

Memorandum

31 January, 2012

From: David Bussard,
Director, Washington Division
National Center for Environment Assessment
U.S. Environmental Protection Agency

Subject: Data request from the SAB for the external review draft Toxicological Review of Libby Amphibole Asbestos

To: Diana Wong, Ph.D.
Designated Federal Officer
Science Advisory Board
U.S. Environmental Protection Agency

We understand the SAB panel has requested additional information on the exposure-response modeling presented in Appendix E of the External Review Draft of the Toxicological Review of Libby Amphibole Asbestos currently under review. According to your e-mail (23 Jan2012) the following has been requested:

- 1) More basic data description for the primary subset and full cohort used for analysis.
- 2) Estimates of the regression coefficient and its SE for exposure in all models (refer to Table E-1).
- 3) All parameter estimates in the models in Table E-2. (Specifically, all models with ln(CHEEC) as exposure at a 10 year lag. That would be the logistic, probit, 3-parameter logistic, Dichotomous Hill, and Michaelis-Menten).
- 4) All coefficient estimates for the model assessing smoking (refer to Table E-4, also E-5)
- 5) Raw data file used in the analysis

We have attached tables addressing requests 1-4 above to this memorandum:

Attachment 1: Descriptive statistics for both the full and subcohorts used in the EPA exposure-response modeling for RfC derivation presented in the Libby amphibole asbestos Toxicological Review.

Attachment 2: For Table E-1: The regression coefficients with standard errors are given in an additional table. We have also provided similar data for Table E-3 which addresses the best-fitting model (Michaelis-Menten with a 10-year lagged exposure; refer to table E-3 in document)

Attachment 3: For Table E-2: All requested parameter estimates are provided in tabular form including the standard errors and associated p-values. (Specifically, all models with ln(CHEEC) as exposure at a 10 year lag. Model forms addressed include: logistic, probit, 3-parameter logistic, Dichotomous Hill, and Michaelis-Menten).

Attachment 4: For Tables E-4 and E-5: All parameter estimates for the smoking evaluation including the standard errors and associated p-values

The fifth request above involves files which include individual level data on the members of the studied cohort. We are in the process of determining in what format these data can be shared, especially given the information would be posted on a the SAB public web-site. These data were collected by the University of Cincinnati and are governed by their Institutional Review Board. We will advise you as soon as we can share some form of the data.

Please contact us if you need additional information regarding the enclosed tables,
Sincerely,
David Bussard

Attachment 1: Descriptive statistics for both the full and subcohorts used in the EPA exposure-response modeling for RfC derivation presented in the external review Draft Toxicological Review of Libby Amphibole Asbestos.

Table 1: Selected demographic characteristics of the full and subcohort used in analysis
(Please see 5.2.3.2 in document for detailed description of datasets) *

Characteristic	Full cohort of workers with x-rays in 1980 or 2002-2005	Subcohort of workers hired in 1972 or later, with x-rays in 2002-2005
Number of workers	434	118
Number of cases of LPT	61	12
Mean/median year of hire	1969/1970	1975/1975
Mean/median age at x-ray (years)	58.6/56.0	51.9/50.0
Mean/median time from first exposure (i.e. hire date) to x-ray (years)	24.5/26.1	28.2/28.4
Mean/median employment duration (years)	19.3/21.4	18.7/22.3
Percent female	6.4	11.0
Percent ever smoker	56.8 (of 250 obs, n=184 missing)	54.2
Mean/median BMI	30.8/29.4 (of 218 obs, n=216 missing)	31.4/30.2 (of 97 obs, n=21 missing)
Mean cumulative exposure (fiber/cc-year)	2.7	0.42
With a 10-year lag	2.2	0.37
Median (25 th , 75 th percentiles) cumulative exposure (fiber/cc-year)	0.20 (0.09, 1.15)	0.16 (0.07, 0.42)
With a 10-year lag	0.13 (0.01, 0.67)	0.13 (0.06, 0.31)
Range of cumulative exposures (no lag) (fiber/cc-year)	0.001-34.15	0.001-5.51
With a 10-year lag	0-34.03	0.001-5.31

*There were originally 513 individuals in the Lockey et al. (1984) cohort; of these, 77 had previous asbestos exposure and were excluded ($n = 436$). Two individuals were excluded because their X-ray date was the same as their employment start date ($n = 434$). These exclusions are also reflected in the subcohort. One individual with diffuse pleural thickening was additionally removed from the subcohort analytic dataset, as DPT is a more severe endpoint than LPT.

Attachment 2: For models included in Table E-1: The regression coefficients with standard errors for the exposure metric and the covariate are given in an additional table. We have also provided similar data for models included in Table E-3 which addresses the significance of covariates in the best-fitting model (Michaelis-Menten with a 10-year lagged exposure; refer to table E-3 in document).

Table 2: Evaluation of covariates for the 2004 post-1972 set, using a logistic model with ln(CHEEC) as the exposure metric (refer to table E-1 in the external review Draft Toxicological Review of Libby Amphibole Asbestos).

Covariate	Beta coefficient (SE), Wald <i>p</i> -value corresponding to covariate	Beta coefficient (SE), Wald <i>p</i> -value corresponding to ln(CHEEC)	AIC
Base model (only ln[CHEEC])	—	0.5676 (0.2420), p=0.0190	75.5
Time from first exposure	0.0194 (0.1376), p=0.8879	0.5551 (0.2574), p=0.0310	77.5
Age at X-ray	-0.0137 (0.0478), p=0.7735	0.5714 (0.2427), p=0.0186	77.4
Gender	0.1713 (0.5756), p=0.7660	0.5856 (0.2506), p=0.0195	77.4
Smoking history	0.9895 (0.7158), p=0.1669	0.5819 (0.2561), p=0.0231	75.4
BMI ^a	0.0458 (0.0556), p=0.4095	0.7768 (0.3025), p=0.0102	56.7

^aNote that only 97 observations were used, due to missing values (AIC not comparable). The base model only including ln(CHEEC) for these 97 individuals has an AIC of 55.4, and a beta for ln(CHEEC) of 0.8280 (SE=0.3108, p-value=0.0077).

Table 3: Evaluation of covariates for the 2004 post-1972 set in the best-fitting model (Michaelis-Menten with a 10-year lagged exposure; refer to table E-3 external review Draft Toxicological Review of Libby Amphibole Asbestos.)

Covariate	Beta coefficient (SE), Wald <i>p</i> -value corresponding to covariate	Beta coefficient (SE), Wald <i>p</i> -value corresponding to plateau	AIC
Base model (only ln[CHEEC])	--	0.5577 (0.3568), p=0.1207	74.0
Time from first exposure	-0.00066 (0.1918), p=0.9973	0.5580 (0.3634), p=0.1274	76.0
Age at X-ray	-0.00978 (0.06122), p=0.8734	0.5707 (0.3793), p=0.1351	76.0
Gender	-0.7895 (1.3317), p=0.5544	0.6167 (0.4138), p=0.1388	75.7
Smoking history	1.8232 (1.0465), p=0.0841	0.5927 (0.3779), p=0.1195	72.3
BMI ^a	0.06681 (0.07585), p=0.3806	0.4622 (0.2810), p=0.1032	55.8

^aNote that only 97 observations were used, due to missing values (AIC not comparable). The base model only including CHEEC lagged by 10 years for these 97 individuals has an AIC of 54.6, and a plateau of 0.4777 (SE=0.3282, p-value=0.1488).

Attachment 3: Parameter estimates for exposure-response modeling in support of Reference Concentration (RfC) derivation in the Draft Toxicological Review of Libby Amphibole Asbestos, Table E-2.

Table 4: Evaluation of different model forms for the 2004 post-1972 subcohort of workers from the O.M. Scott plant in Marysville, OH, (refer to table E-2 external review Draft Toxicological Review of Libby Amphibole Asbestos.) Parameters are specified for all models with ln(CHEEC) as exposure at a 10 year lag. Model forms include logistic, probit, 3-parameter logistic, Dichotomous Hill, and Michaelis-Menten). All requested parameter estimates are provided in tabular form including the standard error and associated p-value.

Model	Form*	AIC	Parameter	Parameter Estimate (SE)	Wald <i>p</i> -value
Logistic	$P(LPT) = 1 \div [1 + \exp(-a - b \times \ln(CHEEC))]$	74.6	Intercept	-1.2399 (0.4214)	0.0033
			Ln(CHEEC, lag 10)	0.5999 (0.2352)	0.0108
Probit model	$P(LPT) = \Phi(a + b \times \ln(CHEEC))$	75.2	Intercept	-0.7905 (0.2462)	0.0013
			Ln(CHEEC, lag 10)	0.2904 (0.1247)	0.0198
3-parameter log-logistic	$P(LPT) = bkg + (1 - bkg) \div [1 + \exp(-a - b \times \ln(CHEEC))]$	74.1	Intercept	-1.2309 (0.4402)	0.0060
			Ln(CHEEC, lag 10)	0.7373 (0.3047)	0.0171
Dichotomous Hill†	$P(LPT) = bkg + (Plateau - bkg) \times CHEEC^b \div [\exp(-a) + CHEEC^b]$	76.0	Intercept	-0.2068 (2.2123)	0.9257
			Plateau	0.5633 (0.5523)	0.3099
			Ln(CHEEC, lag 10)	0.9887 (0.8221)	0.2315
Michaelis-Menten±	$P(LPT) = bkg + (Plateau - bkg) \times CHEEC \div [\exp(-a) + CHEEC]$	74.0	Intercept	-0.1801 (1.0178)	0.8598
			Plateau	0.5577 (0.3568)	0.1207

*'bkg' indicates background rate, fixed at 1%, 'a' indicates the intercept, 'b' indicates the beta coefficient for the exposure variable.

†For statistical modeling, the equivalent model form was used: $P(LPT) = bkg + (Plateau - bkg) \div [1 + \exp(-a - b \times \ln(CHEEC))]$.

± For statistical modeling, the equivalent model form was used: $P(LPT) = bkg + (Plateau - bkg) \div [1 + \exp(-a - \ln(CHEEC))]$.

Attachment 4: Evaluation of smoking as a covariate for exposure-response modeling in support of Reference Concentration (RfC) derivation in the Draft Toxicological Review of Libby Amphibole Asbestos, Table E-4.

Table 5: Evaluation of smoking in the best-fitting model (Michaelis-Menten with a 10-year lagged exposure; refer to table E-4 external review Draft Toxicological Review of Libby Amphibole Asbestos.) All parameter estimates for the smoking evaluation including the standard errors and associated p-values (Table E-4 of the external review Draft Toxicological Review of Libby Amphibole Asbestos.) Note that model (2) was used to generate BMC/BMCL estimates for smokers and non-smokers presented in Table E-5.

Model*	AIC	Parameter	Parameter Estimate (SE)	Wald <i>p</i> -value
1	74.0	Intercept	-0.1801 (1.0178)	0.8598
		Plateau	0.5577 (0.3568)	0.1207
2	72.3	Intercept	-1.5184 (1.1459)	0.1877
		Plateau	0.5927 (0.3779)	0.1195
		Smoke	1.8232 (1.0465)	0.0841
3	74.1	Intercept	-3.7355 (2.3314)	0.1118
		Plateau	0.4675 (0.3265)	0.1548
		Smoke	2.5401 (2.0952)	0.2278
		Ln(CHEEC, lag 10)*Smoke	0.2182 (0.4943)	0.6598

*The following model forms were used for statistical analysis:

$$(1) P(LPT) = bkg + (Plateau - bkg) / [1 + \exp(-a - \ln(CHEEC, \text{lag } 10))]$$

$$(2) P(LPT) = bkg + (Plateau - bkg) / [1 + \exp(-a - \ln(CHEEC, \text{lag } 10) + \beta * \text{Smoke})]$$

$$(3) P(LPT) = bkg + (Plateau - bkg) / [1 + \exp(-a - \ln(CHEEC, \text{lag } 10) + \beta * \text{Smoke} + \beta_2 * \ln(CHEEC, \text{lag } 10) * \text{Smoke})]$$

Where 'bkg' indicates background rate, fixed at 1%, 'a' indicates the intercept