What statements can reliably be made about risk at different exposure levels?
- Comments received on the pre-meeting consultation paper

Comment 1  (received 29 September 2008)

As commented (previously), if WATCH is to adequately assess the applicability of Hodgson and Darnton (2000) to “low level exposures” to asbestos it must fully assess the validity of the epi data on which the model is founded.

From the additional analyses carried out by (HSE) for the June meeting it is clear that the original H&D model is robust.

However, as the H&D model will be applied in the UK to the UK population, I consider that it is essential to address: the effects of mortality in the epi studies on likely asbestos-induced lung cancers and mesotheliomas; validity of the asbestos-induced lung cancer and mesothelioma data in the epi studies; age differences between the epi study cohorts and the current UK population; likely life expectancy of young UK children of today; and effects of exposure at ages below 20.

Effects of mortality in the epi studies on likely asbestos-induced lung cancers and mesotheliomas

When H&D was published in 2000 I queried the fact that mortality in many of the critical studies was low, e.g. in the Sluis-Cremer et al (1992) cohorts, mortality in the amosite only and crocidolite only cohorts was only 21% and 13% respectively to the reporting date of 1980: see Howie and Hodgson (2001).

The following summary of the Quebec data illustrates the effect of mortality on the proportion of mesothelioma deaths in total deaths, from Liddell et al (1997) and McDonald AD et al (1997):

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td>857</td>
<td>2413</td>
<td>4262</td>
<td>6470</td>
<td>8009</td>
</tr>
<tr>
<td>Mortality (%)*</td>
<td></td>
<td>8.8</td>
<td>24.6</td>
<td>43.6</td>
<td>66.2</td>
<td>81.9</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td></td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>21</td>
<td>38</td>
</tr>
<tr>
<td>Mesothelioma as a proportion of all deaths (x 1,000)</td>
<td></td>
<td>0</td>
<td>1.2</td>
<td>1.4</td>
<td>3.2</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Note: * The total cohort was 9,780 men.
It will be noted that as mortality rose from 24.6%, a higher mortality than observed in the Sluis-Cremer et al (1992) study, to 81.9%, the proportion of mesotheliomas to total deaths increased by about a factor of 4.


Yates et al analysed data for 272 mesothelioma cases in south-east England during 1987. The mean latent period for all cases was 41.4 years, range 15-67 years, standard deviation 11.7.

The distribution of mesothelioma latent periods as compared with the distribution of time since first exposure to asbestos prior to the 1980 reporting date for Sluis-Cremer et al is summarised below:

<table>
<thead>
<tr>
<th>No of men</th>
<th>No</th>
<th>Percentage of total</th>
<th>Cumulative No</th>
<th>Cumulative percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First exposed 1971-80</td>
<td>2088</td>
<td>29</td>
<td>2088</td>
<td>29</td>
</tr>
<tr>
<td>First exposed 1961-70</td>
<td>2408</td>
<td>33</td>
<td>4496</td>
<td>62</td>
</tr>
<tr>
<td>First exposed 1951-60</td>
<td>2355</td>
<td>32</td>
<td>6851</td>
<td>94</td>
</tr>
<tr>
<td>First exposed 1941-50</td>
<td>404</td>
<td>5.5</td>
<td>7255</td>
<td>99</td>
</tr>
<tr>
<td>First exposed &lt;1940</td>
<td>62</td>
<td>0.8</td>
<td>7317</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>7317</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From the above, only 62 men, 0.8% of the total, had been first exposed 40 years prior to the reporting date, i.e. for longer than Yates et al's mean latent period, and 29% and 33% respectively had been first exposed within 9 and 19 years respectively of the reporting date. In crude terms, we would expect to have seen about half the likely mesothelioma numbers from the 62 men first exposed before 1940 and, assuming that the Yates et al data are normally distributed, less than about 4% of the likely mesothelioma numbers in the 4496 first exposed after 1961.

For the Sluis-Cremer et al (1992) cohort it can therefore be considered highly likely that both the absolute number and the proportion of total deaths due to mesothelioma will increase with increasing mortality of the cohorts.

It is therefore considered that all of the epi studies should be evaluated to assess the final likely lung cancer and mesothelioma numbers at the same mortality as the Quebec study, about 82%, as, unless such assessments are made, it is likely that both the absolute potency of the amphiboles and the relative potency of the amphiboles as compared with chrysotile will be underestimated.

Validity of the asbestos-induced lung cancer and mesothelioma data in the epi studies due to earlier deaths from pneumoconiosis or respiratory TB
My concerns regarding the above were outlined (previously).

As Sluis-Cremer et al (1992) addressed only white workers, and given the number of cases observed by Talent et al (1973) in black workers over a few years, I am unsure that the Sluis-Cremer et al (1992) figures for health outcomes will be valid for the men and women most likely to have been significantly exposed.

The above concerns need to be addressed.

**Age differences between the epi study cohorts and the current UK population**

In the Quebec cohort the median age at death to the 1992 reporting date was about 67.

For UK adults, the life expectancy for 67 year-old males is about 15.5 years, ONS (2008).

The effect of an additional 15 years of life expectancy of current UK males as compared with the Quebec cohort needs to be addressed.

**Likely life expectancy of young UK children of today**

As noted in my letter of 2\(^{nd}\) February 2008 the toddlers of today are expected to have an average life expectancy of about 90 years.

This addition life expectancy of very young children as compared with the Quebec cohort needs to be addressed.

**Effects of exposure at ages below 20**

Andy reported data on such extension below age 20 at the June meeting.

Given the above life expectancy of our very young children the model needs to be extended to take account of such children’s average life expectancy of about 90 years.

I am aware that there is a theorem that the mesothelioma risk should flatten out as the fibres are cleared from the body.

As a non-toxicologist I do not fully subscribe to the theorem of biological persistence. For example, when we look at rubber workers who were formerly exposed to beta-naphthylamine and who now have developed bladder
cancer, do we reject beta-naphthylamine as the cause if we don't find it or its metabolites in the bladder?

**General comments**

I recall it was suggested by the committee that *(HSE)* should consider preparing an input to the *Annals* describing the application of additional data to the H&D model and noting that such additional data caused minimal necessary modification to the model.

I would be grateful if you could circulate the above to *(HSE)* and the WATCH members prior to the meeting of 23rd October.

As an aside, given the above increase in the proportion of mesotheliomas to total deaths with increasing mortality, the two most crucially important research projects in the asbestos field would be to follow-up on both the Sluis-Cremer and Quebec cohorts.

**REFERENCES**


Comment 2 (received 3 October 2008)

I have an instinctive reluctance to extrapolate beyond the data sets because we are really only guessing. I have never done so for any of the clinical parameters I have dealt with nor in my enzyme kinetics work. But I have had to predict enzyme half lives based on a fraction of the data set that is needed for a reliable measurement and felt uncomfortable about doing so. In the end you simply have to say how you arrived at your figures.

Of the statements we have been sent I tend towards paragraph 4 subsection 2, but with a slight modification. I think the model can be used to compare different situations as a risk management tool. But we need to be 'up front' and say what we are predicting. We also need to say what our estimates of the risk are. Both the linear and non-linear models could be used to do this. We have no idea which is the more valid. And we need to say what the confidence intervals are. Here again it is only a prediction. The confidence intervals are large, as it is, for groups where we have data and we assume that we know what they will be for the extrapolated data but, again, we don't know.

I would be comfortable using the models to say what they predict and then including all the necessary caveats.

There is one other point on which I am confused. What is the reason for the background 25 mesothelioma lifetime risk? Is this background asbestos exposure? I presume it is. We won't have any idea about the exposures that caused these cases. If they were miniscule then this will influence how we interpret the risk for the 0.1 f/ml exposure category. The risk at this level may well be greater than the background 25 cases, or am I missing the point here?

Comment 3 (received 3 October 2008)

(As for comment 2) I am also confused about the 25 per 100 000 background risk which is said would occur in countries without industrial asbestos use. Is the understanding that this has a causative agent other than asbestos? Or is the agent still asbestos but from domestically used (imported) products? If the causative agent is still thought to be asbestos then I have a difficulty interpreting the data from the log scale plots at the low exposure rate end, illustrated by consideration of Figure 2b for the chrysotile asbestos. Maybe I am misinterpreting but my reading of Figure 2b is that the risk at an exposure rate of 10 f/ml.yr (scenario 2) for all plots, except the HD "min/max", results in a lower lifetime risk than that of 25 per 100 000 background risk. If this is so then it suggests that chrysotile at this level has less risk attached to exposure than exposure to background exposure, whereas at a higher level of exposure we can see that there is considerably more risk. I think that it is difficult and dangerous to extrapolate with any confidence from high levels of exposure with what is probably a significant risk to low levels of exposure and conclude that there is no risk attached. I am not sure whether the risk from the low level exposure shouldn't be added to the background level risk or whether we
should be looking for another mesothelioma causative agent that is potentially more potent than chrysotile asbestos that is responsible for the background incidence (outside the remit I know!).

I understand that the risk associated with chrysotile exposure is considerably less than that with amosite but I use the chrysotile example because it illustrates the point about extrapolation clearly.

I agree with (Commenter 2’s) assessment of paragraph 4 subsection 2 and this reflects my position also.

Comment 4 (received 7 October 2008)

I have reviewed the paper entitled "The risk of mesothelioma and lung cancer ...." and can offer observations below.
In case 1 (amosite) I believe the data support conclusion 3 "the HD2000 linear dose-response relationship is considered valid ..." for 10f/ml.yr and 1f/ml.yr based on convergence of the HD best fit and linear models and the lifetime risk being above the background lifetime risk of 25 per 100,000. Unfortunately I have much less confidence in the risk estimate of 0.1f/ml.yr but at a push would argue that conclusion 2 "reliable absolute predications not possible but can be used to make predictions about risk of one situation relative to another..."

In case 2 (chrysotile) given the much lower risks (all at or below background) and the significant differences between risks defined by the H&D min/max model and linear I am unable to conclude that the data are sufficient to consider the HD2000 linear dose-response relationship is valid for any of the exposures described At best the data could support conclusion 2 "reliable absolute predications not possible but can be used to make predictions about risk of one situation relative to another..."

I have to add that I am no expert in statistics or epidemiology and my judgement is based upon careful consideration rather than a significant knowledge base.

Comment 5 (received 8 October 2008)
(Commenter 1) raises some important points about the validity of the data and applicability of the model that I think we ought to try to address at the meeting. For the moment, though, I’ve put those aside and just concentrated on the charts as presented.

I feel comfortable that we can say something about relative risks (option 2). Whether we can say anything reliable about absolute risks (option 3) depends partly in the level of safety we are trying to achieve, and where the predicted risks lie in relation to that level.
I had a look at the HSE R2P2 framework (http://www.hse.gov.uk/risk/theory/r2p2.htm) which suggests on p42 classifying risks into Unacceptable, Tolerable, and Broadly Acceptable regions. It also suggests (p46) that, with all the usual caveats, an individual risk of death of one in a thousand per annum might represent the upper limit of tolerability for any substantial category of workers for any large part of a working life. That might equate to a lifetime (80 years) risk of 8,000 per 100,000 workers. Incidentally, R2P2 suggests dividing this by 10 for the general population.

At the other end of the scale, I think we can assume that the background level of 25 per 100,000 is Broadly Acceptable since there does not appear to be widespread societal concern about it. We could consider multiplying that by 10 for workers, but I haven’t done.

We can then draw these 2 lines on the charts as the upper (8000) and lower (25) limits of tolerability and see where the predicted risks fall.

For amosite:
At 10f/ml.yr all the predictions fall in the middle of the Tolerable range, whichever model is used
At 1f/ml.yr most of the predictions are in the lower part of the Tolerable range
At 0.1f/ml.yr Most of the predictions are Broadly Acceptable, with only the upper confidence limit of the HD prediction breaking into the Tolerable range.

For Chrysotile:
10f/ml.yr is on the lower boundary of the Tolerable range
1f/ml.yr and 0.1f/ml.yr are clearly in the Broadly Acceptable range.

If I were to translate that into risk management actions, I would say that Broadly Acceptable means do nothing, and Tolerable means do what is reasonably practicable to reduce exposure further.

I’m sure people will have lots of “buts” about the numbers, but if the concept is sound it might give us a pragmatic way forward.

Comment 6 (received 16 October 2008)
My conclusions are partially in agreement with the previous responders, broadly accepting the HD2000 model for the upper band of amosite exposure.

I would add the following observations though:

At the lower cumulative exposure ranges for both fibres my failure to accept the HD2000 model is probably based less on the statistics than it is on my lack of confidence in the exposure data itself. At such levels, we are into speculation about how such cumulative exposures might be achieved. The cover paper freely admits that we are extrapolating.
However, what is surely more important is that despite the uncertainties, we are considering a range of exposures which have previously been outwith the conventional control regimes. Does the information that we have now, lead us to conclude that there is a risk of mesothelioma associated with activities which have not previously been under the spotlight? I believe that the information we have is inadequate to conclude a clear exposure/response relationship but is also inadequate to permit us to conclude that such a relationship does not exist.

To me, the next question then becomes - so what? What next?

I am not comfortable with the "do nothing" option but at the same time, see no justification for major control actions especially as we don't really understand what we are trying to control and neither do the potentially affected workers.

Being very careful not to stray into ACTS' territory, I believe there is sufficient evidence of a possible relationship to justify information and guidance programmes aimed at improving awareness of the possible risks from low level exposure. This should certainly be targeted at the most relevant trades.

Response from John Hodgson (HSE) to some of the issues raised by Comments 2 & 3

It has long been considered that there is some "natural" background level of mesothelioma not related to anthropogenic asbestos exposure. The general view was that this gave rise to one or two annual deaths per million of population, which translates broadly to a lifetime risk of 8 to 16 per 100,000.

A comparison of recent international data seems to point to a rather higher background level of 25 per 100,000.

Whether this background level is in fact caused by naturally occurring asbestos, or asbestos-like materials in the natural environment by other causes or by a mixture of causes, is not known, and is not directly relevant to the assessment of risks extrapolated from known exposure to asbestos.

In this context it is probably best to assume that this background level exists and is unrelated to asbestos.