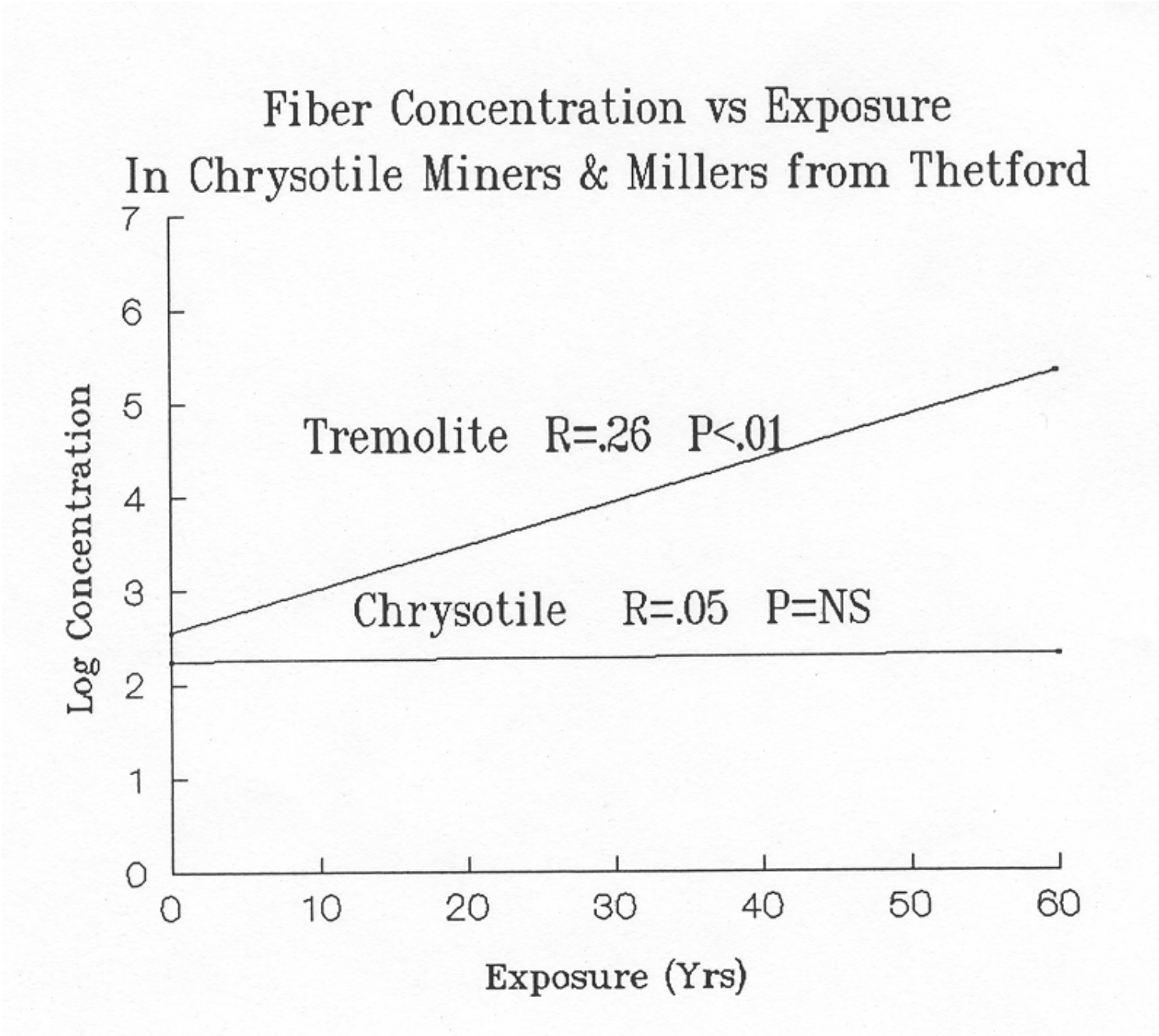
Chrysotile: 1.1 / 24

Tremolite: 1.6 / 6.5

Conclusions: Fibers in the General Population

- Everyone in the population carries a numerically large burden of asbestos fibers
- This is mostly chrysotile and tremolite, although small amounts of amosite and sometimes crocidolite are found
- Different fiber size counting approaches changes the proportion of the fiber types
- There is no evidence that this burden produces disease

Clearance of Chrysotile from Human Lung



Churg: Annals Occup Hyg 1994

Chrysotile vs Amphibole Accumulation in Lung

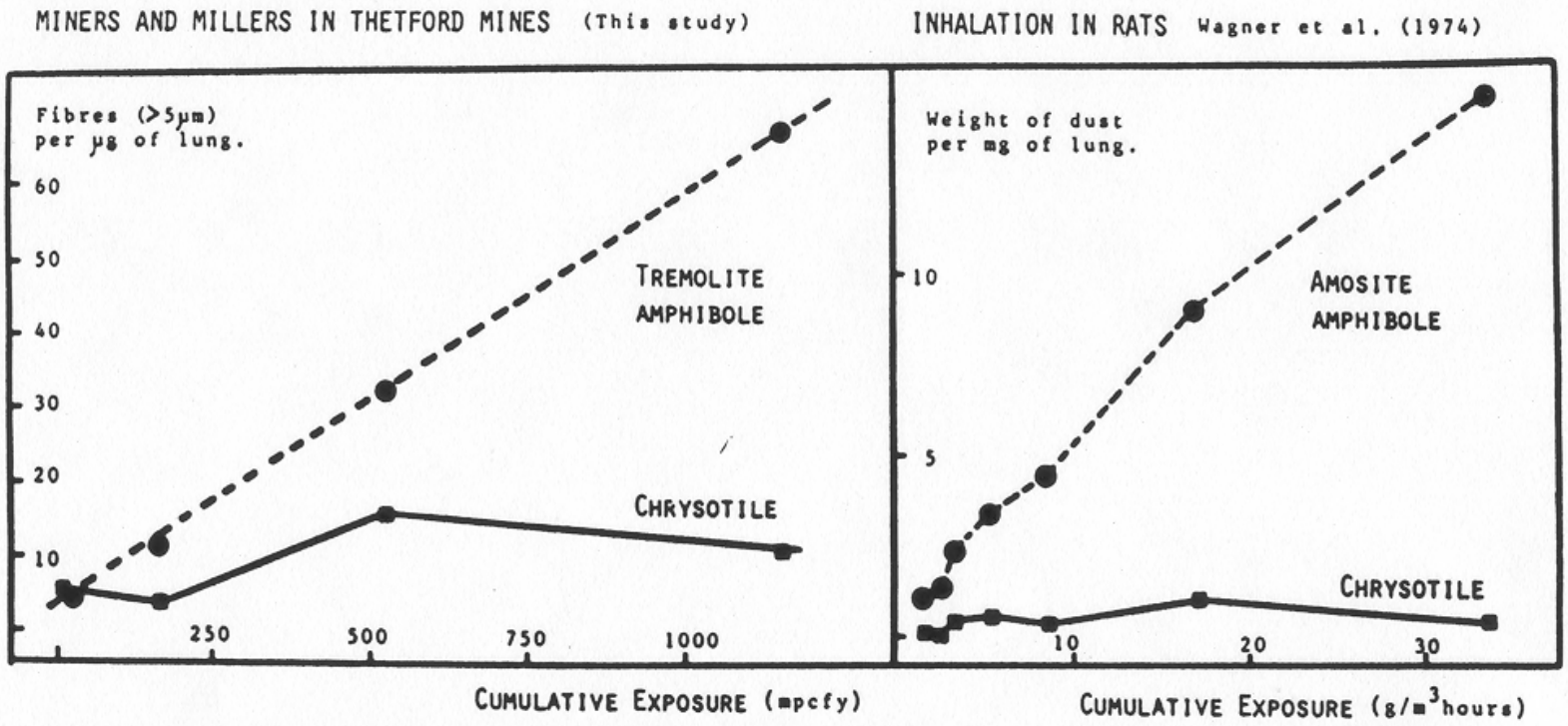
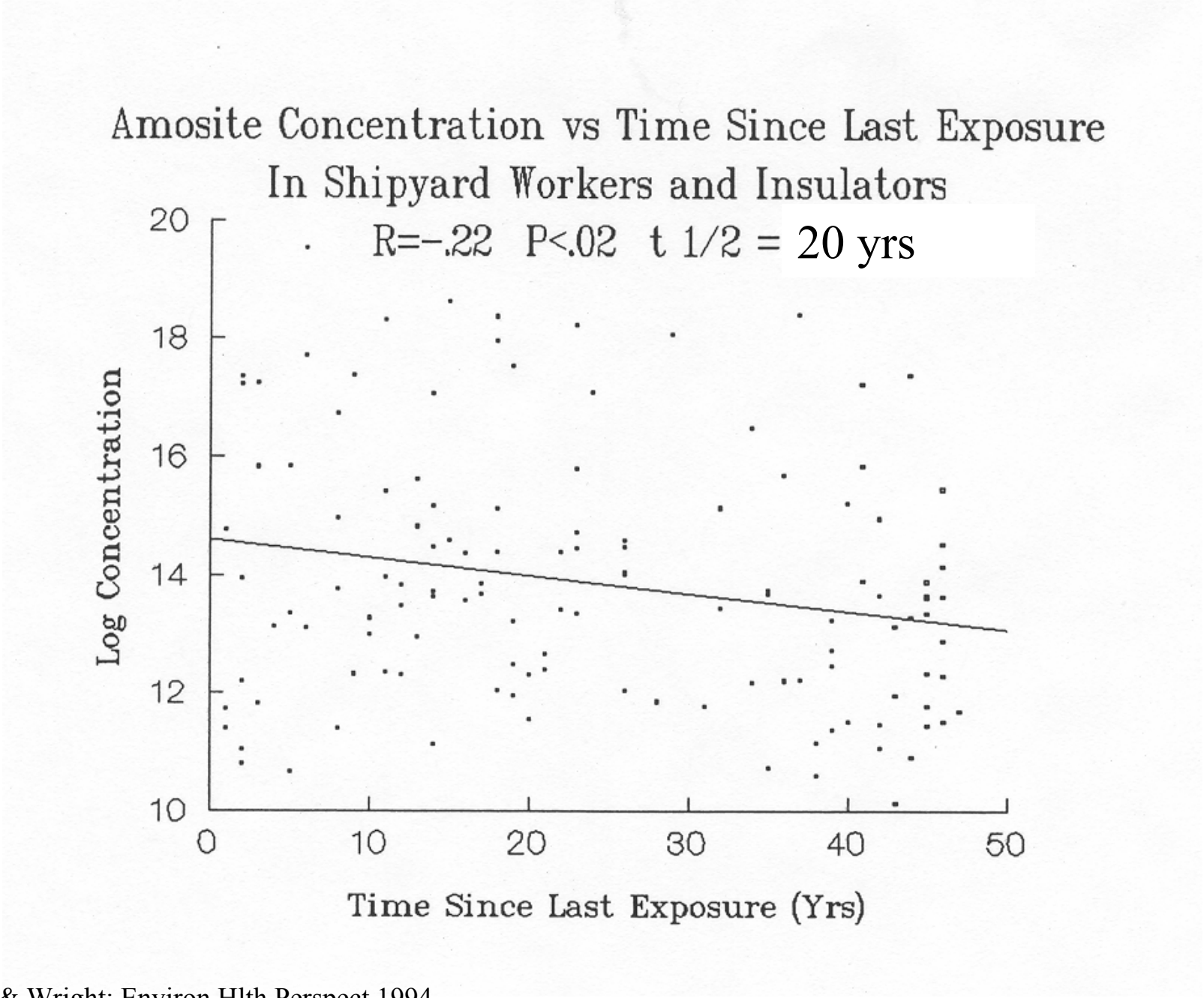
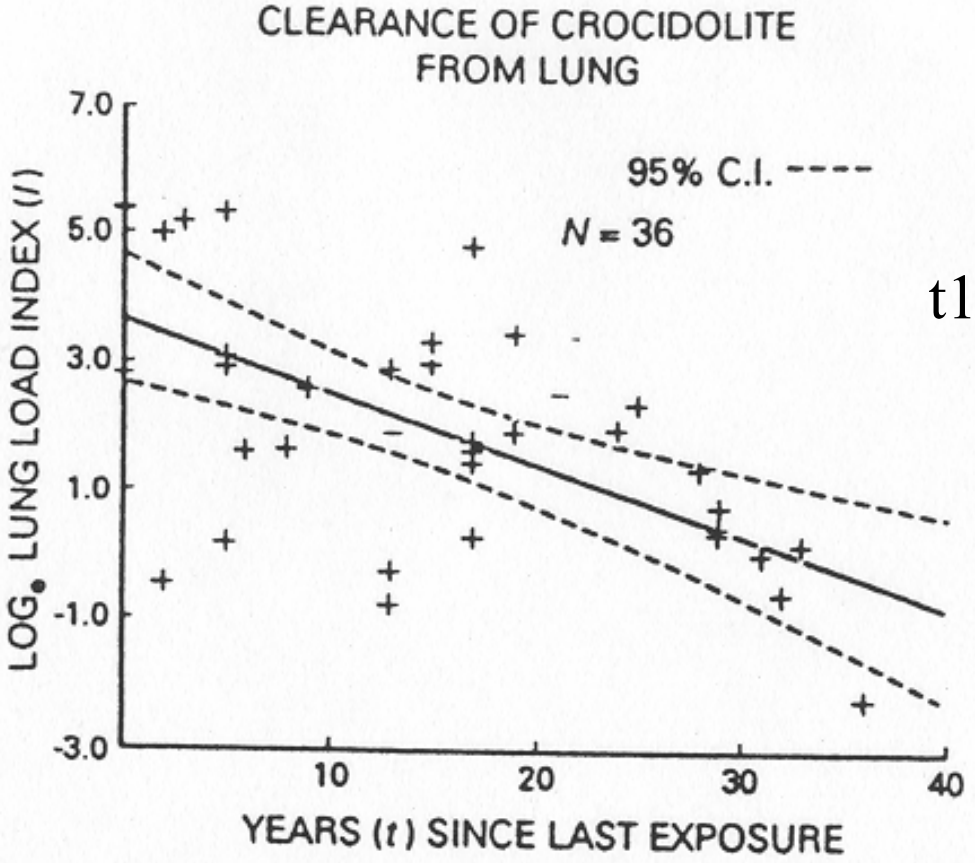


FIG. 1. Human and experimental data on the relationships between cumulative exposure to asbestos dust and lung retention. In the inhalation experiments of Wagner *et al.*,[11] rats were exposed for various periods up to 2 years to concentrations of about 10 mg/m³ respirable dust. The cumulative exposures of Thetford Mines workers were estimated from work histories and dust measurements with the impinger.

Sebastien et al: In, Biological Effects of Chrysotile, edited by JC Wagner, 1986



Churg & Wright: Environ Hlth Perspect 1994



t1/2= 6 Yrs

FIG. 2. Light microscope lung load index (I) vs elapsed time since last exposure in years (t).

DuToit: Ann Occup Hyg 1991

Relative Proportion of Chrysotile and Amphibole Fibers in Various Exposure Cohorts

Cohort (# reports)	Chrysotile	Tremolite	Amosite/Crocidolite
General population (7)	72%	18%	14%
Industries predominantly using chrysotile (8)	47%	46%	15%
Industries using mixed chrysotile/amphibole (5)	40%	4%	58%

- Churg Annals Occup Hyg 1994

Conclusions: Retention and Clearance of Chrysotile

- Chrysotile is retained to a much smaller extent than amphibole in human lung
- This implies an extremely short half life (probably months)
- The half life of commercial amphiboles is measured in years to decades
- Commercial amphibole and tremolite tend to be the predominant retained fiber in worker cohorts, no matter what the nominal exposure
- Low biopersistence is probably the reason that chrysotile is a weak mesothelial carcinogen in humans

Occult exposure to amphiboles

Evidence of Occult Amphibole Exposure in 39 Chrysotile Textile Workers from South Carolina

Geometric Mean Concentrations x 10^6/Gm

Chrysotile	33.5
Tremolite	3.6
Amosite/Crocidolite	0.5

Green et al: Occup Environ Med 1997

Evidence of Occult Amphibole Exposure in Chrysotile Textile Workers with Mesothelioma, from Rochdale

- Mean Fiber Concentrations x 10^6/Gm

Chrysotile	39
Crocidolite	73
Amosite	4
Tremolite	6

- Wagner et al: Br Med J 1982

Fiber Burden Analyses in Brake Workers

Roggli et al: Ultrastruct Path 2002; 26: 55-65

- Analyzed 11 cases
- Analysis showed either elevated commercial amphiboles (amosite & crocidolite) or no elevation in any fiber type
- Indicates that some of these “brake workers” had other types of occupational exposure that lead to their mesothelioma

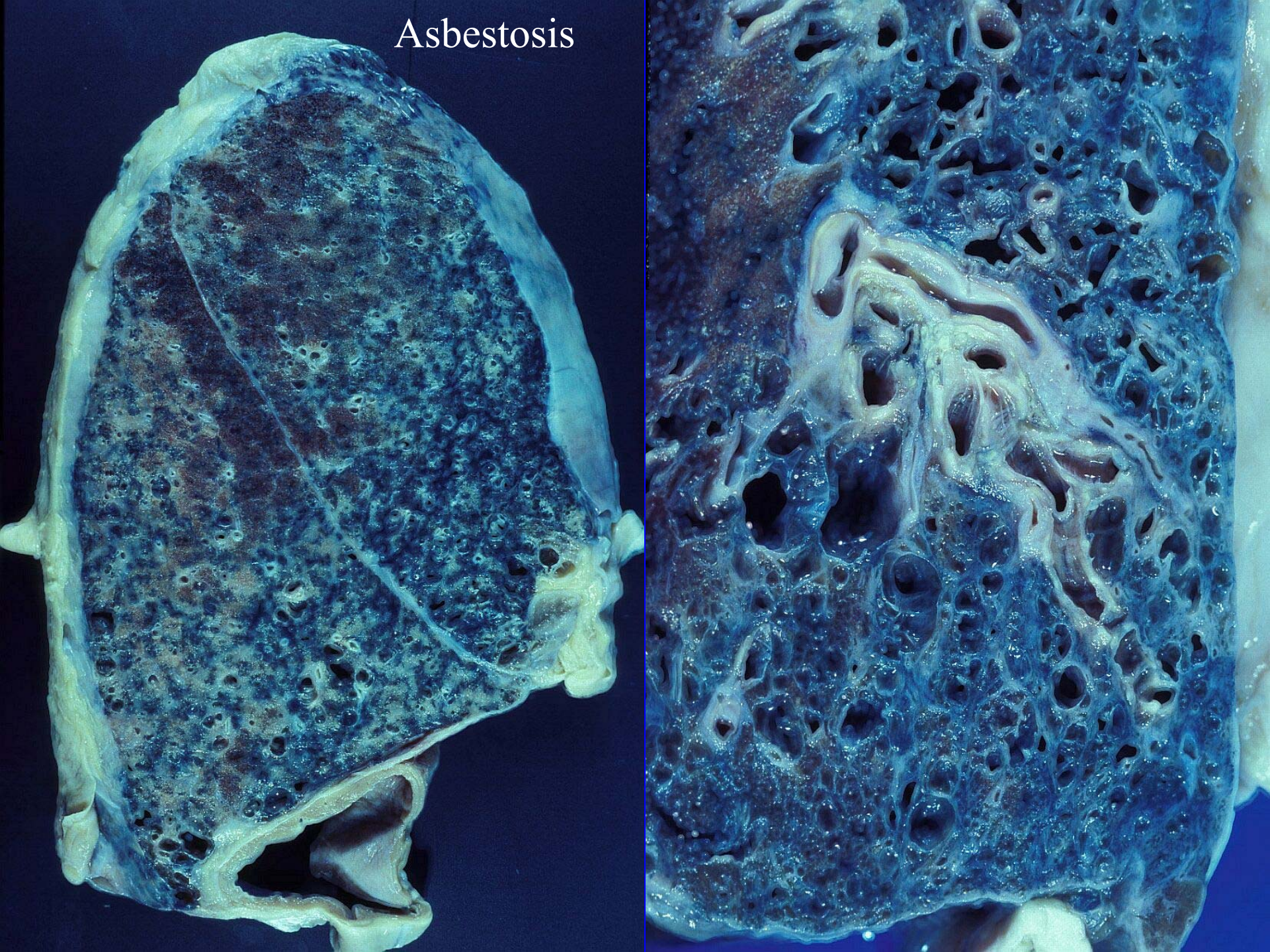
Conclusions: Occult Exposure to Amphiboles

- Occult exposure to amosite/crocidolite is seen in industries and occupations where the notional exposure is to chrysotile
- Given the much greater mesothelial pathogenicity of amosite/crocidolite compared to chrysotile, this observation confounds claims regarding the pathogenicity of chrysotile

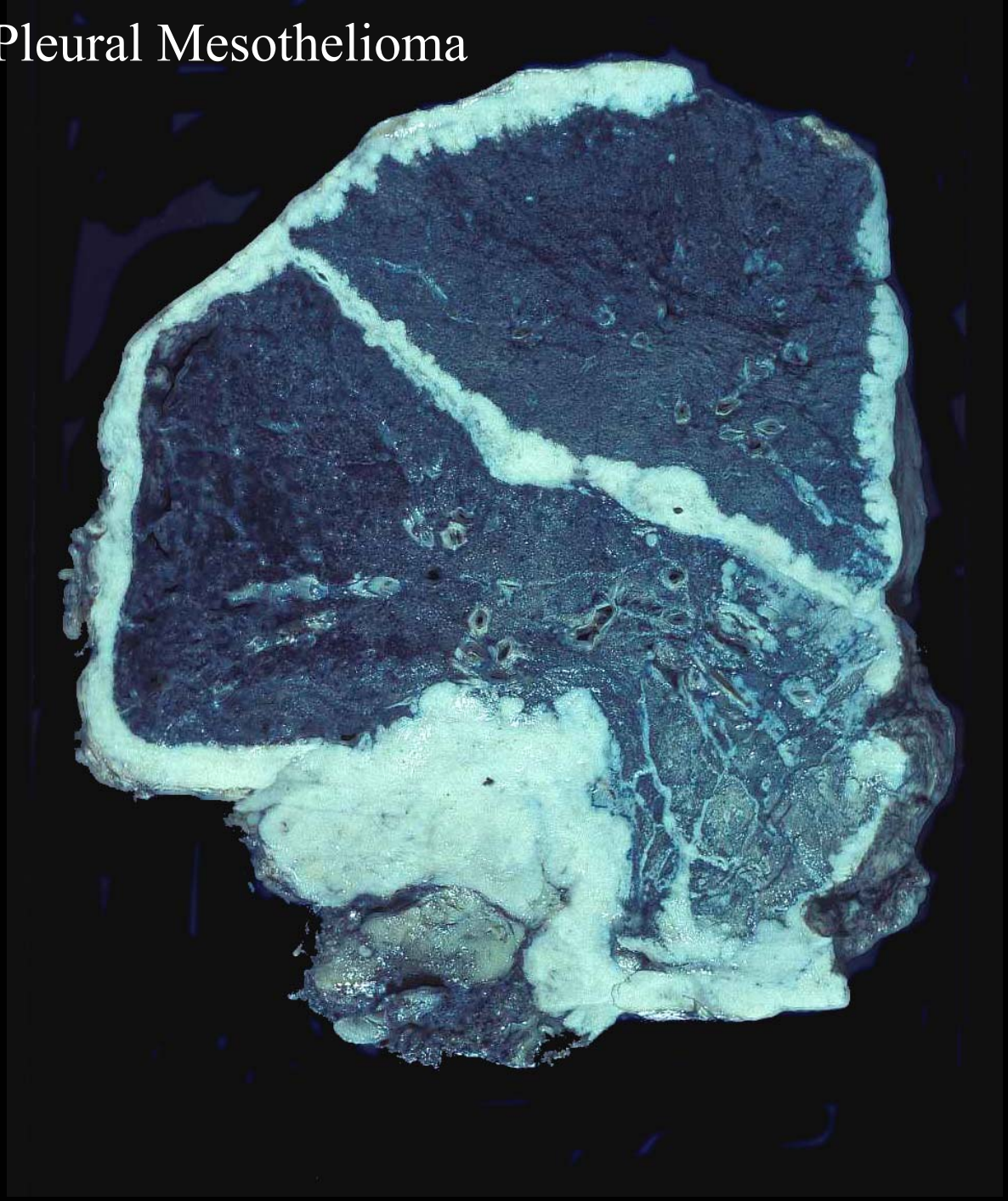
Fiber Burden and Disease

Pleural plaque

Asbestosis



Pleural Mesothelioma



Relationship of Amosite Fiber Burden and Disease (Roggli Br J Indust Med 1986)

Asbestosis	690,000
Mesothelioma	67,000
Pleural plaques	2,200

- Median values from 110 cases, all fibers >5μm by SEM

Fiber Burden Studies: Mean Concentration Fibers by Disease (from Gibbs and Pooley)*

Group	Chrysotile	Amosite	Crocidolite
Asbestosis	69	450	1100
Peritoneal meso	75	100	304
Pleural meso	45	103	53
Controls	2.8-9.3	.09-.93	.14-1.00

- *Millions of fibers/gm dry lung

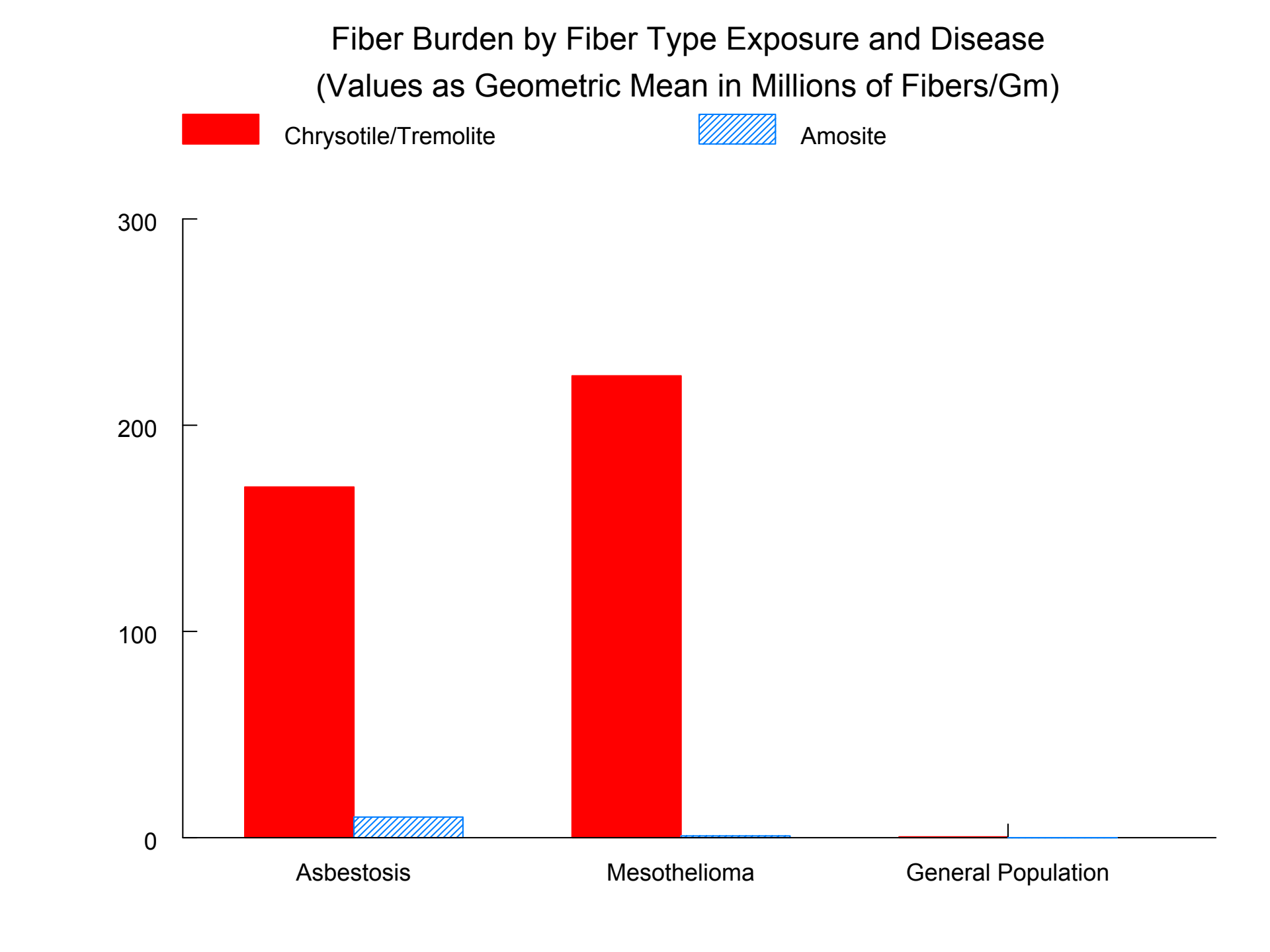
Fiber Burden Studies: Geometric Mean Fiber Concentration by Disease

	Chrysotile Miners		Shipyard & Insulator
	Chrysotile	Tremolite	Amosite
Asbestosis	30	140	10
Mesothelioma*	34	180	0.9
Gen Population	0.2	0.2	0

* N=21. No amosite or crocidolite detected.

Concentration as millions/gm dry lung

From Churg et al 1993, 1994.


Fiber Burden by Fiber Type Exposure and Disease
(Values as Geometric Mean in Millions of Fibers/Gm)
Chrysotile/Tremolite
Amosite
300
200
100
0
Asbestosis
Mesothelioma
General Population

Schematic Representation of Fiber Burden and Disease by Fiber Type

Increasing Fiber Burden

Amosite/Crocidolite

General Population

Mesothelioma

Plaques

Asbestosis

Chrysotile/Tremolite

General Population

Plaques

Asbestosis

Mesothelioma

Estimates of Relative Fiber Risk for Mesothelioma*

From Hodgson and Darnton: Ann Occup Hyg 2000

- Crocidolite 500
- Amosite 100
- Chrysotile 1

– *Based on average cohort cumulative exposure

Conclusions: Fiber Burden and Disease

- There are marked differences between amosite/crocidolite and chrysotile (with its accompanying tremolite)
- For both groups, asbestosis requires a very high fiber burden
- For amosite/crocidolite, mesothelioma appears at a much lower burden than asbestosis

Conclusions: Fiber Burden and Disease

- For chrysotile (with its accompanying tremolite), mesothelioma requires the same burden as asbestosis
- The absolute fiber concentration to induce asbestosis is considerably higher for chrysotile compared to amosite/crocidolite
- Implication: “chrysotile-induced mesothelioma” is a purely historic phenomenon

Role of Tremolite

Evidence that Tremolite is Removed in Processing of Chrysotile Ore*

- Chrysotile:Tremolite Ratio in Lung Tissue

- Churg: Chrysotile Miners/Millers: 1:5
- Green: Chrysotile Textile Workers: 10:1
- Wagner: Chrysotile Textile Workers: 6.5:1

- *We didn't plan it that way, it just happened

Geometric Mean Fiber Sizes in Tissue: Amosite vs Chrysotile

	Length	Aspect Ratio
Amosite[1]	5.5μ	38
Tremolite[2]	2.0μ	10

- [1] Shipyard workers, insulators,etc from Churg and Vedal: Amer J Respir Crit Care Med 1994
- [2] Chrysotile miners & millers from Churg & Wiggs: Am J Indust Med 1986

Odds Ratios for Deaths in Central High Tremolite Compared to Peripheral Low Tremolite Mines (McDonald 1997)

Disease	Central Mines	Peripheral Mines
Ca Lung	2.6	1.1
Mesothelioma	2.0	1.1
Other cancers	1.2	0.9

Fiber Burden Studies: Geometric Mean Fiber Concentration by Disease

	Chrysotile Miners		Shipyard & Insulator
	Chrysotile	Tremolite	Amosite
Asbestosis	30	140	10
Mesothelioma*	34	180	0.9
Exposed, no disease	2.0	9.0	0.7
Gen Population	0.2	0.2	0

* N=21. No amosite or crocidolite detected.

Concentration as millions/gm dry lung

From Churg et al 1993, 1994.

Conclusions: Role of Tremolite - I

- Evidence for removal on processing of chrysotile
- Included in the epidemiologic “black box”
- May be the agent of “chrysotile-induced” mesothelioma
- If so, Quebec chrysotile miners provide the worst case scenario and this indicates that the tremolite in chrysotile is a weak mesothelial carcinogen, even at enormous doses

Environmental Tremolite Exposures

- Significant mesothelioma incidences reported in Turkey, New Caledonia, Corsica, Libby Montana
- In some locations fiber-containing material often used as whitewash--leads to continuous household exposures for whole lifetimes
- Fiber levels may be relatively high
  - Metintas et al Chest 2002: persisting mean of about 0.1 f/cc with excursions up to 20 f/cc
  - Metintas et al Chest 2002: 1100-1600 cases/million in area of Turkey where tremolitic material used for whitewash

Fiber Sizes - Environmental Tremolite Exposure-Turkey (Lavage fluid)

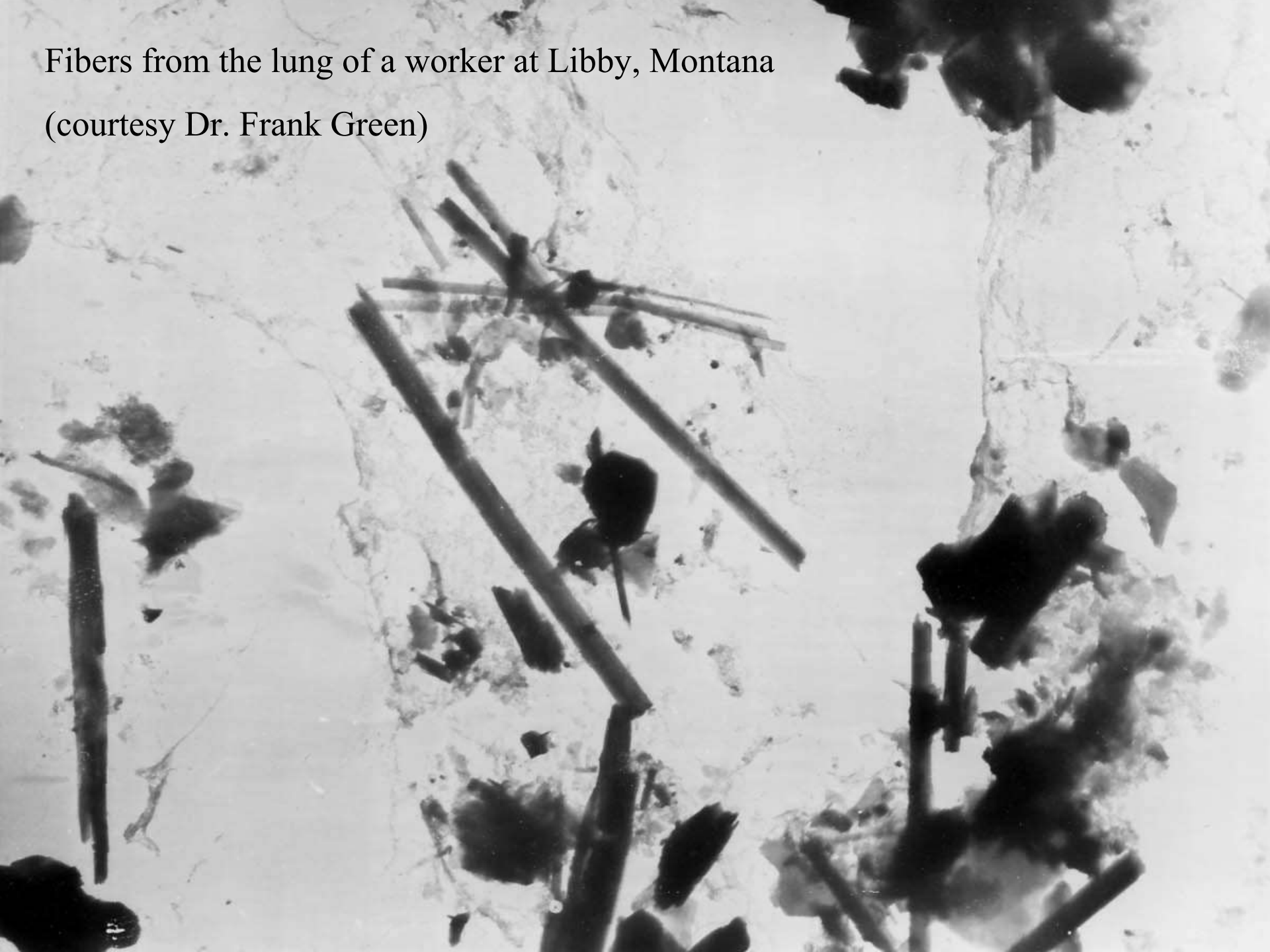
	Length	Aspect	%>5μ	%>20μ
Tremolite	4.0	15	36%	4%
Amosite	8.7	32	61%	32%
Crocidolite	7.5	65	59%	25%

- DuMortier et al 1998, 2001

Comparison of Tremolite Fiber Sizes in Lungs of Chrysotile Miners and an Enviromental Mesothelioma Case from Corsica

	Length	Aspect Ratio
Chrysotile Miners[1]	2.0μ	10
	(10%>5μ, 1%>10μ, 0 >20μ)	
Corsica Case[2]	3.7μ	7
	(37% >5μ, 6%>10μ, 0.5%>20μ)	

- [1]Churg and Wiggs 1986
- [2]Magee et al 1986



Fibers from the lung of a worker at Libby, Montana

(courtesy Dr. Frank Green)

Amosite

Comparison of Quebec and Libby Tremolite

	Mean Length/ Aspect Ratio	% Mesothelioma Deaths
Thetford Mines	2.1μ/10*	0.5%
(fibers from lung)	10%>5μ	
Libby (inhaled fibers)	1-70μ/3–100 **	4.2%***
	62% >5μ	

*Churg & Wiggs Am J Indust Med 1986

**McDonald et al: BJIM 1986

***McDonald et al: Ann Occup Hyg 2002

Environmental Tremolite-Conclusions

- Environmentally encountered tremolite is usually a much longer and thinner fiber than tremolite in chrysotile ore
- It behaves more like amosite and confers considerable risk of mesothelioma, and sometimes pulmonary fibrosis
- Libby “tremolite” is also a long thin fiber and behaves more like amosite
- Environmental/Libby tremolite fibers are quite different from tremolite in chrysotile ore