

The risks of mesothelioma and lung cancer in relation to relatively low-level exposures to different forms of asbestos

What statements can reliably be made about risk at different exposure levels?

Introduction

1. The source data and quantitative risk models for mesothelioma and lung cancer in relation to asbestos exposure have been discussed at three previous WATCH meetings. The main focus of these discussions has been on the quality of the underlying exposure data and the implications of this on the H&D and other risk models. Despite serious limitations, patterns are seen in the data leading to risk models that are notably consistent (though still comprise substantial uncertainty). But the issue of the extent to which these models should be used to make quantitative statements about risk for specific exposure situations – particularly where exposures are below the range of exposures for which empirical observations are available – has so far not been resolved.
2. As a first step towards making progress on this issue, the purpose of this paper is to elicit your views on the kinds of statements about risk that are justified at different points progressing down the exposure scale. Five separate H&D models exist (mesothelioma in relation to crocidolite, amosite and chrysotile, and lung cancer in relation to amphibole and chrysotile) so in order to keep things manageable, in this paper we will restrict attention to two of these cases as follows:
 - (1) Mesothelioma in relation to amosite
 - (2) Mesothelioma in relation to chrysotile
3. For each case we would like to explore what you think can reliably be said about the risk for three cumulative exposure scenarios. We start with 10 f/ml.yr – a relatively high exposure which is still within the range for which empirical observations are available – but then move down below this to 1 f/ml.yr and then 0.1 f/ml.yr – the latter being most relevant in terms of the exposures we might want to make statements about today. In this paper, all exposures are assumed to be accrued over 5 years starting at age 30, since this was typical of the exposures in the source data. We would like to establish what can reliably be said about risk for this pattern of exposure before any further consideration of exposures accrued over longer periods and starting at different ages.
4. For both cases we've provided a table which summarises the main features of the risk estimates for the three exposure scenarios with

space for you to provide statements about risk. The draft minutes of the June 2008 WATCH meeting state at paragraph 6.18 that a member proposed that WATCH might consider adopting one of three positions with regard to risk estimation:

- (1) Risks associated with low-level exposure to asbestos cannot be predicted using the existing evidence base (ie no estimates).
- (2). Reliable absolute predictions about risks associated with low-level exposures to asbestos cannot be made using the HD2000 dose-response model, but it can be used to make predictions about the level of risk of one situation relative to another, in order to prioritise exposure control needs and risk management options (ie relative estimates).
- (3). The HD2000 linear dose-response relationship is considered to be valid, based on the consideration of the existing evidence base, and can be used to make reliable predictions of risk for low-level exposures (ie absolute estimates).

This suggestion might help in your reflections on what you consider can/should be said about the degree of risk involved under the exposure conditions presented in this paper.

5. One important issue in your considerations concerns the question of non-linearity in the H&D models. This is particularly important for the third (ie lowest) exposure scenario where its effect is more pronounced – but where models have been extrapolated far below the range of exposures for which there are empirical observations. Your view about the extent to which reliance should be placed on these extrapolated non-linear relationships will inevitably have an impact on what statements you think can be made.

Case 1: mesothelioma in relation to amosite exposure

- Figures 1a and 1b show mesothelioma lifetime risks for cumulative exposure (X) to amosite accrued over 5 years starting at age 30 derived from non-linear H&D “best”, “minimum” and “maximum” models (black lines) and linear models with confidence intervals (red lines).
- Figure 1a shows risks for exposures up to 100 f/ml.yr and Figure 1b focuses on lower exposures by plotting the data on a log-scale.
- In Figure 1b the three vertical black lines at 10, 1, and 0.1 f/ml.yr represent the three cumulative exposure scenarios we want you to consider.
- The vertical blue line in the charts represents the bottom end of the range of average cumulative exposures for which we have empirical observations about the risk (5 f/ml.yr): to the left of this we are essentially extrapolating.
- The horizontal blue line represents a plausible estimate of the background mesothelioma lifetime risk (25 per 100,000) which would apply in countries without industrial asbestos use. This is included to give an additional benchmark when considering what can be said about the risk.
- At the exposure levels for the three scenarios of interest, the dominant term in the non-linear H&D models is for pleural mesothelioma. For the H&D best model this means the risk is essentially proportional to $X^{0.75}$. For the H&D maximum model the relatively much higher risk predicted at lower exposures arises because of more extreme non-linearity: risk is essentially proportional to $X^{0.6}$. The minimum model is essentially linear.

Figure 1a: lifetime risk of mesothelioma in relation to cumulative exposure to amosite accrued over 5 years from age 30.

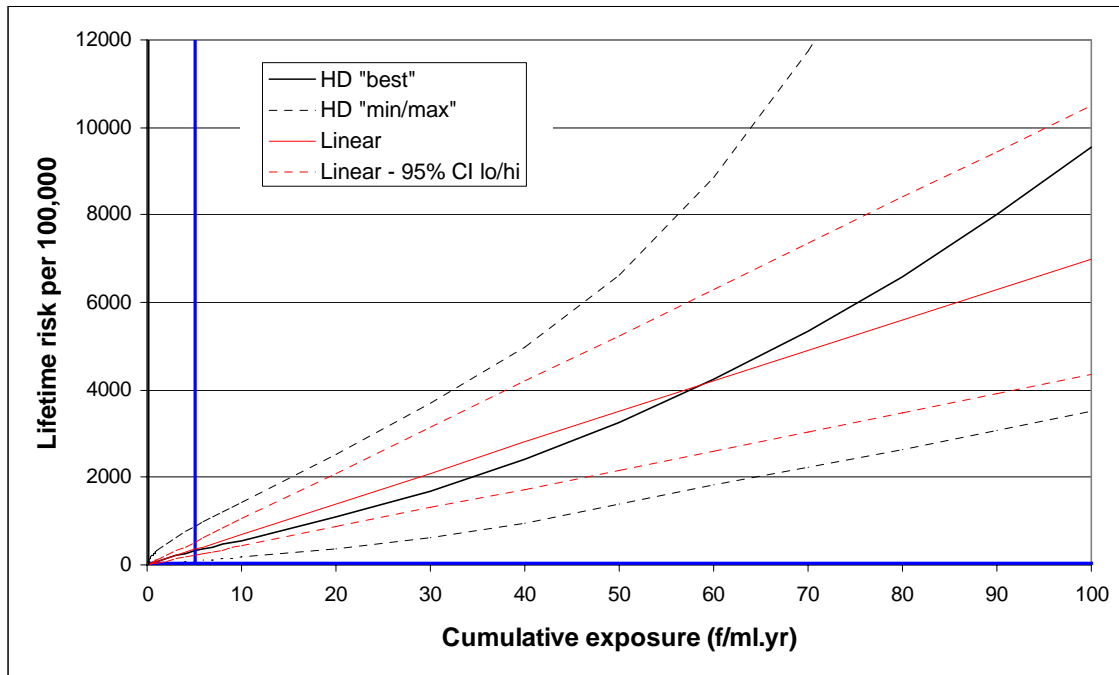


Figure 1b: lifetime risk of mesothelioma in relation to cumulative exposure to amosite accrued over 5 years from age 30 (focussing on lower exposures by plotting on log scale)

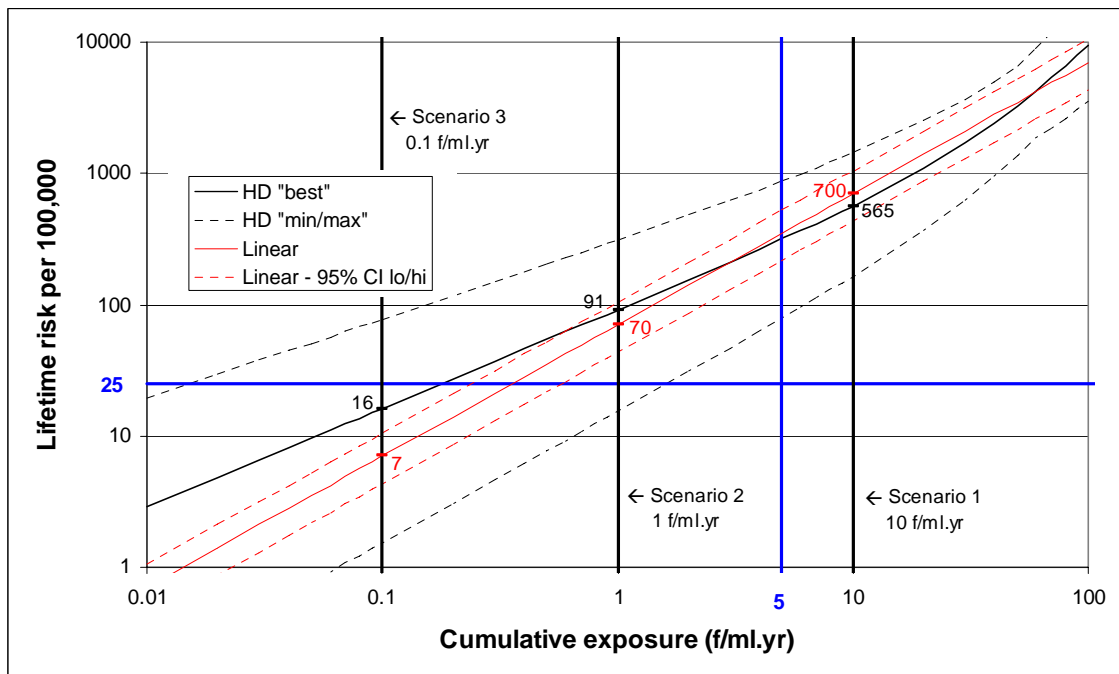


Table 1: Case 1 – mesothelioma in relation to amosite exposure

Exposure scenario	Summary	Your statement about risk at this level (see paragraph 4)
10 f/ml.yr	<ul style="list-style-type: none"> • Equivalent to constant exposure at a concentration of 2 f/ml (20 times the current control limit) during work time for 5 years. • This represents a much higher level of exposure than is likely to be experienced today and is still within the range for which empirical observations are available. • Central estimate based on linear model (700 per 100,000) and best estimate non-linear model (565 per 100,000) broadly consistent. • Upper end of the range defined by H&D min and max models (165-1400 per 100,000) is about twice the linear estimate. 	
1 f/ml.yr	<ul style="list-style-type: none"> • Equivalent to constant exposure at a concentration of 0.2 f/ml (twice the current control limit) during work time for 5 years. • It is conceivable that some of today's workers could achieve these sorts of exposures if they regularly work with asbestos without taking precautions. • However, this exposure is now below the range for which empirical observations are available. • Central estimate based on linear model (70 per 100,000) and best estimate non-linear model (91 per 100,000) still broadly consistent – but the non-linear model is starting to predict higher risks at this level. • Upper end of the range defined by H&D min and max models (15-300 per 100,000) is more than 4 times the linear estimate. 	
0.1 f/ml.yr	<ul style="list-style-type: none"> • Equivalent to constant work-time exposure at a concentration of 0.02 f/ml (1/5 the current control limit) – or exposure at the control limit for about 1 working day per week – for 5 years • This level of exposure could readily be achieved by some workers not taking appropriate precautions today and this scenario is therefore likely to be most relevant to today. • However, this exposure is now 1/50th of the bottom end of the range for which empirical observations are available. • Central estimate based on linear model (7 per 100,000) is less than half that of the best estimate non-linear model (16 per 100,000). • Upper end of the range defined by H&D min and max models (2-80 per 100,000) is now about 10 times the linear estimate. • The lifetime risk likely to be of the same order as the background 	

Case 2: mesothelioma in relation to chrysotile exposure

- Figures 2a and 2b show mesothelioma lifetime risks for cumulative exposure (X) to chrysotile – again accrued over 5 years starting at age 30 derived from non-linear H&D “best”, “minimum” and “maximum” models (black lines) and linear models with confidence intervals (red lines).
- Figure 2a shows risks for exposures up to 600 f/ml.yr and Figure 2b focuses on lower exposures by plotting the data on a log-scale.
- The same benchmarks (blue lines) and scenarios (black lines) are shown as in Figure 1b.
- For chrysotile there is no term for peritoneal mesothelioma in the H&D model – predicted risk relates only to pleural mesothelioma. For the H&D best model this means the risk is again proportional to $X^{0.75}$. For the H&D maximum model the relatively much higher risk predicted at lower exposures arises because of more extreme non-linearity: risk is proportional to $X^{0.6}$. The minimum model is linear.

Figure 2a: lifetime risk of mesothelioma in relation to cumulative exposure to chrysotile accrued over 5 years from age 30.

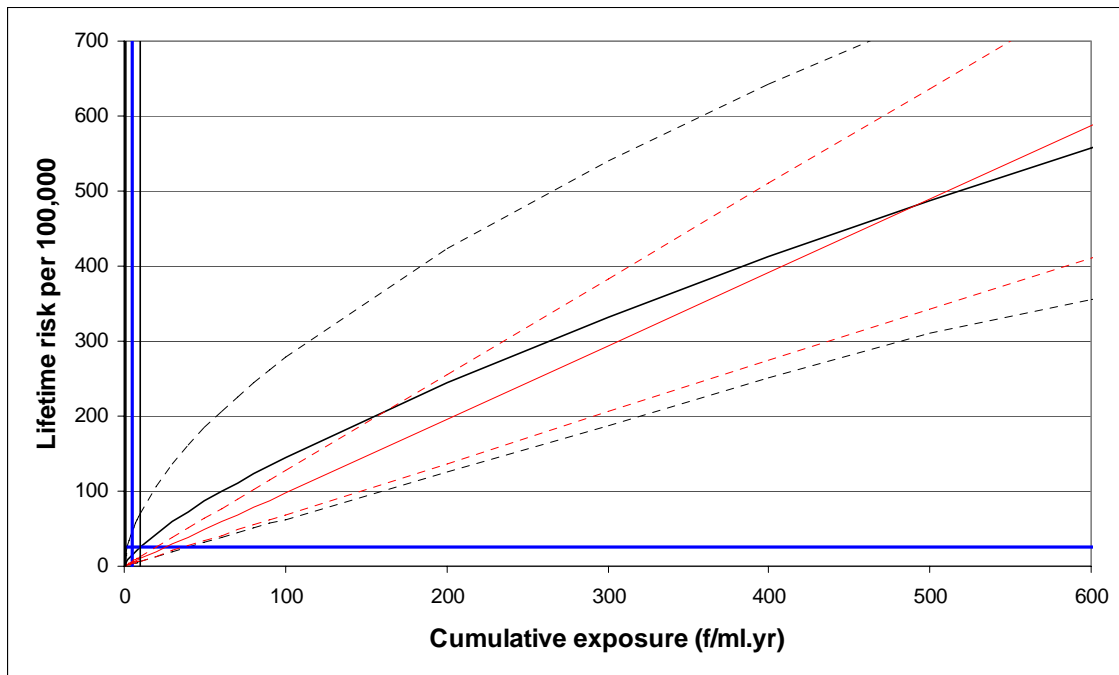


Figure 2b: lifetime risk of mesothelioma in relation to cumulative exposure to chrysotile accrued over 5 years from age 30 (focussing on lower exposures by plotting on log scale)

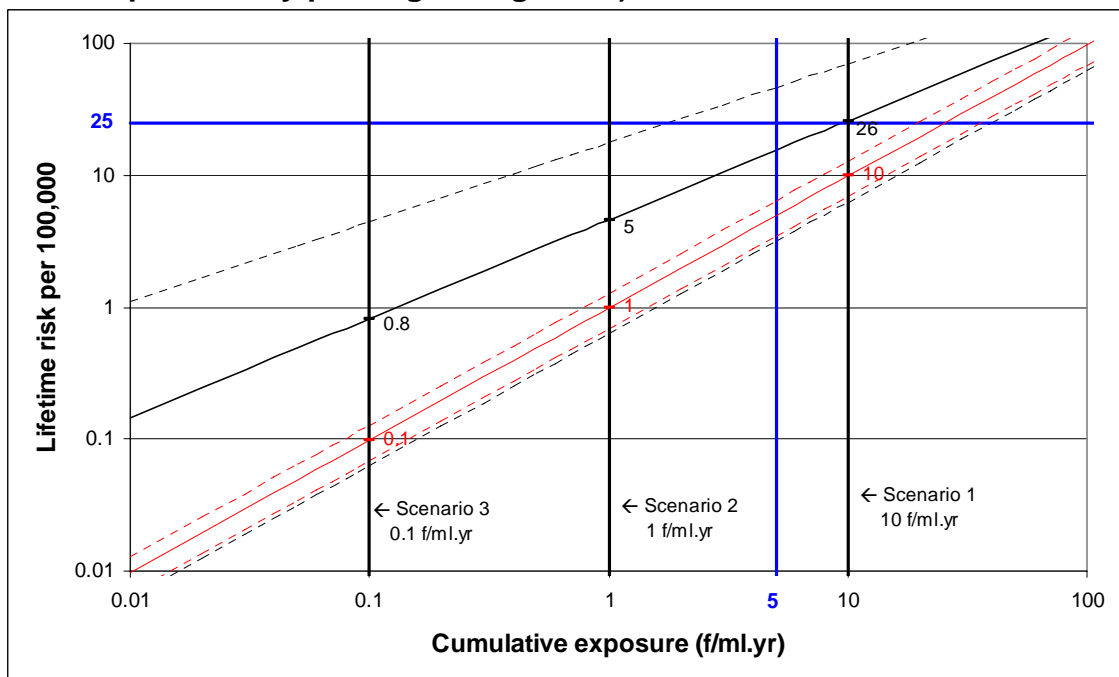


Table 2: Case 2 - mesothelioma in relation to chrysotile exposure

Exposure scenario	Summary	Your statement about risk at this level (see paragraph 4)
10 f/ml.yr	<ul style="list-style-type: none"> • Equivalent to constant exposure at a concentration of 2 f/ml (20 times the current control limit) during work time for 5 years. • This represents a much higher level of exposure than is likely to be experienced today and is still within the range for which empirical observations are available. • Central estimate based on linear model (10 per 100,000) is less than half the best non-linear model estimate (26 per 100,000). • These risks are of the same order as the background • Upper end of the range defined by H&D min and max models (6-70 per 100,000) is 7 times the linear estimate. 	
1 f/ml.yr	<ul style="list-style-type: none"> • Equivalent to constant exposure at a concentration of 0.2 f/ml (twice the current control limit) during work time for 5 years. • It is conceivable that some of today's workers could achieve these sorts of exposures if they regularly work with asbestos without taking precautions. • However, this exposure is now below the range for which empirical observations are available. • Central estimate based on linear model (1 per 100,000) is about 1/5th the best non-linear model estimate (5 per 100,000). • Upper end of the range defined by H&D min and max models (1-18 per 100,000) is 18 times the linear estimate. • The estimates are below the background risk level and approaching the region where it is arguable that the risk is insignificant. 	
0.1 f/ml.yr	<ul style="list-style-type: none"> • Equivalent to constant work-time exposure at a concentration of 0.02 f/ml (1/5 the current control limit) – or exposure at the control limit for about 1 working day per week – for 5 years • This level of exposure could readily be achieved by some workers not taking appropriate precautions today and this scenario is therefore the most relevant to today. • However, this exposure is now 1/50th of the bottom end of the range for which empirical observations are available. • Central estimate based on linear model (0.1 per 100,000) is about 1/8th the best non-linear model estimate (0.8 per 100,000). • Upper end of the range defined by H&D min and max models (0.1-4 per 100,000) is now about 40 times the linear estimate. • Estimates are substantially below background. 	