

Statement for Public Teleconference for the SAB review of “Draft Toxicological Review of Libby Amphibole Asbestos” (EPA/635/r/002a)

David G. Hoel, Ph.D.

Exponent, Inc.

May 1, 2012

Prior Comments

1. Additional Comments from Elizabeth Anderson and David Hoel, Exponent, Inc., (04/09/2012)
 - Selection of critical endpoint
 - Derivation of draft RfC
 - Practical considerations

Exposure Response Models for Pleural Plaque

Prevalence: Michaelis-Menten:

- Michaelis-Menten models the rate of an enzyme-catalyzed reaction of a single substrate, which is a function of the substrate concentration.
- This is a saturable process and thus is unlikely to have anything to do with the prevalence of pleural plaques resulting from asbestos exposures.
- The model has been changed to add a background prevalence term. Since without any substrate the model then will still have a reaction. Since this makes little sense the modified Michaelis-Menten model should be considered to simply be a non-linear function that is used in a curve fitting exercise.
- The background parameter is set at 1% instead of being estimated from the data. This artificially reduces the AIC value. It would be increased by 2 if the background value was indeed estimated to be 1 from the data. This then gives the modified model an unfair advantage over the other competing models from an AIC standpoint.

Exposure Response Models for Pleural Plaque

Prevalence: Hill Model:

- Hill Model models the fraction of occupied sites on a macromolecule by a ligand as a function of the ligand concentration. It estimates the degree of cooperation in the reaction either positive or negative by occupied sites.
- It should be noted that the logit of the fraction of occupied sites is linear in the concentration of the ligand and the log of the dissociation constant (which equals the ligand concentration at $\frac{1}{2}$ occupancy raised to the n th power where n is the Hill parameter). Therefore a simple logistic regression is equivalent to using the Hill model.
- As with the Michaelis-Menten model the Hill model is converted in the analysis into something else by adding a saturation parameter as well as a non-estimated background parameter. The same argument applies to using AIC for model comparisons with other functions which do not include a non-data estimated parameter.

Exposure Response for Pleural Plaque Prevalence:

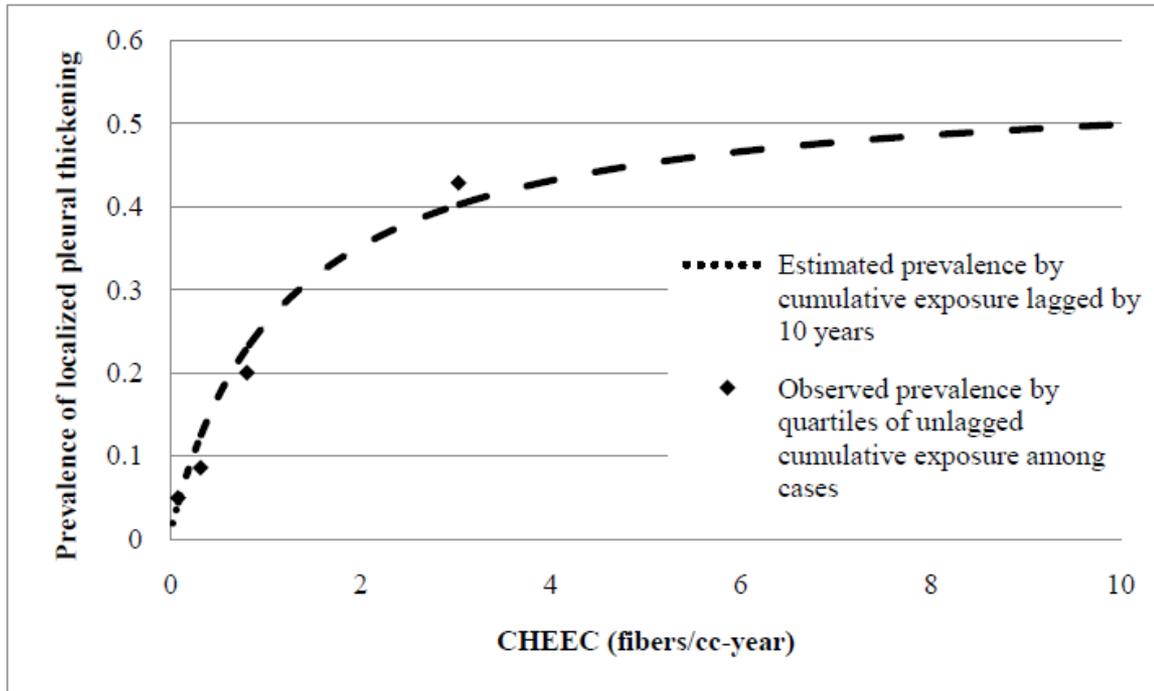


Figure 1. EPA's dose-response model fit for pleural thickening versus raw data in quartiles of cases (Figure E-1 in EPA Draft Toxicological Review)

Exposure Response for Pleural Plaque Prevalence:

- The data used for the curve fitting consists of only 4 data points with some of the models having 3 parameters needing to be estimated. This does seem to approach over-parameterization.
- In determining the 4 data points the exposure intervals are defined by the outcome variable i.e. 3 pleural plaques per exposure interval. The independent variable being the average exposure in the interval is thus also a dependent variable which makes for an interesting error structure in using typical regression methods. This should be discussed.

Exposure Response for Pleural Plaque Prevalence:

- The previously given Figure 1 illustrates the limited nature of the data using intervals based on the number of subjects which is usual instead of defining the intervals by outcome. This also illustrates the very limited nature of model fitting with only 12 outcomes. Also known modifying factors such as BMI and age will not be able to be included because of the limited data.

Table 1. Rohs restricted data set divided into quartiles with even numbers of subjects

Quartile	Exposure (f/cc-yr)	Cases	Subjects	Prevalence
1	0.033	2	29	0.069
2	0.092	0	30	0.000
3	0.20	3	29	0.103
4	1.1	7	30	0.233

Exposure Response for Pleural Plaque Prevalence:

- The background rate that is assumed to be equal to 1% is an interesting modeling assumption. Pleural plaque prevalence appears to increase with age and has been estimated in the U.S. using NHANES II by Rogan et al. (2000) (see EPA section 5.3.2.2.). The reported prevalence for males 45-74 was 7.8% which is quite high for the U.S. considering the 1% assumption. When the preferred modified Michaelis-Menten model was run allowing for background prevalence estimation (estimated at 3.12%) the resulting AIC value was not reported.

Exposure Response for Pleural Plaque Prevalence:

- Using the full Rohs data set restricted to employment beginning at least 20 years prior to screening there are 293 workers. The screening reported 73 workers with pleural plaques and 11 with diffuse pleural thickening.
- None of the cases of pleural thickening had pleural plaques indicating the concept that the plaques are not in the disease pathway of pleural thickening.
- Recommendation:

Apply simple and well understood dose-response models such as logistic regression instead of using biochemical models that are scientifically misleading by being unrelated to the prevalence of pleural plaque formation from asbestos exposures and having been modified in such a way that they are no longer biochemical models.