COMMENTS ON THE EPA DRAFT RISK ASSESSMENT FOR LIBBY AMPHIBOLE

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March 27, 2012

QMS ID: 1106602.000.B0T0 0312 SM01

As a member of the interested public and a consultant to W. R. Grace, I was given a limited amount of time to testify before the SAB in February, 2012. During that meeting, members of the SAB requested that the Agency provide more support for its risk assessments asking for substantive sensitivity analyses of both the IUR for the cancer endpoints and the RfC for the non-cancer endpoint. Members of the SAB also suggested that numerous additional papers be reviewed and requested access to some datasets. Members of the SAB have now posted updated comments, and the EPA has made a limited dataset available to the general public. My comments here are in response to the posted comments by the SAB, and are based, in part, on reviews of the additional papers that the SAB thought should be considered and on analyses of the limited dataset on pleural plaques made available to the public.

A. Reference Concentration (RfC) for non-cancer adverse effects using discrete pleural thickening (pleural plaques) as the relevant endpoint.

Two fundamental issues arise. Are pleural plaques simply a marker of asbestos exposure, or do they represent an adverse clinical condition? Second, if plaques do represent an adverse clinical condition, are the data and methods used by the Agency valid? I address the second question first.

The data used by the Agency for the derivation of an RfC are inappropriate.

This opinion is based on the following facts.

- The RfC is based on a small subcohort of the cohort of vermiculite workers analyzed by Rohs et al. (2008). The Rohs dataset reports 68 pleural plaques among 280 individuals. The Agency subcohort consists of 118 individuals with 12 cases of pleural plaques. The power to detect any confounding in this small dataset is greatly diminished. It is inappropriate to base a risk assessment on such a small dataset, particularly when the Agency is setting a precedent by proposing for the first time an RfC for non-cancer endpoints for asbestos exposure.
- My previous analysis of the full Rohs dataset indicates **strong confounding by age with the parameter estimate for exposure to Libby amphibole becoming greatly attenuated in joint analyses with age**. When both age and BMI are included in the analysis, the coefficient for Libby amphibole becomes borderline insignificant.
- By the Agency's own criteria when rejecting the Amandus study as a basis for the RfC, the Rohs dataset cannot be used for the estimation of an RfC. Selecting a small subcohort to get around the issue of confounding by age and BMI is not the appropriate way to address this issue.
- **Conclusion**: The Rohs dataset and subsets of it are not suitable for the derivation of an RfC.

The model used by the Agency for the derivation of an RfC is inappropriate.

Even if the data chosen by the Agency for developing an RfC were appropriate, the model used is not. This opinion is based on the following facts.

- Despite a choice of a large number of exposure-response models available in the standard benchmark dose software (BMDS) developed and distributed by the Agency, in this risk assessment, the Agency chose to use a model, the Michaelis-Menten model, which is not among

the models in the BMDS. The Michaelis-Menten model is widely used for enzyme kinetics and receptor binding and its properties make it unsuitable for a dose-response analysis for the estimation of an RfC. The model requires the estimation of a plateau, which is biologically unrealistic. Even in the dose-response modeling for cancer, a relatively rare condition even with high exposures, models with a plateau, implying that a certain fraction of the population is immune, are not used.

- The Agency forced the model through a background prevalence for pleural plaques of 1%, even though the model allows the estimation of a background. There is little support in the literature for any specific background prevalence of pleural plaques. Fixing the background at 1% probably increased the slope of the exposure-response relationship at low exposures. The Agency probably chose to fix the background prevalence because the small data set does not permit the estimation of the background, slope and plateau simultaneously. **As it is both estimated parameters were statistically insignificant (table 4 of the supplemental material provided by the Agency), thus suggesting that the data are consistent with no impact of exposure to Libby amphibole on pleural plaques in these data. Ironically, however, statistical insignificance of the parameters implies a wider confidence interval and consequently a lower estimate of the BMCL[1]. The greater the uncertainty, the lower the BMCL.**
- Many of the models tried by the Agency fit the data (by the AIC criterion used by the Agency) almost as well as the Michaelis-Menten model, but exhibit rather different exposure-response relationships. The small dataset simply does not allow discrimination among models. Even as measured by the AIC, however, the Michaelis-Menten model is NOT the best fitting model as I discuss in the next bullet.
- Since the objective is to estimate a reference **concentration**, why does the Agency estimate an exposure-response relationship for **cumulative exposure**? An alternative approach would be to use concentration directly in the statistical analysis. Using the raw data provided by the Agency, I estimated the average concentration for each individual by dividing the cumulative exposure by duration of exposure and then fit a logistic regression model to the data with concentration as the measure of exposure. **This model (AIC = 73) fit the data equally well, or better than the Michaelis-Menten model (AIC = 74). The BMC and BMCL (using the BMDS software package distributed by the Agency) for this model were 0.06 and 0.04, respectively. Since the BMCL is obtained directly in terms of the concentration, it can be used as the point of departure (POD) for an RfC calculation without dividing by 60 (tantamount to adding a third uncertainty factor). With two uncertainty factors of 10 each, this procedure leads to an RfC of 0.0004, about 20 times larger than the RfC estimated by the Agency.**
- **Conclusion:** The data are too sparse to discriminate among models. A model based on concentration yields a better fit than the Agency preferred model and yields an RfC which is more than an order of magnitude lower than that estimated by the Agency. No matter which model is chosen, the sub-cohort used by the Agency should not be used for estimation of an RfC.

[1] BMCL is the lower 95% confidence limit on the benchmark concentration.

The evidence that pleural plaques represent an adverse clinical condition is tenuous at best

Over the years there has been considerable controversy regarding whether pleural plaques are simply a marker of asbestos exposure or whether they are associated with pulmonary deficiencies. Since asbestos exposure is associated with both pleural plaques and decreases in pulmonary function, any study that does not adjust adequately for asbestos exposure is likely to show an association between pleural plaques and decreases in pulmonary function. The SAB Panel identified for its and the Agency's consideration three recent papers on the association between pleural plaques and decreases in pulmonary function, two based on studies in the Libby population (Weill et al., 2011; Larson et al., 2012a) and one based on a study in France (Clin et al., 2011). These papers have attempted to adjust for exposure to asbestos, albeit with modest success. I review these studies here and conclude that any causal association between pleural plaques and decreases in pulmonary function is tenuous at best.

- Studies based on the population of Libby The Weill (2011) and Larson (2012a) studies were both based on the same data, which was collected by the ATSDR. Serious limitations of both studies are the facts that the readers of the X-rays were aware of the exposure status of the subject and no normal X-rays were randomly mixed in with the test X-rays, a practice that is common in studies of this type. Furthermore, precise exposure information was not available. Subjects were classified according to how many 'exposure pathways' they were exposed. Weill reports a small but statistically significant decrease in forced vital capacity (FVC) associated with pleural plaques among men but not among women. This analysis did not control for level of exposure, but Weill reports that he obtains similar results with Grace Workers excluded. A serious problem with this study is the inconsistency of the reported results. For example, Weill reports that his study cohort consisted of 4,524 individuals, but the numbers reported in various tables do not add to this total. In table 6, for example, in which the most important results are reported, there appears to be no consistency in the numbers of men and women in each of the smoking categories.
- Larson (2012a) reports results similar to those reported by Weill. However, Larson's study included a significant number of individuals exposed to non-Libby asbestos. He had no quantitative information on this exposure, which could have been substantial. Therefore, his control for level of exposure was even less precise than that of Weill who excluded subjects with other asbestos exposure. Moreover, his pleural plaque analysis includes individuals with parenchymal abnormalities, although he reports controlling for this in the statistical analysis. It would have been better to repeat the analyses with these individuals excluded. Larson notes also that over 70% of the participants in the study were either overweight or obese. With such a high prevalence of overweight individuals, a number of reported pleural plaques could actually have been pleural fat leading to misclassification of exposure. In a second study, Larson et al. (2012b) examined the association between exposure to Libby amphibole and decreases in pulmonary function among Libby miners and reported that although pleural plaques were significantly increased at cumulative exposures of 1 f/cc-y, restrictive lung disease (a hallmark of which is a decrease in FVC) was observed only at very high exposures (166 f/cc-y). The results of this Larson study would appear to be inconsistent with the study on pleural plaques and

pulmonary function. In summary, in view of the deficiencies in study design (readers not blinded, no normal X-rays mixed in), the very small effect estimates, the ability to adjust for level of exposure only crudely, and the very large exposures associated with loss of pulmonary function in the other Larson (2012b) study, I conclude that these studies provide at best weak evidence of a causal association between pleural plaques and decreases in pulmonary function.

- The Clin et al. (2011) French study This was a study based on high resolution CT (HRCT) scanning, not X-ray, and reported a small but statistically significant decrease in FVC associated with pleural plaques. However, exposures to asbestos could only be estimated and the group with pleural plaques included individuals with 'other abnormalities' not further defined.
- **Conclusion**: Taken together these studies provide only weak evidence of a causal association between pleural plaques and decreases in pulmonary function. Moreover, Weill et al. (2011) and Clin et al. (2011) consider the small reported decreases in pulmonary function to be clinically insignificant.

B. Inhalation Unit Risk (IUR) for Cancer (lung cancer and mesothelioma).

There are two fundamental questions regarding the derivation of the IUR by the Agency. First, is the IUR based on analysis of an appropriate dataset? Second, are the models and methods of analyses appropriate? The answer is no to both questions.

The dataset used by the Agency for estimation of the IUR for cancer is inappropriate.

There is an obvious dataset that should be used for the derivation of an IUR. This is the cohort of vermiculite miners at Libby analyzed by Larson et al. (2010). The Agency chose instead to analyze a greatly truncated sub-cohort of this cohort on the grounds that better exposure assessments were available in the sub-cohort. This is a poor choice for the following reasons.

- The full cohort has 111 deaths from lung cancer and 19 deaths from mesothelioma. The sub-cohort that the Agency analyzed has only 32 lung cancer deaths and 7 mesothelioma deaths. Issues of confounding and effect modification cannot be examined in this small sub-cohort. As Dr. Wayne Berman points out in his recently submitted comments to the SAB, there is much to be gained from analyses of the entire data. SAB Panel preliminary comments strongly advised the Agency to consider the entire data set and address exposure uncertainties using Monte Carlo techniques. I strongly endorse this advice.
- The sub-cohort selectively eliminates older individuals in the full cohort and thus the estimates of risk are based on younger individuals. As discussed below, there is evidence of strong effect modification of the lung cancer risk by age in this cohort, with relative risk (RR) reaching a peak and then dramatically declining. This phenomenon is discussed in some detail in my previous reports. Selectively eliminating older individuals in the cohort has the effect of biasing estimates of the lung cancer risk upwards.
- By drastically reducing the size of the dataset and selectively eliminating older individuals, the Agency has lost the statistical power to detect effect modification of lung cancer risk by age. Dr.

Peto has made the equivalent comment that the Agency has ignored the departure from proportionality of hazards in the data.

- The SAB Panel identified for its and the Agency's consideration the recent paper by Lenters et al. (2011), which, at first glance, might appear to support the Agency's contention that exposure measurement error always biases estimates of risk downward. However, the Lenters paper does not support this conclusion for the following reasons. First, the Lenters analysis uses cumulative exposure as the measure of exposure to asbestos. Cumulative exposure is generally a poor measure because both intensity of exposure and duration of exposure are important for both lung cancer and mesothelioma. Second, the Lenters paper ignores the strong effect modification of lung cancer RR by age, with the RR being substantially lower in older individuals. In fact, if the cohorts with better exposure measurement in the Lenters study are younger, then effect modification could explain the higher RRs in these cohorts. Finally, the theorem about non-differential covariate measurement errors leading to risk estimates biased towards the null is often misinterpreted. This statement, although widely repeated by epidemiologists, is incorrect. First, not only must the misclassification be non-differential, it must satisfy other conditions (e.g., Jurek et al., 2005) for the result to hold. Second, the statement applies to the expectation of the risk estimate, not to the value of the estimate from any single study. Thus, it is possible to have non-differential misclassification that satisfies all the required conditions but the result of a single study may actually overestimate the risk. As Jurek et al. (2005) state, "…exposure misclassification can spuriously increase the observed strength of an association even when the misclassification process is non-differential and the bias it produced is towards the null." Similar discussion is provided by Thomas (1995) and Weinberg et al. (1995).
- **Conclusion:** There is not a single good reason for the selection of the sub-cohort for estimation of the IUR. There are many good reasons for using the entire cohort.

The models used by the Agency for analyses of lung cancer and mesothelioma deaths are inappropriate.

- I know of no lung carcinogen for which cumulative exposure is a reliable determinant of risk. For cigarette smoking, exposure to asbestos, and exposure to radiation, lung cancer risk is determined by intensity of exposure, duration of exposure, and time since exposure stopped. Yet, the Agency has made no attempt to investigate and use models that would have allowed the explicit incorporation of these factors for the estimation of lung cancer risk in the Libby cohort. One approach, which I strongly recommend, is to use methods based on ideas of multistage carcinogenesis, such as the two-stage clonal expansion (TSCE) model, an approach endorsed by Dr. Kreibel[2]. The risk of mesothelioma is well-known to depend on intensity of exposure, duration of exposure, and time since exposure stopped. The Agency recognized this fact in 1986 when it adopted the Peto-Nicholson model. Yet, in this risk assessment the Agency has dropped this model in favor of a model that makes no biological sense. Clearly, the decision

[2] I am mystified by Dr. Kreibel's recommendation that the Agency adopt the Richardson rather than the Moolgavkar approach since Richardson got his software code from my group. Furthermore, the code used by Richardson is dated and we now have more efficient ways of fitting the model with time-dependent exposures.

to jettison a large part of the data makes it impossible to fit the Peto-Nicholson model, which provides further justification for using the full cohort.

- The model used for analyses of lung cancer deaths completely ignores the strong effect-modification by age. Particularly because ultimately the IUR is based on a life-table analysis it is important to estimate and use age-specific RRs.
- **Conclusion**: For both lung cancer and mesothelioma, the Agency needs to use the entire Larson cohort, and investigate explicitly intensity and duration of exposure in determining risk. In addition, for lung cancer, the Agency should explore effect modification by age and use age-specific RRs for estimation of IUR.

RECOMMENDATIONS TO THE AGENCY

1. Abandon the attempt to derive an RfC for Libby amphibole. A suitable dataset does not appear to be currently available. If the Agency feels obligated to estimate an RfC, this estimate should be based on the full Rohs dataset and a realistic biological model should be used.
2. The IUR for cancer should be based on the entire Larson cohort, the roles of intensity of exposure and duration should be explored using models based on ideas of multistage carcinogenesis, and, for lung cancer, the strong effect modification by age should be recognized and incorporated in the estimation of IUR.
3. It is incumbent upon the Agency to discuss the carcinogenic potency of Libby amphibole in relation to the potencies of other asbestos fibers. The Agency argument that such a discussion could be highly controversial is not convincing. This is not like the 'amphibole hypothesis', which has been hotly debated. In fact, analyses of the Libby miners' data have provided us with solid estimates of the potencies of Libby amphibole for lung cancer and mesothelioma. The analyses by Hodgson & Darnton (2000) and Berman & Crump (2008a, b) provide us with a range of estimates for other asbestos fibers. It is clear that the potency of Libby amphibole for mesothelioma lies somewhere in the middle of the range and is approximately half the potency assumed by the Agency in its 1986 asbestos risk assessment. For lung cancer, the potency of Libby amphibole is rather low compared to other asbestos fibers, considerably lower than the potency assumed by the Agency for its 1986 risk assessment. As it is, the general perception is that Libby amphibole is much more toxic than other asbestos fibers. It is time for the Agency to dispel this myth, at least for cancer risks.

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