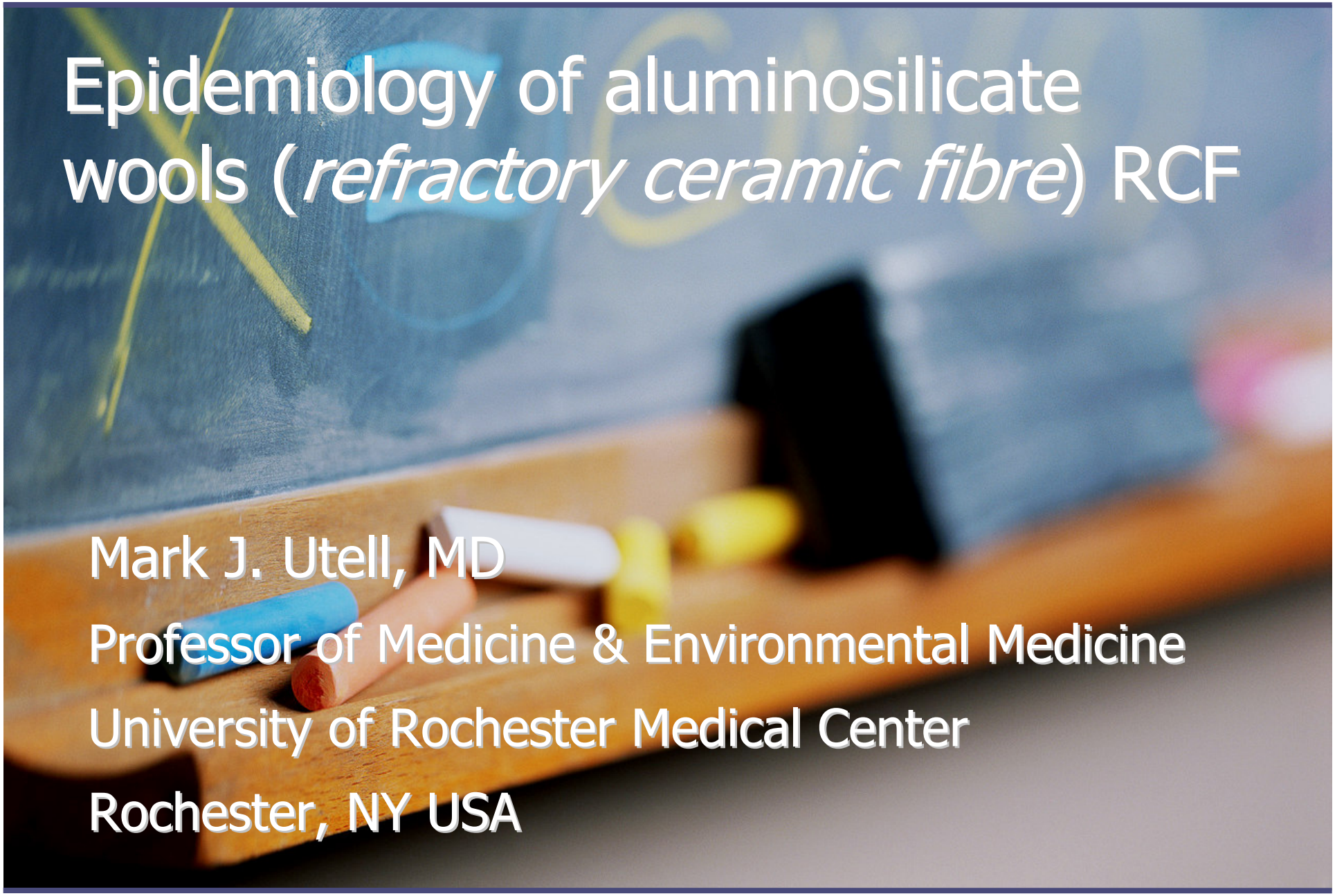
Epidemiology of aluminosilicate wools (*refractory ceramic fibre*) RCF



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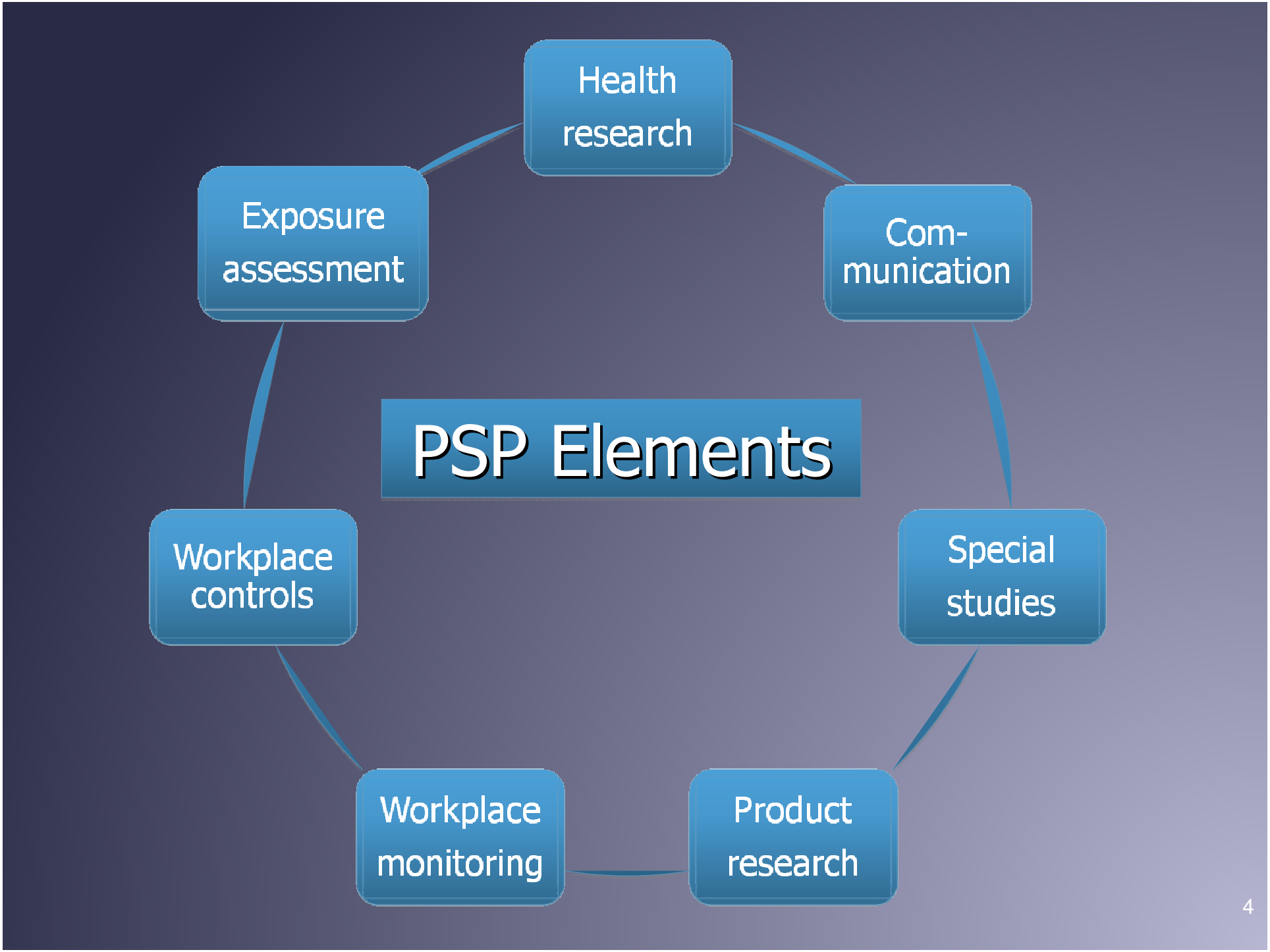
Background

- Aluminosilicate wool, also called *refractory ceramic fiber* (RCF) is a useful high temperature insulation
- RCF was discovered in the 1940s and commercialized during the 1950s
- Early studies with laboratory animals indicated that it was no more toxic than a "nuisance dust," but later animal studies raised concerns over possible health effects

Epidemiology studies

- The industry developed a *product stewardship program* (PSP) to identify and control any risks associated with use of RCF
- Epidemiology studies beginning in 1987 were one key component of the PSP
- Epidemiology studies were conducted in both Europe (*Institute of Occupational Medicine* [IOM], Edinburgh) and the United States (University of Cincinnati)


PSP Elements
Health research
Com-munication
Special studies
Product research
Workplace monitoring
Workplace controls
Exposure assessment

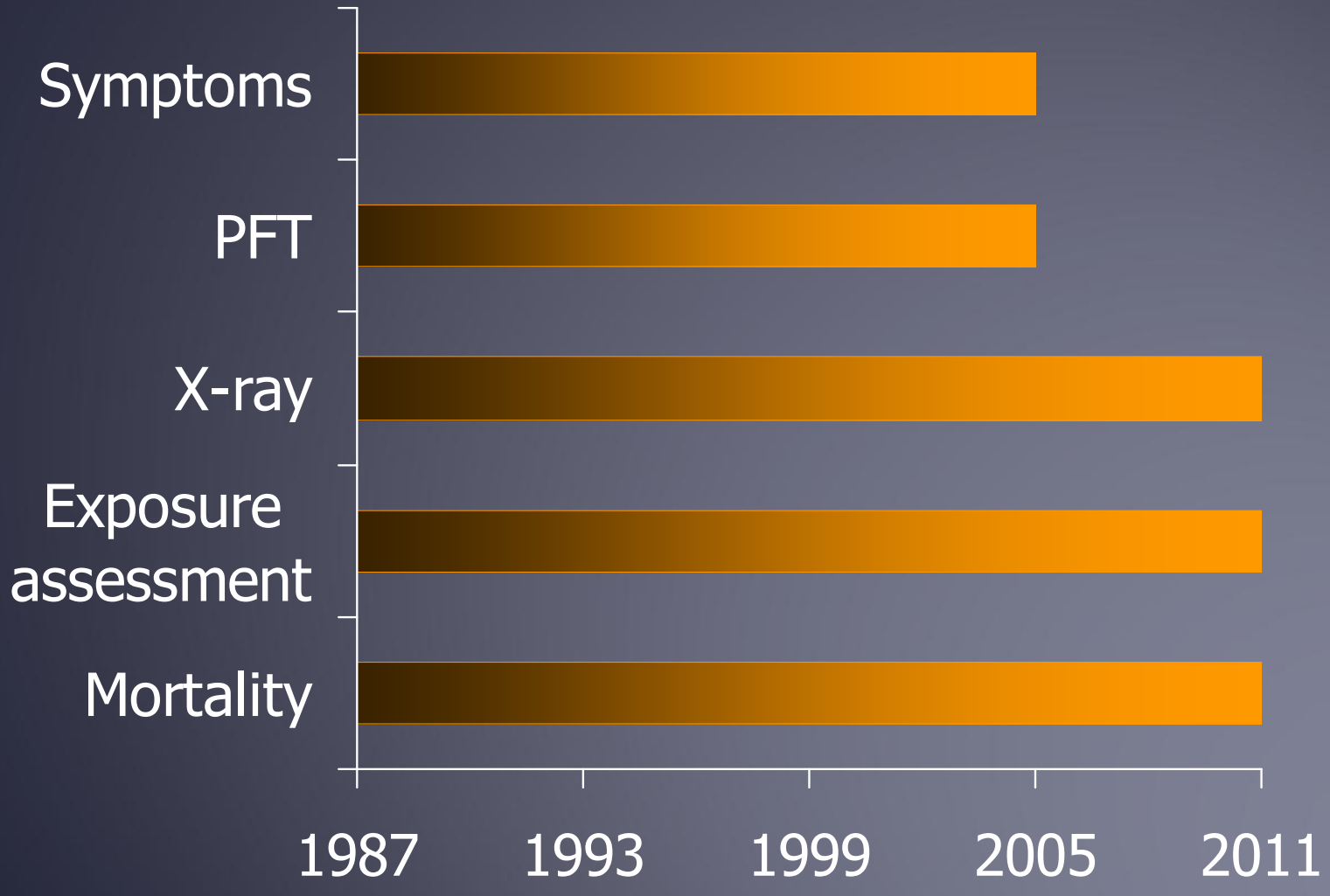
Scope of epidemiology studies

Symptoms	• Collected data on respiratory symptoms
Spirometry	• Conducted periodic pulmonary function tests
X-ray	• Collected chest radiographs
Mortality	• Analyzed mortality data from plants in US

Start up: US studies (1987-1992)

- Began with current employees at three facilities and former employees at two facilities
- Reconstructed historical fiber exposure; exposures have decreased in recent years
- Established study protocols
- Located/recruited former workers
- Initiated collection of occupational histories, respiratory symptoms, pulmonary function tests and chest X-rays

Follow-up for different endpoints



X-ray findings: methods

- One year employment or greater from 1953-1996
- Workers with < 5 years between hire into RCF industry and date of last film excluded (237) as were workers involved in sales (86)
- Total of 1,008 workers included in radiographic analysis
- X-ray endpoints: pleural changes, interstitial disease, parenchymal or pleural tumors

Duration & latency of RCF employment for workers (n=27, 2.7%) with pleural changes (Lockey, 2002)

	Duration of time employed in RCF industry (yr)		Latency time since hired in RCF industry (yr)	
Variable	≤ 20	> 20	≤ 20	> 20
Number workers	22	5	12	15
Mean duration / latency (yr)	9.9	27.9	12.9	28.8
SD	5.6	7.9	4.1	7.5

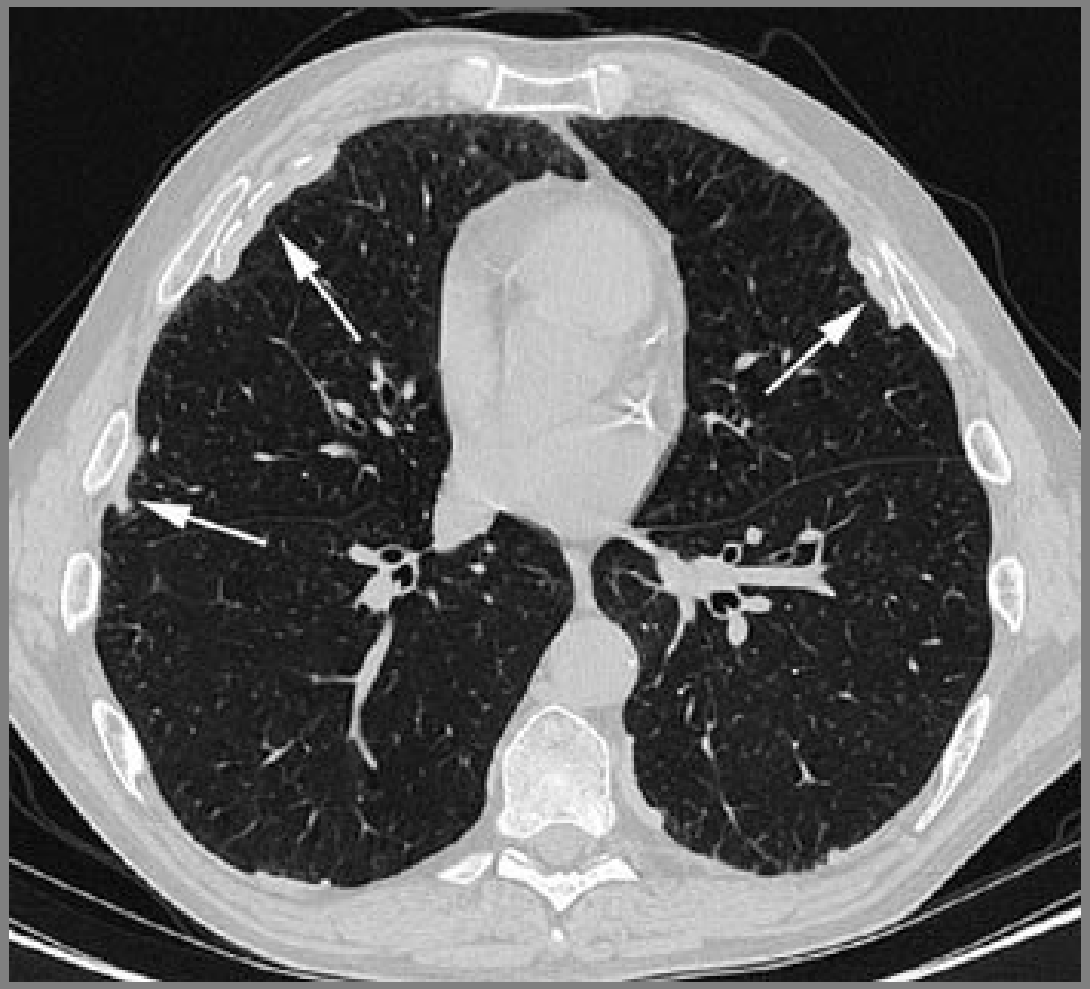
Duration, Latency, & Cumulative Fiber Exposure & Pleural Changes Adjusted for Asbestos Exposure & Age

Exposure Metrics	Pleural Changes, No. (% Subjects)	Subjects No.	OR (95% CI)
RCF production duration (all plants, n = 1,008), yr			
0 – 10	10 (1.6)	645	
> 10 – 20	12 (4.0)	301	2.5 (1.0 – 6.1)
> 20	5 (8.1)	201	3.2 (0.9 – 9.7)
Cumulative exposure (two plants, n = 637) fiber-mo/cm^3			
> 0 – 15	3 (1.1)	265	
> 15 – 45	4 (2.5)	163	2.2 (0.5 – 11.8)
> 45 – 135	8 (5.4)	148	5.6 (1.5 – 28.1)
> 135	6 (9.8)	61	6.0 (1.5 – 31.0)

What are pleural plaques?

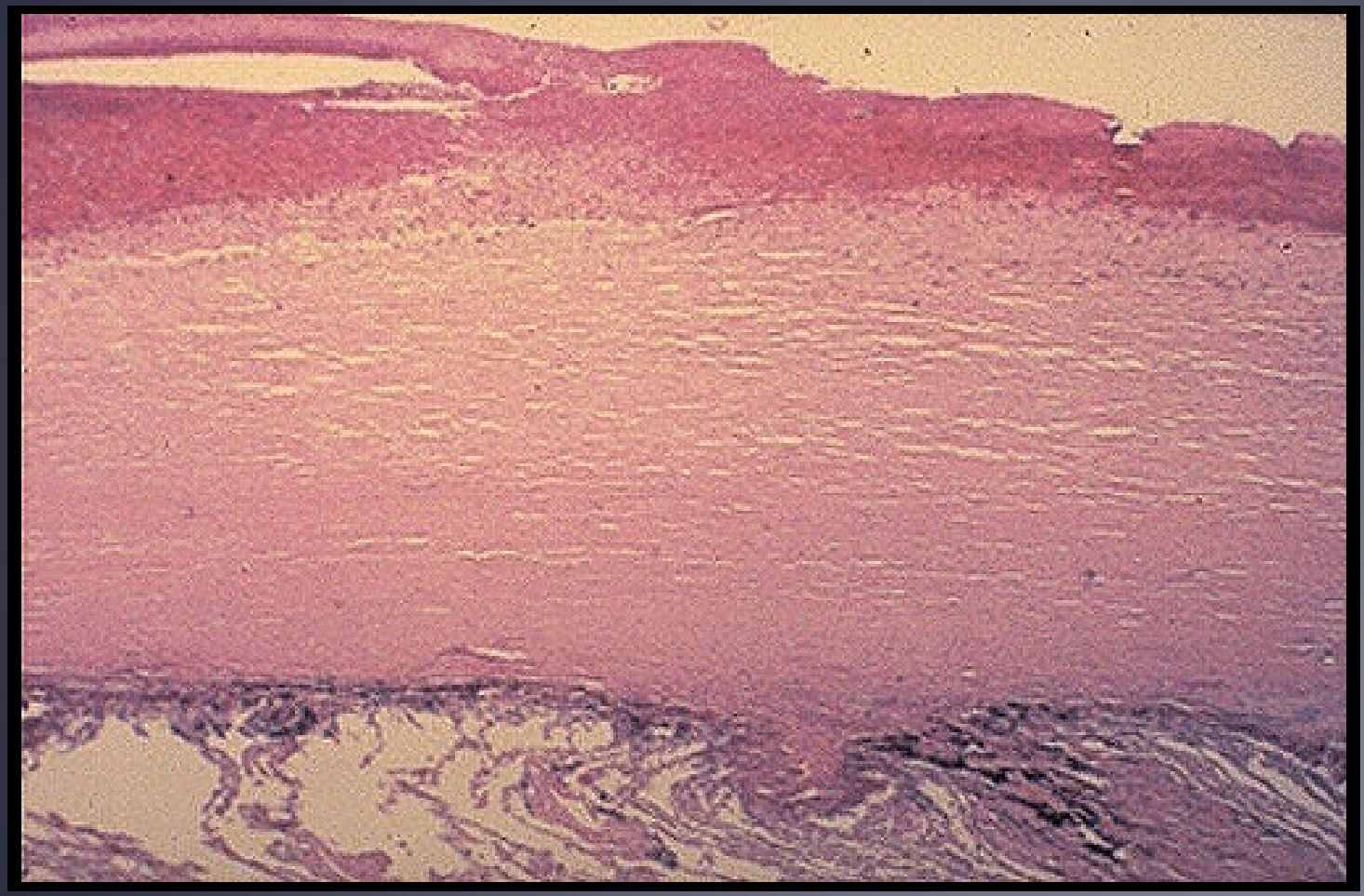
- Collagenous thickening of parietal pleura
- Found in the lateral and lower-half of the pleural cavity
- Plaques almost always bilateral with well-defined borders
- Latency reported to be 15 - 40 years

Plaques as shown in *computed tomography* (CT)



Arrows show pleural plaques

Microscopically, the pleural plaque is composed of dense layers of collagen



Epidemiology studies (U.S.)

- Radiographic findings (Lockey *et al*., 2002)
  - Study included 625 current and 383 former workers
  - Pleural changes seen in 27 workers (2.7%). Percent of workers with plaques stable over time (2.5-3.0%)
  - Pleural plaques related to RCF exposure: latency, duration, and higher cumulative fiber exposure (fiber-months/cc)
  - To date, no evidence that pleural plaques occur at current exposure levels

Clinical Significance of Plaques

- There is no evidence that plaques are precursor lesions for either lung cancer or mesothelioma
- Plaques are viewed as evidence of (asbestos) exposure, however, and it is this exposure that is of possible importance for future health
- Plaques are not associated with symptoms or loss of lung function

What is the incidence of plaques?

- Incidence varies with population:
  - Urban incidence greater than rural
  - Males typically higher than females
  - General populations 0.5 - 8%
  - Occupationally exposed cohorts 0.1 - 69%
- Overall incidence in RCF population 2.5%; incidence varies with latency, duration, and cumulative exposure

Epidemiology studies (U.S.)

- Radiographic findings (Lockey *et al*., 2002)
  - Study included 625 current and 383 former workers
  - For interstitial changes at profusion level ≥ 1/0, the relationship with exposure variables was non-significant based on currently available data
  - Incidence of irregular opacities ≧ 1/0 similar to other dust-exposed populations
  - No evidence for interstitial disease from ongoing analysis

Epidemiology studies (Europe)

- Radiographic findings (Cowie *et al.*, 2001)
  - Relationship between RCF latency and plaques but not duration or intensity of exposure
  - Weak association for 0/1 opacities & cumulative exposure but no association between category 1/0 opacities & exposure
  - No evidence for interstitial disease

Epidemiology studies (Europe & U.S.)

- Symptoms
  - Trethowan (1995) significant increase in prevalence of dyspnea with cumulative exposure
  - Cowie (2001) observed a small increase in recurrent chest illness with cumulative exposure; no relationship to dyspnea or pleuritic chest pain
  - LeMasters (1998) symptom prevalence rates higher in production vs non-production groups; dyspnea on exertion most common symptom
  - Comparable to other dust exposed populations

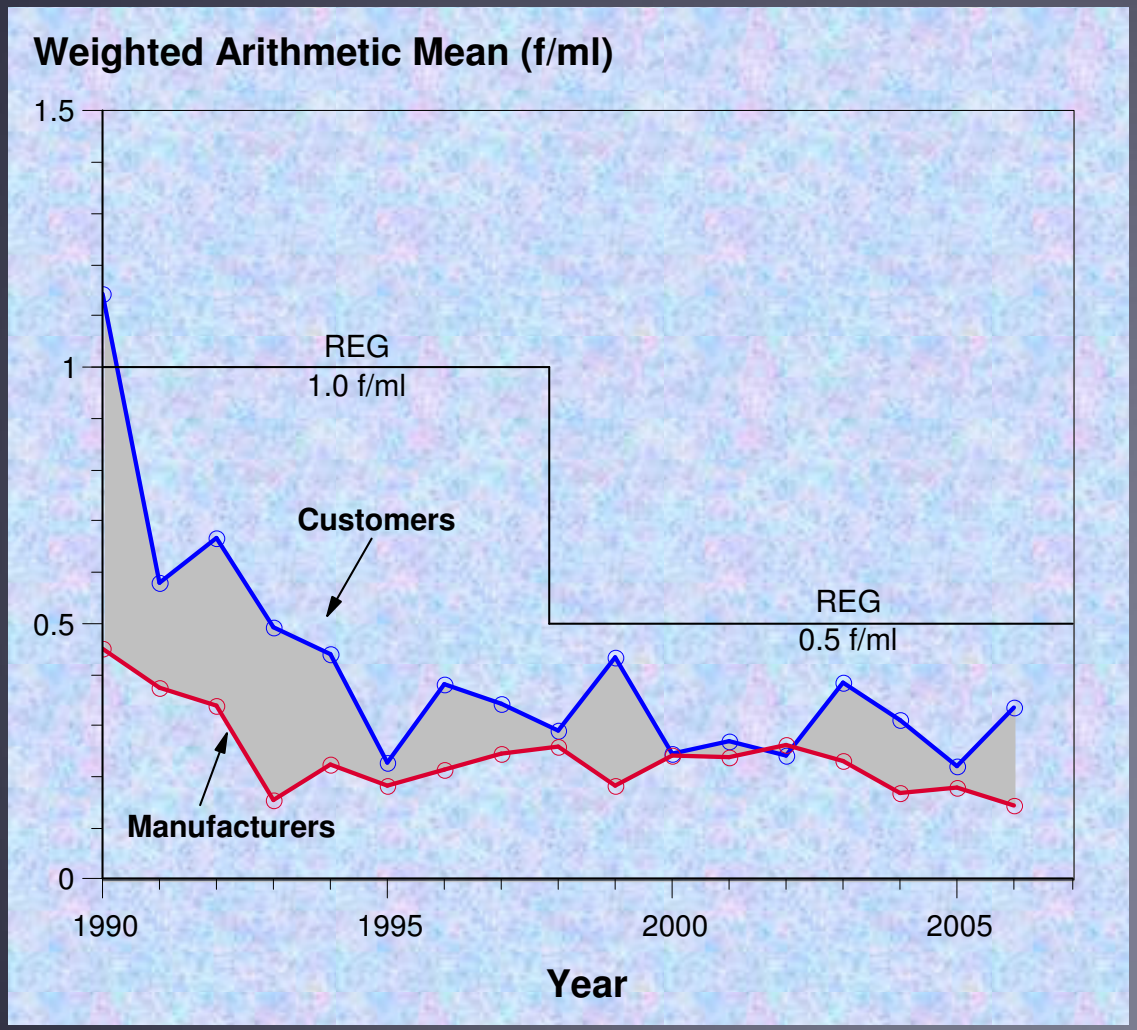
Epidemiology studies (Europe)

- Lung function (Trethowan *et al.,* 1995)
  - No association between RCF & lung function in non-smokers; significant association for FEV_1 & cumulative exposure in past smokers; non-significant trend in cumulative exposure & FVC for all smokers (cross-sectional)
  - In follow-up (Cowie et al., 2001), effects smaller but mild decrements in FVC and FEV1 associated with estimated cumulative exposure for smokers
  - No longitudinal study performed

Epidemiology studies (U.S.)

- Lung function
  - Statistically significant decreases seen among workers employed in production jobs (cross-sectional analysis; LeMasters et al., 1998)
  - Findings did not persist with analysis of follow-up production yrs (longitudinal analysis; Lockey,1998)
  - Decreasing RCF exposure levels possible explanation for finding (2) above

Fiber concentrations have decreased



Epidemiology studies (U.S.)

- Lung function (McKay *et al.,* 2008)
  - 2008 extension and expansion of lung function analysis
  - 1396 participants (933 m, 244 f, 219 former) followed for up to 17 years with multiple tests
  - Using a cumulative exposure model (<15, >15 to 60, and >60 f-mo/cc), no consistent decline in FVC or FEV_1 with increasing RCF exposure
  - No evidence for accelerated rate of loss of lung function

Epidemiology studies (U.S.)

- Mortality (LeMasters *et al.*, 2003)
  - Study included 942 current and former male workers at two RCF manufacturing facilities
  - No excess mortality related to all deaths, all cancers, or malignancies or diseases of the respiratory system, including mesothelioma
  - Anomalous finding of increased urinary tract tumors; investigators conclude may be "chance" finding based on analysis
  - Study ongoing

Risks based on human data

- Risk analysis of mortality data (Walker *et al.*, 2002)
  - Best estimate—no incremental risk of lung cancer or mesothelioma
  - Lung cancer results incompatible with hypothesis that RCF as potent as amphibole asbestos—not yet powerful enough to exclude chrysotile
  - Ability to detect mesothelioma risk limited

Key epidemiology results

- Symptoms similar to other dust-exposed groups
- Pleural plaques statistically significant, but thought to be indicator of exposure rather than precursor of disease
- No increase in interstitial fibrosis
- No increased malignancy of respiratory system
- No accelerated decline in lung function