

## Comments from Dr. David Hoel, 7/23/2012

The SAB has not in my opinion given an adequate review of the proposed RfC methods given in the EPA document. Dr. Suresh Moolgavkar has clearly expressed the failings of the review on a number of important issues and for which I totally concur with his conclusions. To reiterate several points that I had offered previously the following should be considered by the SAB.

- The most scientific questionable position taken by the SAB is that pleural plaques (localized pleural thickening) are “predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma, and lung cancer.” Arguably, plaques are biomarkers of asbestos exposure but is there any evidence that they are biologically involved with lung cancer? Other well known markers of exposure such as the presence of dicentric chromosomes in lymphocyte chromosomes from radiation exposures are clearly specific indicators of radiation exposure and thus measures of increased cancer risk but are in themselves not biological cancer risk factors since cells with unstable chromosome aberrations such as dicentric chromosomes will not divide.
- The reference to biochemical models such as Michaelis-Menten and the Hill model is most inappropriate in that it gives a false sense of scientific credibility to a simple curve fitting activity. The formation of pleural plaques has nothing to do with these two biochemical reaction models and as such the impression that they do should not be given. A less deceptive approach would be to use simple polynomial regression or logistic regression which is the same statistically as the Hill model.
- The EPA model assumed a plateau of pleural plaque formation of 56% in a population while data has shown 85% among some worker groups. Using a value less than 100% requires some biological explanation since it is not clear that there is a percentage of individuals who will never have a pleural plaque no matter what are their exposure rate and duration of exposure. In other words they are somehow genetically or otherwise immune. The SAB should justify biologically why they recommend that a value less than 100% be used by EPA and that the value is to be obtained from some study found in the open literature.
- The SAB discusses that cigarette smoking is not an issue with respect to pleural plaques. No mention is however given to BMI and its association with false positive radiograph findings. Further BMI is also associated with pulmonary function deficits which in turn relates to the SAB's conclusion that pleural plaques cause pulmonary function effects.
- Using a single small data set to derive an RfC or RfD is generally inappropriate. Estimated values should be obtained from many other data sets and compared.