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We thank Drs Liddell and Browne and Mr Howie for their interest in our paper (Hodgson and Darnton, 2000), and their generally supportive comments. Between them they make a number of points which we would like to respond to. We will first deal with the comments from Drs Liddell and Browne.

CAROLINA COHORT

Both correspondents challenge in one way or another our treatment of the Carolina cohort. It is clear that there are difficulties in interpreting the observations from this cohort and a number of approaches are possible. As far as the assessment of mesothelioma risk is concerned, whether one counts the Carolina cohort along with the other chrysotile cohorts or not makes very little difference to the overall risk estimate. With only two mesothelioma cases, the Carolina cohort's statistical weight here is small. Our suggested risk is 0.001% per f/ml.yr, implying that the Carolina observations (0.013) do indeed overstate the true risk (whether by chance or otherwise).

Dr Browne thinks we should have made more of the possible role of amphibole in the Carolina cohort. It is true that this is a possible explanation for this cohort's "exceptional" status, though as we point out, the fact that significant levels of amphibole were found post mortem in the lungs of only one of ten lung cancer cases examined (Green *et al.*, 1997) limits the confidence one might otherwise have in this explanation.

COHORT AVERAGES

Another general criticism focuses on our use of what we have called "cohort average" data, rather than using (where available) more detailed exposure specific breakdowns within cohorts. Our reasons for this are discussed in the paper, and amount to a judgement that more is gained by improving the stability of observations and avoiding the probable errors of

individual exposure estimation than is lost by pooling observations on individuals with very different exposures. Where both cohort average and internal analyses are available, we compare the two measures (figures 10 and 11 of our paper) and show a good degree of concordance between them. It is not true that "regression between cohorts is irrelevant to [the form of the individual dose response]". For a linear relationship the two approaches will give identical estimates. It is of course true that non-linearity will distort the correspondence between individual and cohort level measures but the extent of this distortion for the degree of non-linearity we suggest will be small.

SMOKING

Dr Liddell also challenges our treatment of smoking effects. Clearly the reality of the joint effect of asbestos and smoking is more complicated than implied by a simple multiplicative adjustment for "smokers" and "non-smokers". However in the context of other substantial uncertainties such refinements are arguably inappropriate and in any case our paper was challenging the limits of reasonable length already.

TREMOLITE

Dr Browne refers to evidence that the tremolite contamination in Quebec chrysotile is a major factor in the observed mortality there, coupled with the claim that levels of asbestos related disease are very low or non-existent in cohorts exposed to chrysotile uncontaminated by tremolite, in South Africa, the former USSR and Brazil. The evidence from Quebec that tremolite plays an important role in the observed mortality there is reasonably convincing. Unfortunately there is no good epidemiology on the low tremolite cohorts elsewhere. The reference cited in this connection by Dr Browne (Rees *et al.*, 1999) does show that in a sixteen month case-ascertainment period covering most of South Africa no cases of mesothelioma associated with chrysotile mining were

detected (out of a total of 123 observed). This certainly suggests (in agreement with our conclusions) that the risk from chrysotile is low. However the much larger chrysotile mining operation in Quebec has only generated about one death from mesothelioma per year, so the absence of South African cases in a sixteen month period does not establish that the risk there is materially different from that in Quebec (though it certainly may be).

THRESHOLDS AND FORM OF DOSE-RESPONSE

Dr Browne also challenges our description of arguments for a threshold based on identifying the lowest dose received by an observed case as “logical nonsense”. This description was perhaps a touch intemperate, but it does seem to us that—particularly if it is accepted (as most observers do) that there are some “spontaneous” mesothelioma cases not associated with asbestos exposure—that this datum (the lowest dose received by an observed case) on its own carries no information about the level of any possible “threshold”.

Dr Browne suggests that the term threshold should be identified with a level of exposure below which any excess mortality would be epidemiologically detectable. Such a concept would be inadequate in any regulatory context, since we are concerned with lowering risks well below any such level.

We agree with Dr Browne that the Sluis Cremer evidence for adverse effects of amphibole exposure below 5 f/ml.yr is not compelling. Nevertheless we believe these data do show that there are effects well below the levels at which a threshold for chrysotile toxicity is arguable. As we point out, the adoption of a slightly concave dose response curve for lung cancer does mean that we predict less than proportionate risk at low levels of exposure.

We could have extended our discussion of the “threshold” argument, and both Liddell *et al.*'s (1998) breakdown of Quebec lung cancer mortality by intensity groups and Vacek (1998) more extensive modeling of the relationship to mortality of different functional forms of exposure and exposure timing are valuable contributions to the literature. However the possible conclusions are twofold: either cumulative exposure is so misleading a metric that no quantitative conclusions can be drawn, and we must wait for better analyses (which are very unlikely ever to be available); or we can cautiously see how far this measure can take us. The coherence of the picture revealed by the cumulative dose approach (particularly for mesothelioma) encourages us that it is adequate as a first approximation.

CONSISTENCY WITH OTHER OBSERVATIONS

Dr Browne suggests that we should have “subjected our calculations and guesses to the test of

reality”, and refers us to two authors Liddell (1993) and Camus *et al.* (1998) who have done so. Although we did not make these comparisons in the paper, we do not believe our conclusions are contradicted by the realities recorded in either of these papers. The main conclusions of Camus *et al.* is that the EPA risk assessment overstates the lung cancer risk from chrysotile by at least a factor of ten. Our suggested risk coefficient is one tenth of the EPA's. It is clearly consistent with the observations of Camus *et al.*—as indeed a very wide range of estimates (down to zero) would be: we are at the limits of what can be resolved by epidemiological observation.

Liddell (1993) argues for a “sub-linear” (concave) response for mesothelioma on the basis that the expected number of cases from person years generated by subjects with exposure durations below the minimum exposure duration for an observed case (in each cohort) is significantly greater than the (by definition) zero cases observed. This is an ingenious argument, but it is not clear that the simple observed to expected comparison it is based on can be tested statistically in the usual way, since the upper duration of exposure considered is defined by the minimum exposure duration seen among cases. Some sort of extreme value test is needed here. Furthermore, this analysis is based only on duration of employment, not on dose.

LOW EXPOSURE RISK ESTIMATES

Browne and Liddell take different views of our suggested risk estimates at low exposures. Dr Liddell proposes modifications to the risk estimates in our table 11, using linear models for lung cancer and for mesothelioma at high (above 50 f/ml.yrs) exposures, but retaining (on precautionary grounds) our suggested convex ($r = 0.75$) non-linear relationship for mesothelioma at lower exposures. Dr Browne is much more critical, suggesting that our risk estimates “have no sound basis”.

Certainly these estimates are much less soundly based than one would wish. Some view does however need to be taken, and in presenting both range and point estimates we have sought to convey both a reasoned best estimate and the degree of uncertainty (which, of course, increases as doses fall below epidemiologically observed levels). It is difficult to convey the balance between what is reasonably arguable in the way of risk estimation, and the associated uncertainties. That is why we chose in table 11 to give verbal summaries and use heavily rounded figures, rather than displaying estimates graphically, or otherwise implying inappropriate precision.

Mr Howie's main concern is that the low overall mortality in some cohorts may have led to under estimation of the true risk. It is true that overall mortality in several of the underlying cohorts is low, and consequently that a substantial amount of asbestos related

mortality will occur in these cohorts that does not form part of the present observations. We were very aware of this aspect of the data, and the problems it poses are discussed in detail in our Appendix A. Briefly, we argue that the pattern of mortality over time revealed by those cohorts which do have extended follow-up justifies the assumption that after allowing for a 10 or 20 year latency period the relative mortality excesses (for lung cancer relative to expected lung cancer, for mesothelioma relative to total expected mortality) remain broadly the same over time (at least for 20 or 30 years—beyond this the probability is that relative risks decline, which is part of our justification for truncating “lifetime” risks at age 80). If relative risk is broadly constant over time then provided one does have some observations from the relevant time period, a valid estimation of the long term risk can be made.

Mr Howie also asks for an indication of how one might estimate risks starting at ages below 20. Here the possibility of later decline in relative risk cannot reasonably be avoided. We tentatively suggest in our paper that risk might then be truncated at 60 years follow-up. The effect of this would be to predict approximately the same absolute risk for any age of exposure from age 20 downwards.

It is not clear why “the inclusion of data for mining severely skews the risk estimates”. It is true that the chrysotile mines produce lower per fibre risk estimates than most manufacturing cohorts, but as our data shows, if the amphibole fibres are (as Mr Howie

agrees) substantially more potent both for mesothelioma and lung cancer than the higher mortality levels in manufacturing can (with the sole exception of the Carolina lung cancer observations) readily be explained by differences of fibre mix.

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