



# **The quantitative risks of mesothelioma in relation to low-level asbestos exposure**

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# Outline

- Reminder of risk models for mesothelioma and source data
- What do we mean by “low-level” exposure?
- How far are we extrapolating the risk models?
- Setting risk estimates in context and other issues that need to be considered
- Does the national mesothelioma data tell us anything?

# Risk models for mesothelioma

Health Effects Institute (HEI):

$$r = K_M \cdot L \cdot [ \{t-10\}^3 - \{t-10-D\}^3 ]$$

Where:

L = exposure conc (f/ml)

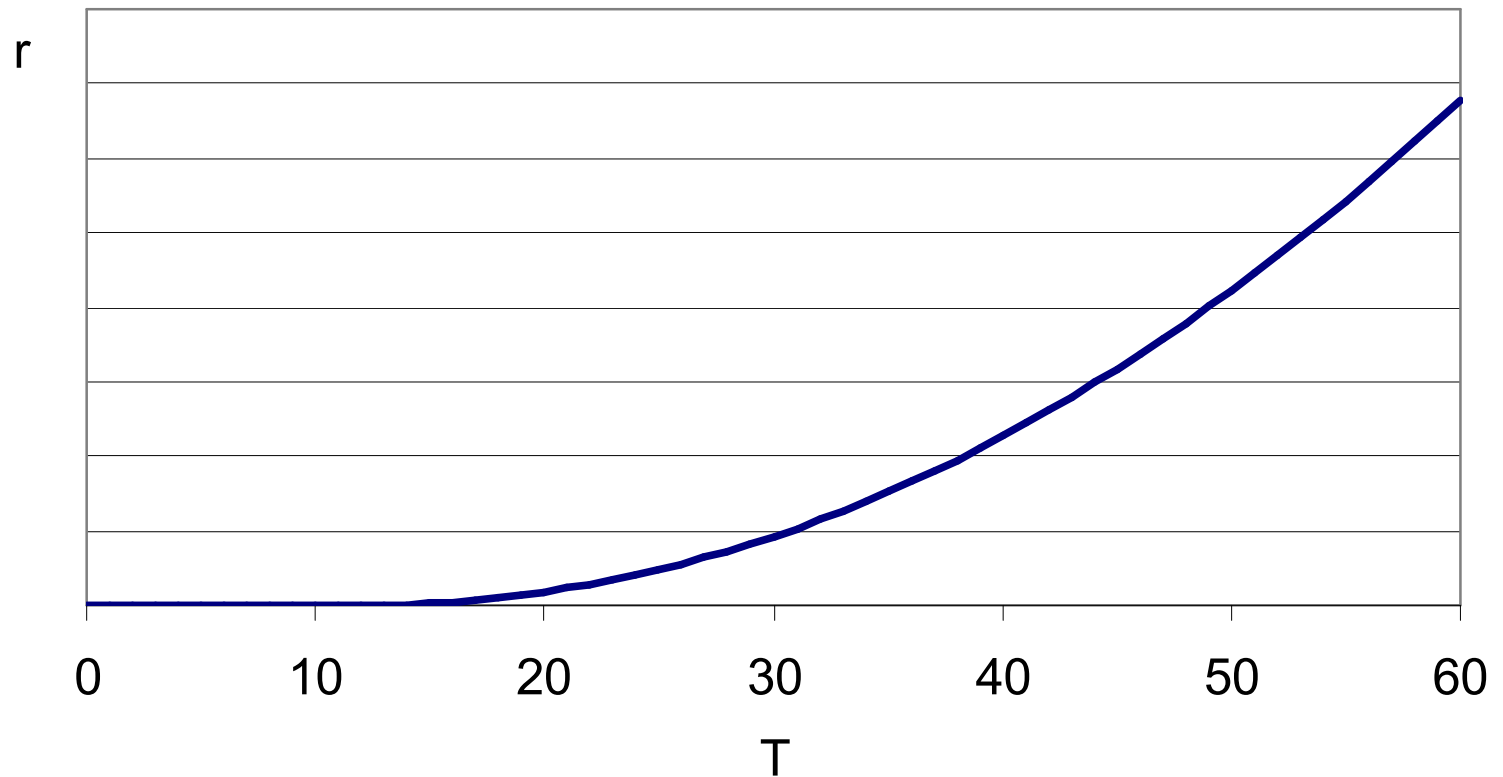
D = exposure duration (yrs)

{.} taken to be zero if <0

# Risk models - HEI



$$r = K_M.L. \left[ \{T-10\}^3 - \{T-10-D\}^3 \right]$$



# Berman and Crump

- Applied HEI model to cohort-level mesothelioma dose-response data for asbestos exposed cohorts
- $K_M$  value for each cohort
- Variation explained by fibre type and size distributions in different industrial settings

# Example – amosite insulation workers, Paterson, New Jersey (Seidman *et al.* 1986)

**Table A-14**  
**Mesothelioma Mortality among Amosite Insulation Workers in New Jersey**  
**Seidman et al. (1986)**

Years After First Exposure Range	Mean	Duration	f/ml	Person Years	Observed	Predicted
( 5-9 )	7.5	1.5	46.9	3952	0	0
( 10-14 )	12.5	1.5	48.3	3628	0	0.1
( 15-19 )	17.5	1.5	44.1	3198	0	1.1
( 20-24 )	22.5	1.5	43.2	2656	2	2.8
( 25-29 )	27.5	1.5	40.3	2094	5	4.2
( 30-34 )	32.5	1.5	33.5	1576	8	4.4
( 35-39 )	37.5	1.5	31.1	1086	2	4.3
<b>Totals</b>				18190	17	17.0
<b><math>K_M * 10^8</math></b>			3.9			
<b>(90% Confidence Interval)</b>			(2.6, 5.7)			
<b>Goodness of Fit P-value</b>			0.35			

# Risk models for mesothelioma

HD model:

$$P_M = A_{pl} \cdot X^r + A_{pr} \cdot X^t$$

Where:

$$P_M = 100 \times O_M / E_{Adj}$$

$X$  = cumulative exposure (f/ml.yr)

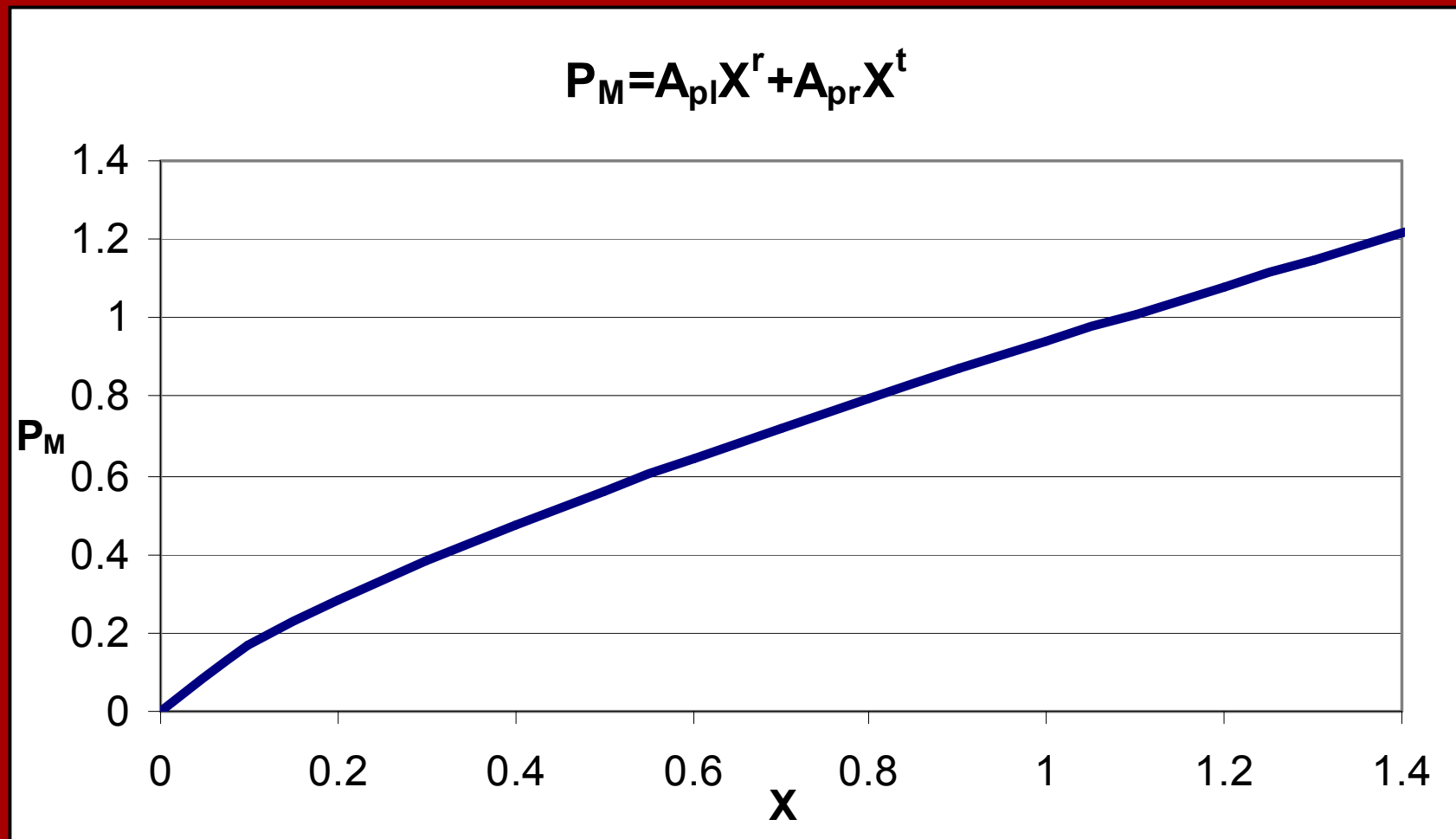
Best model:  $r = 0.75$ ,  $t = 2.1$

croc:  $A_{pl} = 0.94$ ,  $A_{pr} = 0.0022$

amos:  $A_{pl} = 0.13$ ,  $A_{pr} = 0.0006$

chrys:  $A_{pl} = 0.0047$

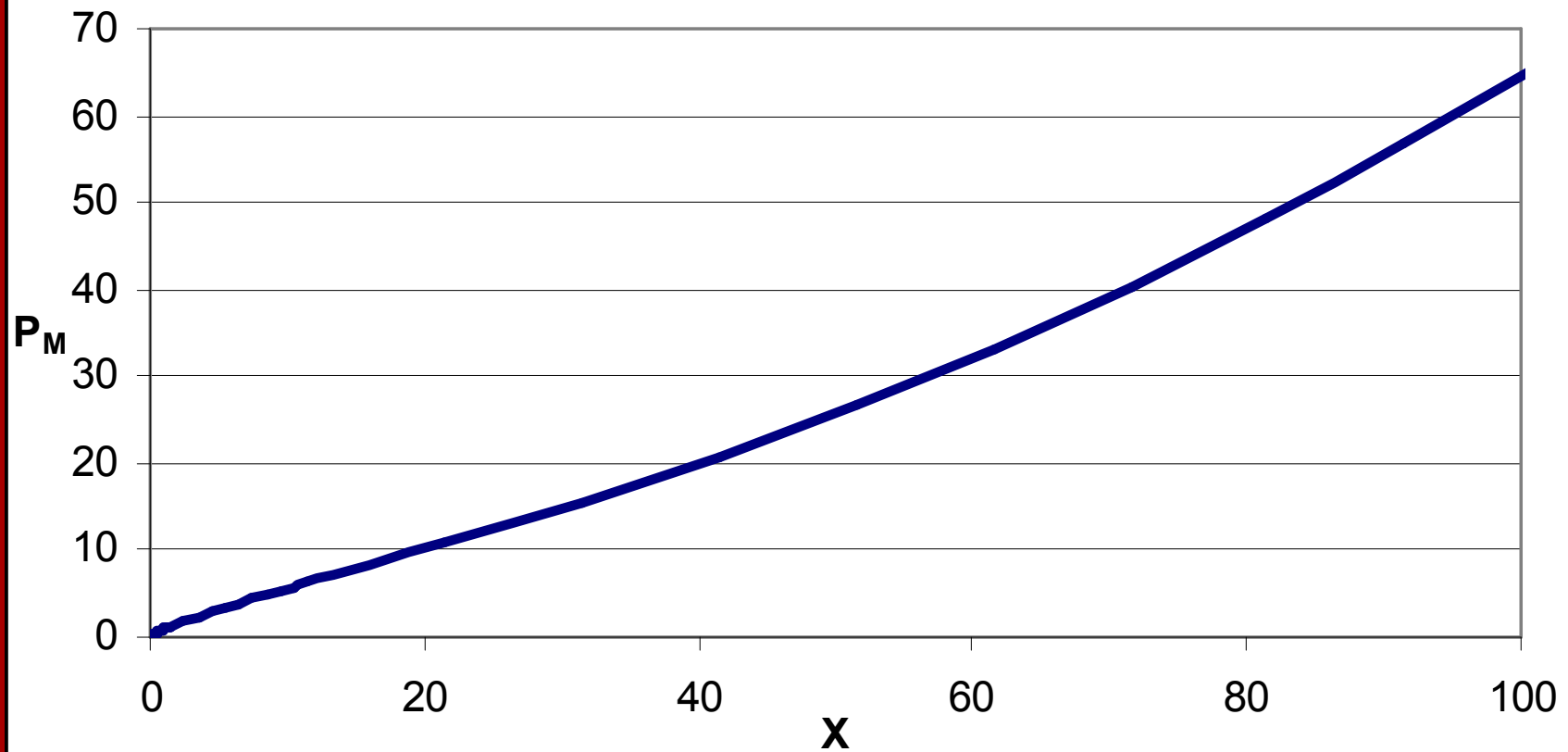
# HD model



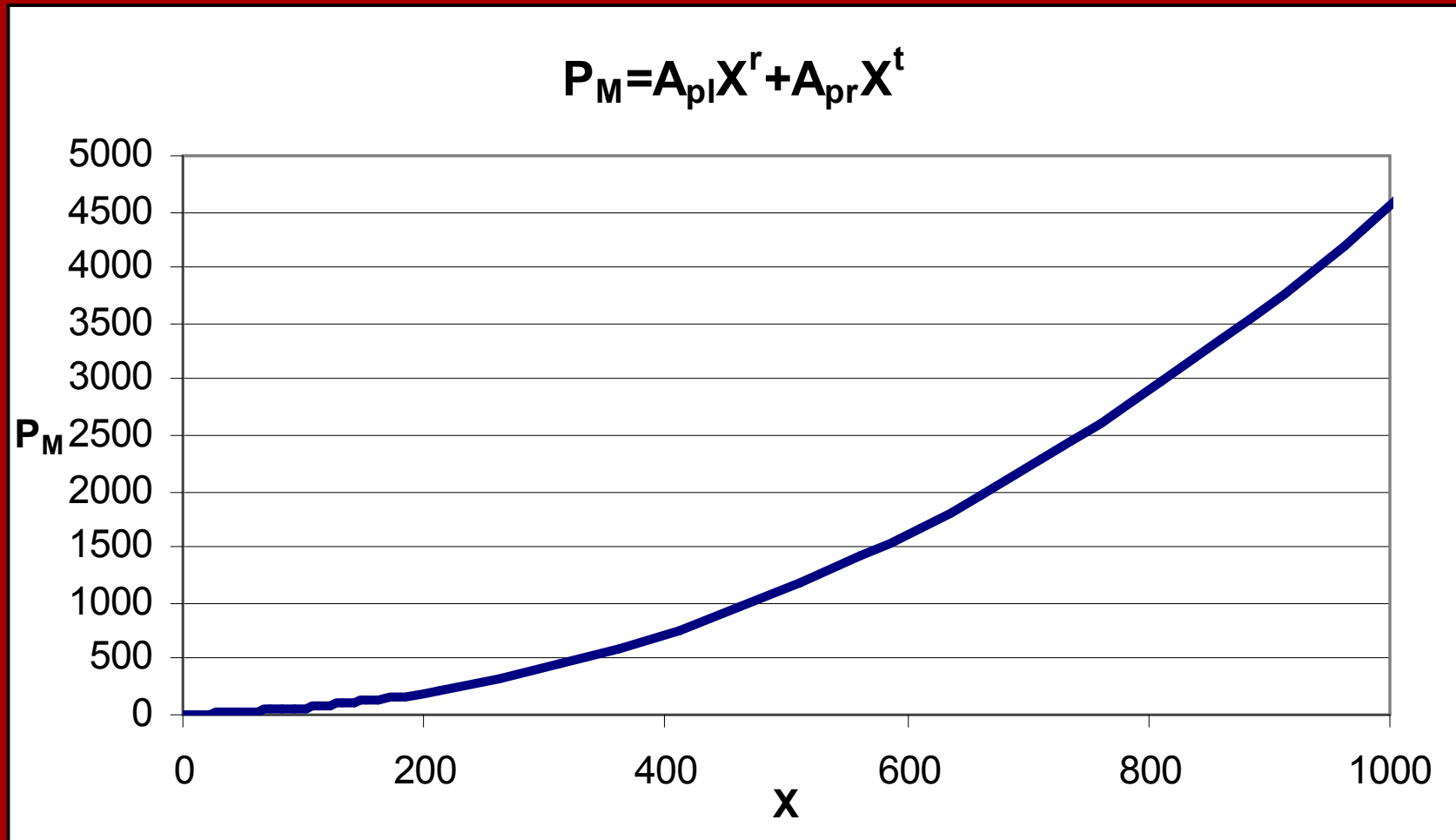
# HD model



$$P_M = A_{pl}X^r + A_{pr}X^t$$



# HD model



# Calculating lifetime risks

- Both models require use of all-cause mortality lifetable
- Apply HEI model directly to all cause mortality lifetable
- For HD need to know how many survivors to age 30 will die (any cause) during period when mesotheliomas occur (we took this to be age 40-80)
- For HD need to adjust for exposure at ages other than 30 using HEI model...
- Issue of how long the risk continues to increase after first exposure...

# Comparison of BC and HD - chrysotile

Estimated lifetime risk of mesothelioma and lung cancer per 100,000 in relation to chrysotile asbestos by model (HD or BC) and cumulative exposure.

Cumulative exposure (f/ml.yr)	Mesothelioma			Lung cancer		
	HD	BC	HD/BC	HD	BC	HD/BC
10	25 (5-70)	10	2.7	30 (15-250)	100	0.3
1	5 (1-20)	1	4.8	2 (<1-25)	10	0.1
0.1	1 (<1-5)	<1	8.4	<1 (<1-5)	1	0.1
0.01	<1 (<1-1)	<1	15	<1	<1	0.03
0.005	<1 (<1-1)	<1	18	<1	<1	0.03

# Comparison of BC and HD - amphibole

Estimated lifetime risk of mesothelioma and lung cancer per 100,000 in relation to amphibole asbestos by model (HD or BC) and cumulative exposure.

Cumulative exposure (f/ml.yr)	Mesothelioma			Lung cancer		
	HD	BC	HD/BC*	HD	BC	HD/BC
10	croc: 4000 (2500-6000); amos: 550 (150-1500)	3000	0.7	1500 (800-2500)	300	6
1	croc: 650 (250-1500); amos: 90 (15-300)	300	1.3	85 (20-250)	30	3
0.1	croc: 100 (25-350); amos: 15 (2-75)	30	2.2	5 (1-25)	3	1.5
0.01	croc: 20 (2-85); amos: 3 (<1-20)	3	4	<1 (<1-3)	<1	0.8
0.005	croc: 10 (1-55); amos: 2 (<1-15)	1	5	<1 (<1-1)	<1	0.6

\*Ratio for amphibole based on the average of HD amosite and crocidolite estimates.

# Source data for risk models



Cohort	Asbestos fibre type	Industrial process	Average cumulative exposure
Quebec	Chrysotile	Mining/milling	600
Balangero	Chrysotile	Mining/milling	300
Connecticut	Chrysotile	Friction	46
New Orleans	Chrysotile	Cement	22
Carolina	Chrysotile	Textiles	28, 26
Ferodo	Mixed	Friction	35
Ontario	Mixed	Cement	60
New Orleans	Mixed	Cement	79, 93
Albin	Mixed	Cement	13
US retirees	Mixed	Factory	750
US insulation workers	Mixed	Insulation	500
Pennsylvania	Mixed	Textiles	60
Rochdale	Mixed	Textiles	74
Vocklabrook	Mixed	Cement	25
Wittenoom	Crocidolite	Mining/milling	23
Massachusetts	Crocidolite	Cigarette filter manufacture	120
South African crocidolite mine	Crocidolite	Mining	16.4
South African amosite mine	Amosite	Mining	23.6
Patterson	Amosite	Insulation	65

# What exposures are we interested in?

Exposure durations for five exposure scenarios in order to produce each cumulative if the exposure concentration was 0.1 f/ml

Cumulative exposure (f/ml.yr)	Exposure scenario				
	Continuous	Working time	Half working time	1 hour per work day	1 hour per work week
10	50 years	> lifetime	> lifetime	> lifetime	> lifetime
1	5 years	10 years	20 years	80 years	> lifetime
0.1	6 months	1 year	2 years	8 years	40 years
0.01	2.5 weeks	5 weeks	10 weeks	38 weeks	4 years
0.005	6 days	2.5 weeks	5 weeks	19 weeks	2 years

- Low level background exposures?
- Acute exposures?

## What exposures are we interested in?

- Background  
Eg. 0.0001 f/ml for 50 years  
=> 0.005 f/ml.yr
- Acute  
Eg: 1 f/ml for 1 week  
=> 0.02 f/ml.yr

## Applying the HD model for extended periods and earlier exposure start ages

- In HD model cumulative exposures are assumed to be accrued over ~5 years starting at age 30
- For longer periods, have to account for change in age across exposure period and fact that models are non-linear in cumulative exposure
- Age adjustment based on HEI model...

# Age adjustment factors

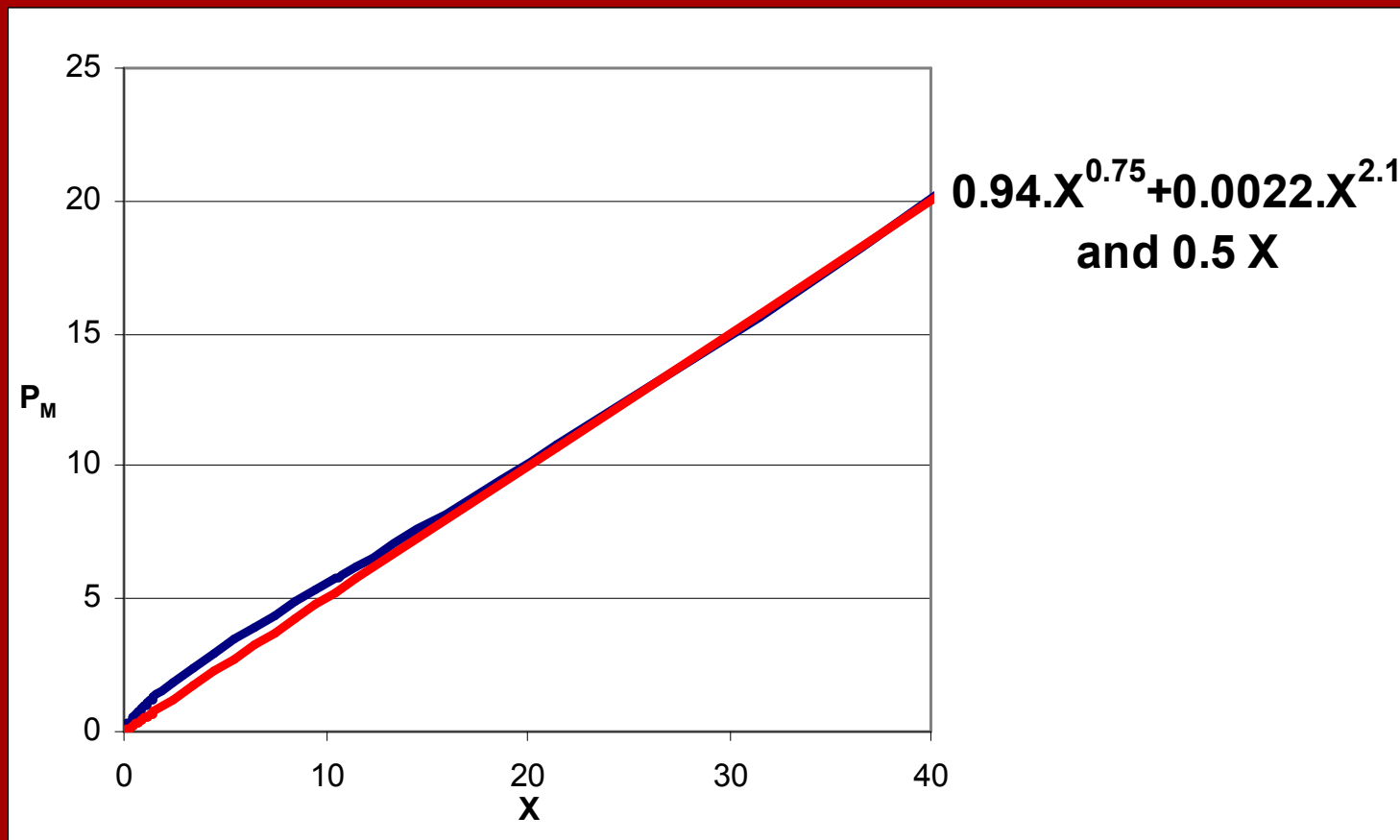
**Adjustment factors to convert estimates of mesothelioma mortality due to asbestos exposure starting at age 30 to other exposure start ages for assuming risk persists for 60 and 80 years after the start of exposure.**

Age	0	5	10	15	20	25	30	35	40	45	50	55
Factor (at risk for 60 years)	2.8	2.7	2.6	2.4	2.1	1.5	1	0.6	0.4	0.3	0.2	0.1
Factor (at risk for 80 years)	6.6	5.2	4	3	2.1	1.5	1	0.6	0.4	0.3	0.2	0.1

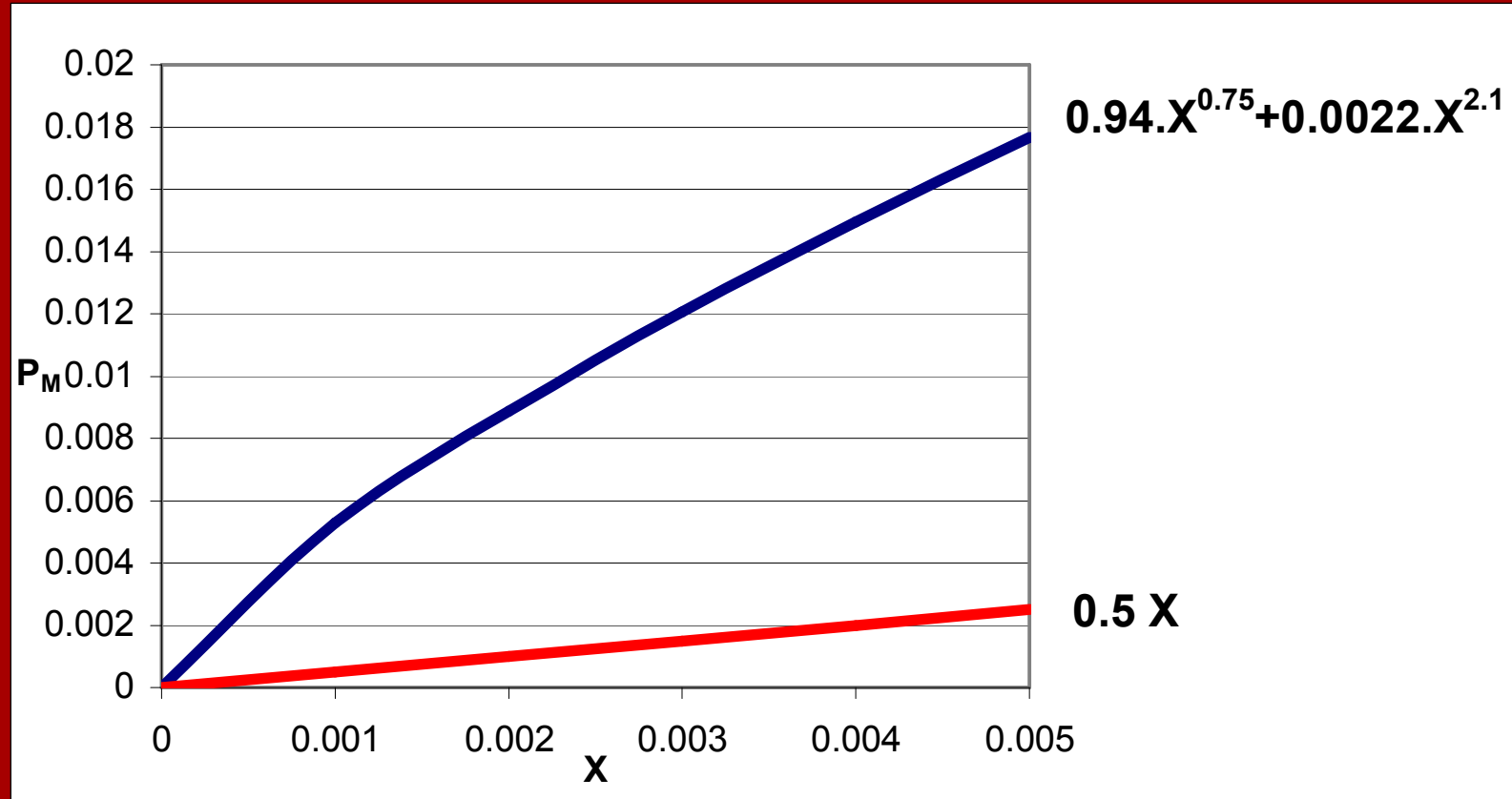
# Exposure metric

- Based on PCM
- How close do estimates of exposure relate to personal exposures
- How well to exposures measured via PCM relate to biologically relevant doses?
- Berman and Crump suggest a metric based on TEM which considers only long thin fibres

# Form of risk model (1)



## Form of risk model (2)



# Other issues:

## (1) Is there a threshold?



- Arguments based on toxicology seem to suggest that there might be a threshold at some level:
- Asbestos non-genotoxic which suggests that mechanism is to do with “frustrated clearance” of asbestos from the lung leading to tissue damage and cell proliferation. This would imply some burdens of fibres can be accommodated in lung

However....

- Cohorts with observed mesotheliomas but no excess of lung cancer
- Occupational PMRs – and trends in national deaths among females
- Other studies of cases where Job history or reported exposure suggests no substantial exposure

## Other issues:

### (2) Background mesothelioma mortality



- “Spontaneous” cases are those that would have occurred anyway in absence of any industrial exploitation of asbestos in UK
- Some evidence that incidence could be 1 per million per year
- => ~30 male and ~30 female deaths each year
- The lifetime risk is therefore 1 per 10,000 (or 100 per million)

## Other issues:

### (3) Non-occupational mesothelioma mortality

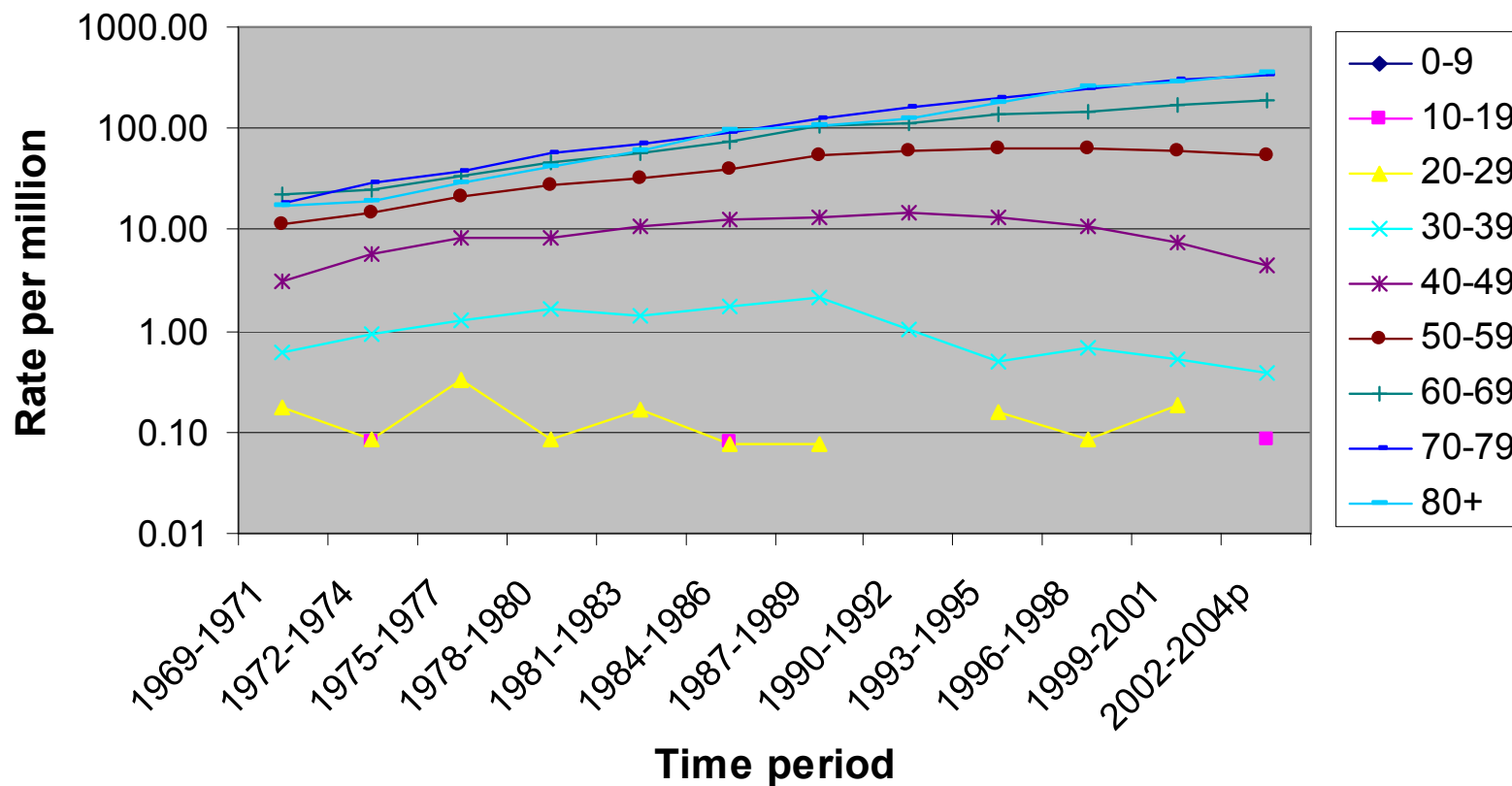


- ~2% of male mesotheliomas and 10% of female mesotheliomas are “spontaneous”
- Some studies estimate about 85% of male cases and 25% of female cases attributable to direct occupational exposures
- This suggests about 13% of male cases and 65% of female cases are due to other exposures - equivalent to about 200 cases per year in each sex
- Equivalent to a lifetime risk of about 70 per 100,000

# National mesothelioma mortality rates by age group (1)



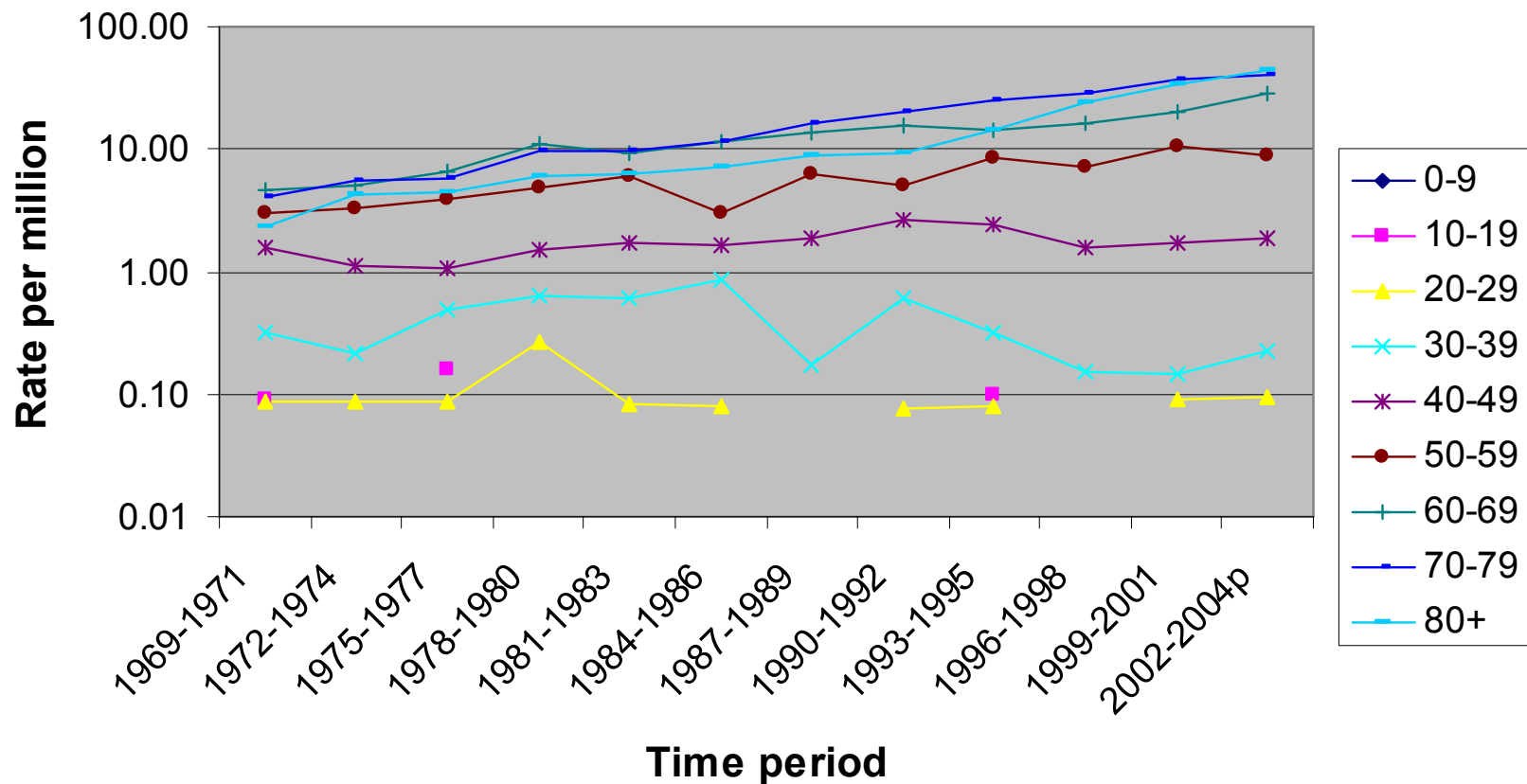
Mesothelioma rates for males by age group and 3-year time period, 1969-2004, Great Britain



# National mesothelioma mortality rates by age group (2)



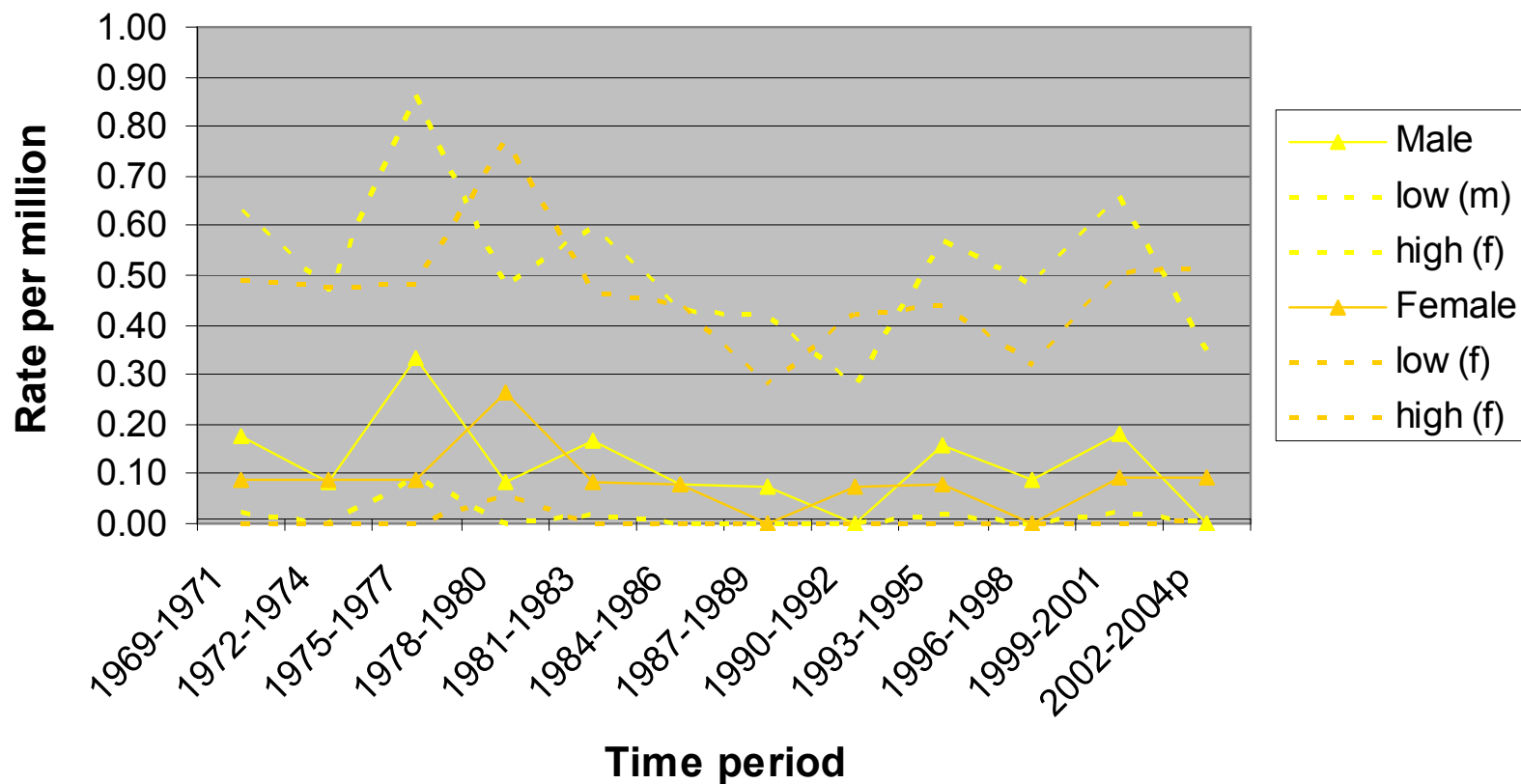
Mesothelioma rates for females by age group and 3-year time period, 1969-2004, Great Britain



# National mesothelioma mortality rates by age group (3)



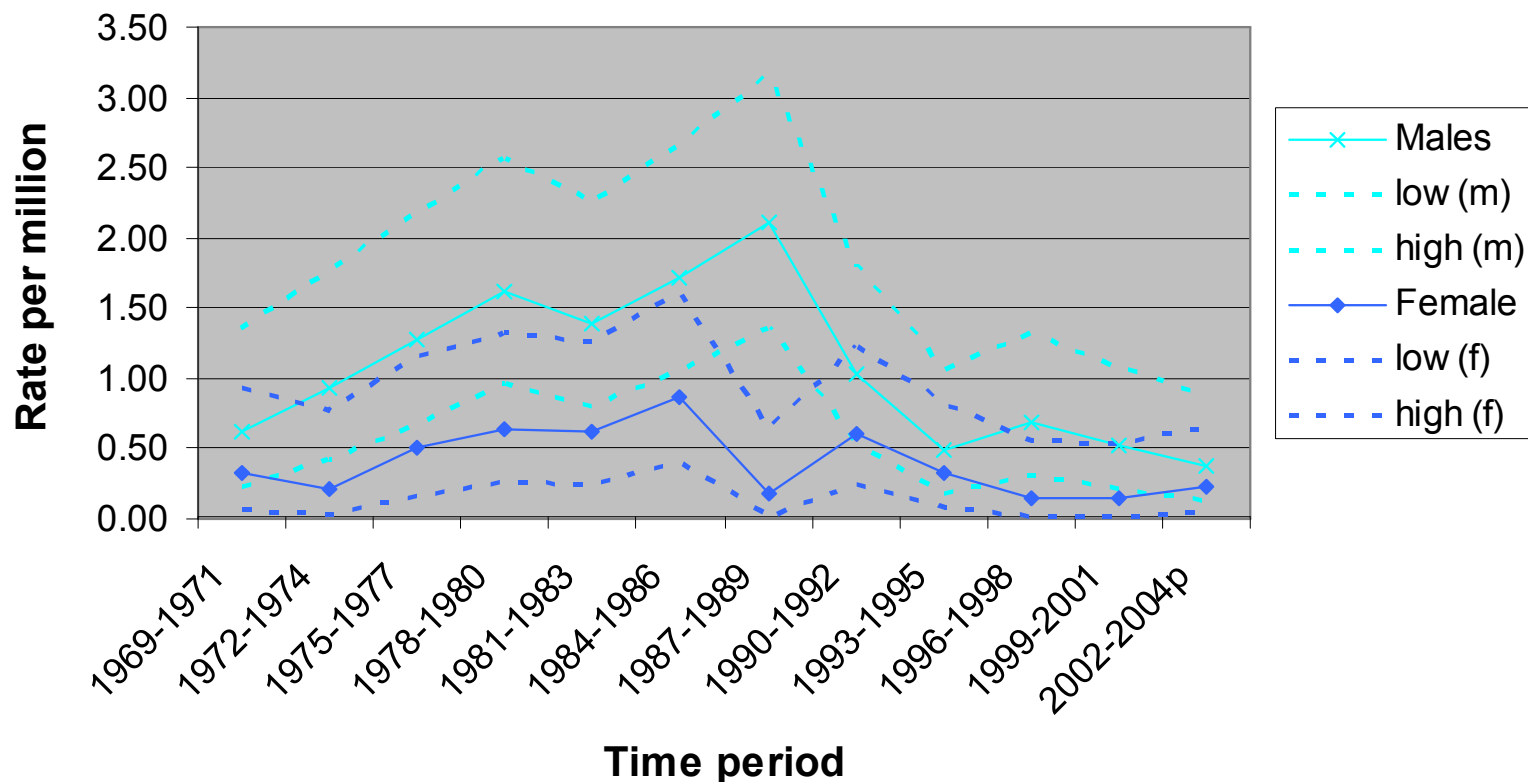
Mesothelioma rates for age group 20-29 by 3-year time period, 1969-2004, Great Britain



# National mesothelioma mortality rates by age group (4)



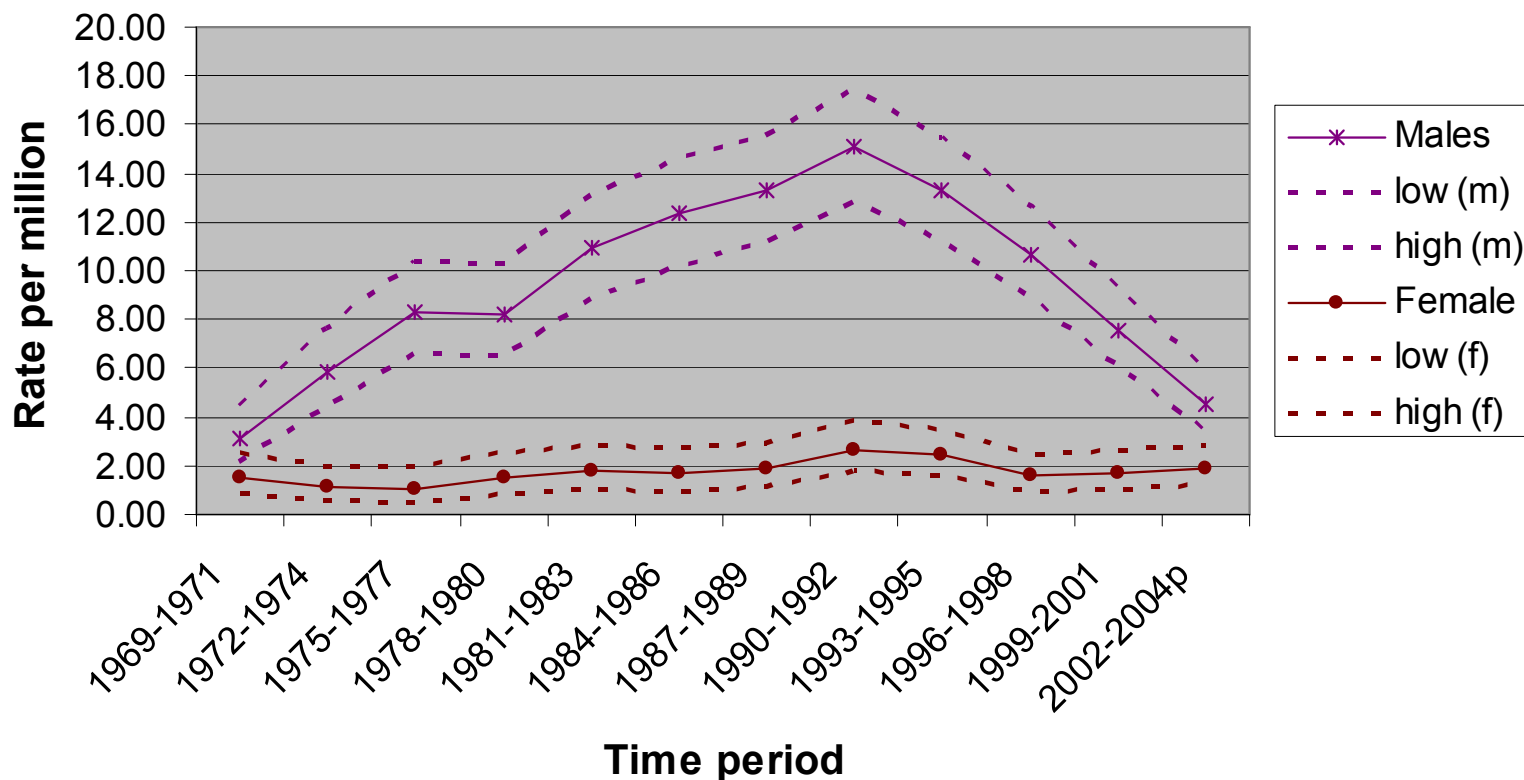
Mesothelioma rates for age group 30-39 by 3-year time period, 1969-2004, Great Britain



# National mesothelioma mortality rates by age group (5)



Mesothelioma rates for age group 40-49 by 3-year time period, 1969-2004, Great Britain



# National mesothelioma mortality rates by age group (3)



Mesothelioma rates for age group 50-59 by 3-year time period, 1969-2004, Great Britain

