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Letter to the Editor

Response to the letter from Dr. Ulm

Dear Editor,

On behalf of myself and the co-authors, I would like to thank Dr Ulm for his comments on our article about a pooled analysis of exposure-response for lung cancer in ten silica exposed cohorts [1].

We agree with Dr Ulm that based on the spline curve in Figure 1 that there appears to be a threshold at about 4 units (log cumulative exposure, mg/m^3-days), before which there is no increase in risk. This implies, as Dr Ulm states, that there would be little or no increase in lung cancer risk at cumulative exposures below 55 mg/m^3-days, or below an average exposure of 0.005 mg/m^3 over a 45 year working lifetime (taking into account a 15 year lag). We note, however, that in the U.S. the permissible level of exposure to quartz (100% quartz) is 0.10 mg/m^3, 20 times higher than the suggested threshold in this model.

We have conducted further analyses of possible thresholds using several different models with either cumulative or average exposure, as any presumed threshold might be model-dependent. In each model we used an iterative procedure to evaluate a large variety of possible thresholds until finding the one with the largest log-likelihood. For the model using the log of cumulative exposure with a 15 year lag, the best threshold was at 4.8 log mg/m^3-days (similar to the spline model); the threshold model fit the data better than a model with no threshold (model likelihood 23.4 vs 18.8). A model using the log of average exposure found the best threshold at an average exposure of 0.011 mg/m^3, which again was a slight improvement over the model with the log of average exposure with no threshold (model log likelihood 22.6 vs. 20.0). A model with cumulative exposure alone did not show any improvement by using a threshold, nor did the piece-wise linear model presented in the paper. Models with untransformed cumulative (or average) exposure, however, tended to display more heterogeneity between studies, probably due to the extreme skewness of some of the exposure data, and may therefore be less preferable.

In other words, there was evidence for a threshold which was consistent across several but not all models. However, the suggested threshold is quite low, an order of magnitude below current standards. Furthermore, we note that a priori biological considerations argue against assuming a threshold for carcinogens.

We also note that the data for silicosis morbidity, consistent across four reasonably well-designed studies with long followup, also suggests that average permissible exposure should be approximately an order of magnitude lower to prevent silicosis [2, 3]. Appreciable silicosis continues to occur today in the U.S. Kriebel and Rosenberg have pointed out that for many current uses of silica (abrasive blasting, manufacturing), those which account for most current silicosis cases in the US, it may be possible to replace silica by other materials [4].

We investigated further the dependence of our spline curve on the number of knots and the location of the knots, and we also used a penalized likelihood model. The latter model with 5 degrees of freedom is quite similar to the spline curve with five knots. Increasing the number of degrees of freedom or knots in both types of models introduces more curvature, as would be expected. The spline curve itself with five knots is not particularly sensitive to the location of the knots.

Regarding a separate analysis of the US diatomaceous earth study [5], this study was one of the ten studies in our pooled analysis, representing about 8% of the lung cancer deaths in our study. Whether or not there is evidence in the diatomaceous earth study for a high threshold of exposure prior to increased lung cancer risk, the whole purpose of a large pooled analysis is to get a best estimate of lung cancer risk (including any estimate of a possible threshold) across all relevant studies, not to emphasize results from one of them.

Regarding the debate whether prior silicosis is required to develop lung cancer among silica-exposed workers, this is a debate which cannot be resolved by current epidemiological data [6]. Silicosis is indicative of high silica exposure. Separation of the independent effects of silicosis and silica exposure is not possible with currently available data; it would require very detailed data over time on both exposure and silicosis. Furthermore, silicosis itself can be defined variably – either by X-ray, clinical diagnosis, or autopsy. In any case, we do not believe there is any evidence to support Dr Ulm's statement that in the absence of silicosis (however defined) there is no lung cancer risk for silica-exposed workers.

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