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Attachments

Appendix A: Moolgavkar Slides for presentation at the SAB meeting, Feb 6-8, 2012.

EXECUTIVE SUMMARY

This Executive Summary identifies my principal scientific concerns set forth more fully in the following report regarding the U.S. EPA’s proposed quantitative risk assessment for cancer and non-cancer endpoints for Libby amphibole asbestos.

The EPA draft risk assessment for Libby amphibole (“2011 Draft”) uses data on lung cancer and mesothelioma from a sub-cohort of the full cohort of Libby miners to estimate an Inhalation Unit Risk (IUR) for Libby amphibole. The 2011 Draft also uses data on localized pleural thickening from a sub-cohort of a cohort of workers at a vermiculite processing plant to estimate a Reference Concentration (RfC) for non-cancer adverse impacts on human health. While the current draft represents an enormous amount of effort, it has a number of significant scientific deficiencies.

1. Instead of using the full Libby cohort with follow-up through 2006, the 2011 Draft uses a greatly truncated sub-cohort of workers employed after 1959. This selection reduces the number of lung cancers from 111 in the full cohort to 32 in the sub-cohort and the number of mesotheliomas from 19 in the full cohort to 7 in the sub-cohort. The reduction in cohort size biases estimates of risk because older individuals are selectively eliminated from the sub-cohort.

2. The reduction in cohort size also leads to diminished power to detect departures from proportionality (effect modification by age) in the Cox model analyses of lung cancer and precludes the use of the Peto-Nicholson model for mesothelioma. The use of the Peto-Nicholson model is important because it recognizes the significant role of temporal factors, such as duration of exposure and time since exposure stopped, in determining mesothelioma risk following asbestos exposure.

3. For lung cancer, I recommend that a revised draft report analyze the entire Libby cohort and investigate carefully the effect modification of lung cancer risk by age. Since the lung cancer risk assessment is based on a life-table analysis, it is imperative to estimate age-specific relative risks.
4. For mesothelioma, I recommend that a revised draft report use the full cohort with 19 mesotheliomas and perform a full likelihood based time-to-tumor analysis using the Peto-Nicholson model as described in the body of my report, instead of the inadequately-justified Poisson regression that is used in this draft.

5. For the non-cancer risk assessment the 2011 Draft uses a small sub-cohort of workers employed at a vermiculite processing plant at Marysville, Ohio. While the full cohort investigated in Rohs et al. (2008) consists of 280 individuals with 80 cases of localized pleural thickening, the sub-cohort chosen in the 2011 Draft consists of 119 individuals with 12 cases of localized pleural thickening. Thus, the 2011 Draft discards without justification much of the available data.

6. The 2011 Draft does not provide adequate evidence to support the selection of localized pleural thickening as an adverse health impact for asbestos exposure. In previous Agency documents, no attempts have been made to derive an RfC for non-cancer adverse impacts on human health because the choice of an appropriate end-point was not clear. Therefore, the 2011 Draft sets a new precedent and it is imperative that a revised draft make clear why localized pleural thickening should be considered an adverse health impact rather than just a marker of asbestos exposure.

7. I recommend that a revised draft reevaluate the choice of localized pleural thickening as an adverse health impact and analyze the entire Rohs cohort data using appropriate statistical methods as described in the body of this report.

8. I recommend that a revised draft discuss the carcinogenic potency of Libby amphibole in context. Our understanding of the differential carcinogenic potencies of the different types of asbestos fibers has advanced considerably over the last decade. It is incumbent upon a revised draft to describe the contemporary literature on this topic and discuss the carcinogenic potency of Libby amphibole in relation to that of other asbestos fibers.
Background and Qualifications

I am a physician with a Ph.D. in Mathematics and post-doctoral training in Pharmacology, Biophysics, Epidemiology and Biostatistics. In April 2007, I became a Corporate Vice President and the Director of the Center for Epidemiology, Biostatistics and Computational Biology at Exponent, Inc., an international scientific consulting company. I retired from my position as a Full Member of the Fred Hutchinson Cancer Research Center in August 2008. I continue to be an Affiliate Investigator at the Center and Professor of Epidemiology and Adjunct Professor of Applied Mathematics at the University of Washington in Seattle. I am a cancer epidemiologist and research scientist. My main research interest is cancer epidemiology. I was instrumental in developing a biologically-based mathematical model, the two-stage clonal expansion (TSCE) model, often called the Moolgavkar-Venzon-Knudson (MVK) model, for the quantitative estimation and prediction of cancer risk. This model is recognized and used by cancer researchers worldwide.

I have served on the faculties of the Johns Hopkins University, Indiana University, the Fox Chase Cancer Center and the University of Pennsylvania. I have been a visiting scientist at the Radiation Effects Research Foundation in Hiroshima, the International Agency for Research on Cancer (IARC) in Lyon, and the German Cancer Research Center in Heidelberg.

I have served on numerous review panels and as a consultant to the National Cancer Institute (NCI); the Environmental Protection Agency (EPA); the California Air Resources Board; Health and Welfare, Canada; IARC; the CIIT Centers for Health Research; and the Health Effects Institute. I am the author or co-author of more than 160 papers in the areas of Epidemiology, Biostatistics, and Quantitative Risk Assessment, and have edited three books in these areas. Among these is a monograph, “Quantitative Estimation and Prediction of Human Cancer Risk,” published by IARC, the agency that conducts cancer research under the auspices of the World Health Organization. I have served on the editorial board of Genetic Epidemiology and Inhalation Toxicology and am currently one of the editors of Risk Analysis – An International Journal. I am an elected member of the American
Epidemiological Society. I was given the Founders’ Award by the CIIT Centers for Health Research in 1990 and the Distinguished Achievement Award by the Society for Risk Analysis in 2001. I am a Fellow of the Society for Risk Analysis, the pre-eminent international scientific society for risk assessment.

Among my publications are several papers on carcinogenesis following exposure to fibers. I was an Invited Expert at a workshop, “Mechanisms of Fiber Carcinogenesis,” held at IARC in Lyon, France, in early November, 2005. I was the lead panelist for a symposium on fiber carcinogenesis held in Brussels in 2005.

**Purpose of this Report**

I have been retained by W.R. Grace to review and comment on the scientific issues in the draft risk assessment of Libby amphibole asbestos, which is a mixture of tremolite, winchite and richterite. The purpose of my review and comment is to assist the SAB and the EPA in ensuring that the final assessment of Libby amphibole is based on the best available science. I am intimately familiar with the Libby cohort data. I have analyzed these data with follow-up through 2002 (Moolgavkar et al., 2010) and many of my comments reflect the results of these analyses. I also had access to the Rohs database on a subset of which the 2011 Draft bases its estimate of the RfC for Libby amphibole. I have analyzed these data as well, but have not published the results.

I had previously made oral comments on the 2011 Draft at a “listening session” organized by the EPA in October, 2011. At that time, I also provided written comments to address more fully the technical details that could not be covered in a short verbal presentation. I attach my previous written comments to this document as appendix B. The slides of my October presentation at the listening session are appended to those written comments.

In these comments to the SAB, I summarize the main scientific issues raised by the 2011 Draft risk assessment. I do not discuss the specific toxicity values derived in the 2011 Draft because such numbers can be meaningfully discussed only after the scientific issues have been properly addressed.
The main goals of the 2011 Draft risk assessment are to develop an inhalation unit risk (IUR) for cancer (lung cancer and mesothelioma) and a reference concentration (RfC) for non-cancer endpoints associated with exposure to Libby amphibole.

**Cancer Risk Assessment**

The current IRIS Inhalation Unit Risk (IUR) for asbestos-associated cancer is based on combining separate slope factors for lung cancer and mesothelioma using a life-table analysis. The general framework for developing an IUR in the 2011 Draft is similar to that used by the Agency for the development of an asbestos cancer slope factor for the IRIS database in 1993, which was based on the risks estimated in an earlier Agency report by Nicholson (1986). The models and methods used in the 2011 Draft to derive individual slope factors for lung cancer and mesothelioma are different, however.

In the 2011 Draft, the EPA develops an IUR for cancer in the following three steps. The procedure is similar, but not identical, to the procedure used in the 1993 IRIS document.

1. **Estimate potency for lung cancer** ($K_L$) from the occupational cohort data using a relative risk (RR) model. The RR is assumed to be a function of cumulative exposure. Whereas the 1986 Nicholson analysis was based on regressions through standardized mortality ratios (SMRs), the current 2011 Draft document uses the Cox proportional hazards model applied to a (truncated) Libby worker cohort.

2. **Estimate potency for mesothelioma** from the occupational cohort data using an absolute risk model. The 1986 analysis was based on a model originally developed by Peto et al. (1982) and then adopted by Nicholson, and which I call the Peto-Nicholson model. In this model, which is based on ideas of multistage carcinogenesis, the hazard function for mesothelioma is a function of exposure concentration, duration of exposure, and time since exposure stopped. The model is
linear in exposure concentration, but non-linear in the time variables. Therefore, this model recognizes explicitly the role of pattern of exposure in determining risk. In this model, risk cannot be expressed as a function of cumulative exposure. The 2011 Draft bases its estimate of potency instead on a Poisson regression analysis of mesothelioma deaths in the same truncated data set used for the lung cancer potency estimate, using cumulative exposure as the measure of exposure. In a giant step backwards, the 2011 Draft does not recognize the important role of the time variables in determining risk.

3. In the final step, risk estimates for mesothelioma and lung cancer are combined using a life-table analysis for lung cancer to arrive at the IUR for cancer.

For its current analyses of lung cancer and mesothelioma, the 2011 Draft uses the sub-cohort of workers employed after 1959 and followed up through 2006. The Draft give two reasons for the choice of this dataset rather than the full Libby cohort. First, it argues that exposure is better characterized in this sub-cohort and second, proportionality of hazards for lung cancer holds in this sub-cohort, and therefore the issue of effect modification by age does not have to be addressed. There is some merit to the first reason, but the second reason does not stand up to scrutiny. In fact, as explained below, effect modification by age is an important feature of many epidemiologic cohort data sets that span several decades and should, in fact, be explicitly addressed in any risk assessments, particularly ones that rely on life table analyses as does the Agency assessment for lung cancer.

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1 The 2011 Draft repeats the old canard (page 5-78 of the report) about non-differential covariate measurement errors leading to risk estimates biased towards the null. 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 produces is towards the null.” Similar discussion is provided by Thomas (1995) and Weinberg et al. (1995).
**Lung Cancer**

The Libby workers’ cohort is the logical choice of dataset on which to base risk estimates for lung cancer and mesothelioma. Over the years there have been numerous publications based on analyses of this cohort (Amandus et al., 1987; McDonald et al., 1986, 2002, 2004; Sullivan, 2007; Moolgavkar et al., 2010; Larson et al., 2010). As the most contemporaneous studies with the longest follow-up, the studies by Sullivan, Moolgavkar, and Larson are the most relevant to this risk assessment. Both Moolgavkar et al. (2010) and Larson et al. (2010) used the Cox proportional hazards model, as does the 2011 Draft, and arrived at similar estimates of RR (~1.1 for 100f/cc-y cumulative exposure). I note here that this RR is quite a bit smaller than that estimated in other asbestos occupational cohorts.

The RR associated with exposure to asbestos in the South Carolina Textile Workers’ cohort, for example, is substantially larger² (Hein et al., 2007; Richardson, 2009).

The estimation of a single RR for all ages should be interpreted as an averaging of risks over all ages and is appropriate only as a summary measure of risk in the entire cohort. However, a life-table analysis as conducted by the Agency in the 2011 Draft and previous risk assessments, involves the use of age-specific lung cancer mortality rates from a standard population multiplied by the RR to estimate the number of excess lung cancer deaths as a consequence of exposure to asbestos. Therefore, when a life-table analysis is performed, it becomes important to investigate RR as a function of age, i.e., to investigate effect modification by age. The 2011 Draft had a great opportunity here to investigate effect modification by age but appears to have gone to great lengths not to do so. In fact, the 2011 Draft chose a sub-cohort for analyses in which effect-modification by age had been eliminated. As a result, the Draft fails to evaluate the critical importance of effect modification thus biasing the IUR for lung cancer.

There are compelling reasons to use the entire Libby cohort rather than the sub-cohort that the Agency chooses to use.

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² Hein et al. (2007) report an RR of about 3 associated with 100 f/cc-yr cumulative exposure as compared to an RR of about 1.11 in Libby for the same cumulative exposure.
1. By discarding more than two-thirds of the lung cancers (111 in the full cohort followed up until 2006 (Larson et al., 2010) as opposed to 32 in the sub-cohort used by the Agency), the power to detect effect-modification by age is greatly diminished. Effect modification by age is an important feature of many epidemiologic data sets (Moolgavkar, 2012), as discussed in more detail in my comments at the October listening session (see Appendix B of this report) and age-specific relative risks should be applied in a life-table analysis. In particular, there is strong evidence of effect modification of lung cancer risk by age in the Libby cohort as can be seen in figure 1 below. The 2011 Draft recognizes that effect modification by age is important in the entire cohort (page 5-76), but then effectively ignores it by choosing a sub-cohort in which it is no longer statistically significant. The single estimate of RR used in the 2011 Draft under-estimates risk at the younger ages and over-estimates it at the older ages (see figure 1 below).

2. The sub-cohort consists of workers who entered the work force after 1959. With follow-up until 2006, there are probably few sub-cohort members over the age of 65 by the end of the study, the age at which the incidence of lung cancer begins to increase rapidly. Therefore, the Agency potency estimates for lung cancer are based primarily on individuals below the age of 65. In particular, with the life-table analysis going out to age 85, it is important that lung cancer at the older ages make some contribution to the estimate of RR. As stated above age-specific RRs should be used in the life-table analyses. If the Agency insists on using a single estimate of RR, it should clearly be estimated from a dataset that spans the entire range of ages. At the very least, a comprehensive uncertainty analysis should be undertaken to investigate how the choice of sub-cohort and the assumption of no effect modification affects the IUR for lung cancer.
Figure 1. Analysis of lung cancer in the full Libby cohort followed up through 2002 (Sullivan, 2007; Moolgavkar et al., 2010) using natural splines to model RR as a function of age. RR on the y-axis is associated with a cumulative exposure of 1 f/cc-yr. Note the strong effect modification by age, which can also be seen in figure 2 below and in slides 8 and 9 in my presentation at the listening session. These slides are appended to my October written comments (Appendix B). A test for effect modification by age is statistically significant. More details are in my October report (Appendix B).

Figure 2 below is taken from a publication by Richardson (2009) analyzing the lung cancer risk associated with asbestos exposure in that cohort. The figure shows the strong effect modification by age in this cohort. Richardson uses the biologically-based two-stage clonal expansion (TSCE) model also known as the Moolgavkar-Venzon-Knudson (MVK) model and shows not only strong effect modification by age, but also that cumulative exposure to asbestos is a poor measure of exposure...
for lung cancer risk assessment. In fact, as is the case of mesothelioma, temporal pattern of exposure is important in determining risk. We have conducted similar analyses for lung cancer in the Libby cohort using the TSCE model and can confirm Richardson’s findings in the South Carolina cohort, although the magnitude of the lung cancer risk associated with exposure to Libby amphibole asbestos is much smaller.

Thus, there is strong evidence that 1) effect modification by age is an important feature of asbestos-associated lung cancer risk, and 2) lung cancer risk after asbestos exposure is a function of the entire exposure history, not just cumulative exposure. In my oral and written comments for the October listening session, I provided other examples showing that effect modification by age, i.e. non-proportionality of hazards is ubiquitous in epidemiologic data sets that span a wide range of ages. Please see the Appendix B for details.

Recommendations for lung cancer risk assessment
1. Utilize the entire Libby data set of Larson et al. (2010) for risk assessment using the proportional hazards model.

2. Use flexible statistical methods, such as spline smoothers, to explore carefully effect modification by age in the data.

3. Explore the role of patterns of exposure in determining risk by using biologically-based models, such as the multistage model and the TSCE (MVK) model.

4. Explore approaches other than the life-table approach for estimating IUR. For example, robust estimation of excess risk may be directly possible from analyses using approaches based on ideas of multistage carcinogenesis, such as the TSCE model.

5. If a life-table approach is necessary, use age-dependent RRs to account for effect modification by age.

Mesothelioma

Analyses of mesothelioma in the Agency report is based on the same sub-cohort as the lung cancer analyses. Whereas there are 19 mesotheliomas in the full cohort, there are only 7 in the sub-cohort used by the Agency. The risk estimate obtained by analysis of these 7 cases is adjusted upward to address under-ascertainment of mesothelioma cases using a method proposed by Kopylev (2011). As discussed below, this adjustment is poorly justified and ill-advised.

It is well known from the work of Peto and Nicholson that temporal factors, such as duration of asbestos exposure and time since exposure stopped, play an important role in determining mesothelioma risk from exposure to asbestos. The 2011 Draft has chosen to ignore this fundamental fact in abandoning the Peto-Nicholson model, which was used in its 1986 risk assessment and which has been shown to describe the data well in multiple occupational cohorts (Berman & Crump, 2008), in favor of a poorly-justified Poisson regression model.

The Peto-Nicholson hazard function for mesothelioma mortality is of the form \( h(t) = K_M \times g(t) \), where \( g(t) \) is a power of time since exposure started and depends also on fiber concentration, and \( K_M \) is a constant that depends on fiber type. I
recommend that a revised draft use a generalization (Berman & Crump, 2008) of the original formula to accommodate time-varying exposure concentrations:

\[ g(t) = 3 \int_{0}^{t-10} E(u)(t-u-10)^2 du, \]

where \( g(t) \) is the mortality rate (per year) at year \( t \) after start of exposure and \( E(u) \) at time \( u \) is the concentration of asbestos fiber expressed as fibers/ml.

The 2011 Draft states that the Peto-Nicholson model was tried, but did not describe the data as well as the Poisson model that it ultimately used. It is not at all clear, however, that the Peto-Nicholson model was tested appropriately. The version of the model used by Berman and Crump (2008), which accommodates time-varying exposure concentrations, should have been used and a full likelihood time-to-tumor analyses performed to estimate not only \( K_M \), but also the exponent of the duration of exposure. With only 7 cases, such an analysis is probably not feasible. In my opinion, the full Larson data set should be analyzed using the Peto-Nicholson model. With the Poisson regression adopted in the 2011 Draft, all information about time-to-tumor is lost. It is also not clear from the description provided in the report how the Poisson regression was performed. For example, the report should state clearly what contribution each individual in the cohort made to the expectation of the Poisson model. Even if Poisson regression is used for these analyses, it is not clear why it is necessary to use Bayesian MCMC methods. Likelihood-based analyses using generalized linear models appear to be straightforward. The numerous analyses performed and reported on this small dataset are unjustified. How can one discriminate among the many models used with only 7 cases of mesothelioma in the dataset? Small differences in the deviance information criterion (DIC), or whatever criterion is used to measure relative fits, are hardly informative with this small dataset.

Finally, the Agency used a method proposed by Kopylev (2011) to adjust risk upward by a factor 1.39 to compensate for under-ascertainment of mesothelioma deaths in the sub-cohort. I believe this adjustment is ill-advised for the following reasons. First, the under-ascertainment of total asbestos exposure because of
exposure to asbestos from other sources should be considered before any adjustment is made for under-ascertainment of mesothelioma (or any other) deaths. Many of the workers at the Libby mines worked there only for short periods of time. A substantial number in the full Libby cohort was employed there for less than one year. It is clear from the data in Peipins et al. (2003) that residents of Libby were employed in other jobs that could have exposed them to asbestos. It is therefore highly likely that exposure to asbestos is under-estimated in the cohort, particularly among short-term workers. This is not a problem peculiar to Libby. It is ubiquitous with occupational cohort studies and the only way to get around it is to perform a case-control study nested within the cohort. Second, I do not believe that the data on under-ascertainment used for estimating the adjustment factor is reliable because standards for the reporting of mesothelioma as a cause death varied from place to place. Third, the adjustment factor is based on a Poisson regression analysis and it is not clear that the same Poisson models were used in the report and in Kopylev et al. (2011). The adjustment factor using a proper likelihood based analysis using the Peto-Nicholson model would likely be different. Fourth, the adjustment factor applied in the Agency report is the one derived by Kopylev et al. (2011) based on the full dataset. It is not clear that the same adjustment factor would be obtained if the method were applied directly to the sub-cohort. Finally, with the amount of scrutiny received by the Libby population it is hardly likely that under-ascertainment is a problem. A revised draft should not apply any adjustment factor for under-ascertainment.

Recommendations for mesothelioma risk assessment

1. Use the entire Libby data (follow-up through 2006) used by Larson et al. (2010) with 19 cases of mesothelioma.
2. Use a likelihood-based time-to-tumor analysis with the Peto-Nicholson model and attempt to estimate both $K_M$ and the exponent in the hazard function so that the dependence of risk on pattern of exposure is explicitly recognized. Moolgavkar et al. (2010) estimated $K_M = 0.5$, half the estimate used in the 1986 EPA asbestos risk assessment. Moolgavkar et al. (2010) could not estimate the exponent because they had information only on the
number (15) of mesothelioma deaths in the cohort followed through 2002, but not on which specific individuals died of the disease. With this information, only \( K_M \) can be estimated. Another option would be to use the TSCE model. Both the Peto-Nicholson and the TSCE model recognize and explicitly incorporate pattern of exposure in the hazard function.

3. Abandon the attempt to adjust for under-ascertainment of mesothelioma deaths for reasons set forth above.

4. Abandon the attempt to estimate half-life of Libby asbestos in the pleura. The simple formulation used has no biological interpretation as discussed in my report for the October listening session (Appendix B).

**Non-Cancer Risk Assessment**

The previous Agency IRIS document for asbestos provides no estimate of an RfC for non-cancer endpoints because of the absence of suitable data for. Thus, the 2011 Draft sets a new precedent in estimating an RfC for non-cancer endpoints. It is therefore of critical importance that the health endpoint on which the RfC is based be carefully evaluated, the appropriate datasets for analyses be identified, and the proper statistical methods be used. The 2011 Draft bases its risk assessment for non-cancer endpoints on a cohort of workers involved in the processing of vermiculite at a plant in Marysville, Ohio, and analyzed by Lockey et al. (1984) and Rohs et al. (2008). The Agency risk assessment is based on a sub-cohort of the cohort analyzed by Rohs et al. (2008). The end-point of interest for the analyses is localized pleural thickening. The Rohs et al. cohort consists of 280 individuals with 80 cases of pleural thickening. The sub-cohort chosen by the Agency includes 119 participants with 12 cases of pleural thickening. Therefore, as is the case for lung cancer and mesothelioma, the 2011 Draft discards much of the data for the analyses in this report.

A fundamental question that is not adequately addressed in the 2011 Draft is whether localized pleural thickening is an adverse health impact or simply a marker of asbestos exposure. While the 2011 Draft cites literature to suggest that localized pleural thickening is associated with various clinical endpoints, such as chest pain, it provides no evidence that these associations are causal. For
example, urinary cotinine, because it is a marker of cigarette smoking, is undoubtedly associated with lung cancer but it clearly does not cause lung cancer.

The 2011 Draft says, “...more accurate exposure data are considered to be those from 1972 and later, as these data were based on analytical measurements.” Based on these considerations, the Agency chose from the Rohs cohort the sub-cohort consisting of workers who began work in 1972 or later. The radiographic examination of these workers was conducted over the period 2002-2005. However, in their paper, Rohs et al. identified 1973, not 1971, as the year after which “…more comprehensive environmental exposures were available…” The sub-cohort of workers hired after 1973 consists of 94 individuals with 10 cases of pleural abnormalities. I had access to the original Rohs database and it includes an identifier for workers hired after 1973 but not for those hired after 1971. The report does not explain this discrepancy.

I have analyzed the full Rohs dataset using logistic regression and spline smoothers to explore exposure-response relationships. The results are shown in figure 3 below. This figure shows that most of the exposure data (the thickness of the rug at the bottom of the figure reflects the number of data points) lies in the range of 0-3 f/cc-yr. In this range of exposure, the flexible exposure-response model does not support a monotonic increasing exposure-response relationship. While the exposure-response relationship is consistent with linearity above 3 f/cc-yr, it is statistically insignificant in this range, possibly because of the paucity of data. There also is evidence of confounding by age (see figure 3).

One of the important criteria enunciated by the Agency for study selection for non-cancer risk assessment is that the exposure-response relationship be robust to adjustment for potential confounders. Thus, on page 5-11, the report states, “Amandus et al. (1987b) report that although cumulative exposure and age are both significant predictors of small opacities, cumulative exposure was not significantly related to pleural abnormalities when age is included in the model, thus limiting the usefulness of these data for RfC derivation based on pleural

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3 As the 2011 Draft describes in appendix F, the exposure estimates in the original Rohs database have been revised for the current risk assessment. I do not have access to the revised estimates of exposure.
abnormalities.” In listing the advantages of the Rohs sub-cohort the Agency used, the report on page 5-14 (number 6) clearly states that it considers the absence of any evidence of confounding in this dataset a distinct advantage. I do not have access to the exact data used by the Agency, but I have analyzed full Rohs dataset as described above and there is strong evidence of confounding by age. By its own criteria, the Agency should not be using this dataset for derivation of an RfC.

Finally, the 2011 Draft uses various lags in the analyses of the sub-cohort. The use of lags for the analyses of pleural abnormalities makes no sense. Lags can be used in analyses of hazard or incidence functions when the diagnosis of an end-point, such as cancer, is made at a well-defined point in time. It is unscientific to use lags in the analyses of prevalent conditions, which could have occurred many years before the condition was noted. In the Rohs database all radiography was performed between 2002 and 2005, when pleural abnormalities were noted. These could have occurred many years before the radiography was done. What is the interpretation of a lag in this situation?
Figure 3 Exposure-response for localized pleural thickening as a function of cumulative exposure in the Rohs dataset.

Recommendations for Non-Cancer Risk Assessment

1. If localized pleural thickening is retained as the endpoint of interest, the full dataset should be used.
2. However, the Agency should acknowledge that the Rohs data does not satisfy its own criteria for use as a dataset for derivation of an RfC.
3. Although I am not a pulmonologist, I am concerned about calling localized pleural thickening an adverse event of clinical significance. The 2011 Draft does not provide adequate evidence to support this position.
4. Fat in the pleura is often mistaken for localized thickening on plain X-ray. Therefore, there may be considerable misclassification of the end-point in the data.
5. The Agency should recognize, as it did in the 1986 risk assessment, that there may not be an appropriate dataset for the derivation of an RfC for non-cancer end-points.

Other Issues

1. There is little doubt that mortality from lung cancer, mesothelioma and non-malignant respiratory disease (NMRD) was increased among workers employed at the mines in Libby. The real issue here is whether environmental exposure to Libby amphibole asbestos increased the risk of mortality from asbestos-associated diseases in the population of Libby. To address this question, the Agency for Toxic Substances and Disease Registry (ATSDR) conducted a mortality study in Libby in 2000. The Agency report should discuss this study in more detail.

The ATSDR undertook a study of mortality from specific causes in the Libby area over the 20-year period 1978-1998. Numbers of deaths from specific causes were compared with numbers that would be expected under national and Montana death rates. Standard epidemiological and statistical techniques were used to compute SMRs and their confidence intervals.
Given the asbestos exposure in this population the main cancers of interest were lung cancer and mesothelioma. Mortality over the period of this study would be expected to reflect the impact of environmental exposure to high levels of Libby amphibole.

The ATSDR reports a small non-significant increase in lung cancer deaths within Libby City and the extended Libby area using Montana death rates as the standard. With US death rates as the standard, no increase in lung cancer deaths is reported. Thus, the number of lung cancer deaths over the period of the study offers no evidence that environmental exposures contributed to the lung cancer mortality over the period 1978-1998.

The ATSDR reports four cases of mesothelioma over the period of the study. Since the background rate of mesothelioma is close to zero, this number points to a significant elevation of risk in the Libby area. However, four cases of mesothelioma are identified in the McDonald (2002, 2004) occupational cohort, and it seems highly likely that these are the cases identified by ATSDR. Thus, the cases in the ATSDR study can, in all likelihood, be explained on the basis of occupational exposure. As in the case of lung cancer, this study offers no evidence that environmental exposure contributed to mesothelioma deaths in the Libby area.

Among the causes of death other than cancer, of most interest are the non-malignant respiratory diseases (NMRD), particularly asbestosis. Eleven deaths from pneumoconioses are reported over the period of the study. All of these are labeled asbestosis in the ATSDR report, although it is not clear how this diagnosis was verified. In any case, the SMR is reported to range between 36 and 47 (depending on the geographic area of analysis) using the Montana rates as the standard, and between 60 and 75 using the US rates as the standard. It is clear that deaths from asbestosis were significantly elevated. Of note, however, is the fact that 10 of the 11 deaths were among males suggesting strongly that occupational exposures were involved in these deaths. There is little evidence that environmental
exposures were involved in the deaths from asbestosis, which is known to be associated with high levels of exposure to asbestos.

In conclusion, there is little evidence that environmental exposure to asbestos contributed to the deaths from respiratory cancer, mesothelioma and asbestosis in the Libby area over the period 1978-1998.

2. A serious deficiency of the 2011 Draft is that it fails to provide context for the carcinogenicity of Libby amphibole. In the last decade, our understanding of the differential carcinogenic potencies of the different types of asbestos fibers has advanced considerably (Hodgson & Darnton, 2000; Berman & Crump, 2008). It is important that the Agency put the carcinogenicity of Libby amphibole in perspective by discussing where in the range of potencies of the various asbestos fibers, the potency of Libby amphibole lies. The paper by Hodgson & Darnton (2000) is not even referenced in this Agency draft and the paper by Berman & Crump (2008) is only mentioned in passing.

References


Thomas DC. Re: "When will nondifferential misclassification of an exposure preserve the direction of a trend?". Am J Epidemiol 1995;142(7):782-4.


Docket I.D.
EPA-HQ-ORD-2011-0425
Review of EPA document
EPA/635/R-11/002A “Draft
Toxicological Review of Libby
Amphibole Asbestos”

Docket I.D.
EPA-HQ-ORD-2011-0425

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Executive Summary

Exponent, Inc. has been retained by W.R. Grace & Co. to review the draft risk assessment document for Libby asbestos.

This review focuses on a critical evaluation of the epidemiologic studies and statistical methods used by the Agency for examination of exposure-response relationships and derivation of inhalation unit risks (IUR) for cancer and reference concentrations (RfC) for non-cancer endpoints. Despite the considerable investment in time and effort by the Agency, the report is deficient in numerous respects.

1. The dataset chosen for the cancer risk assessment is a small sub-cohort of the full cohort of Libby miners. This sub-cohort discards the vast majority of lung cancers and mesotheliomas in the Libby cohort, particularly in individuals over the age of 65. Thus, Agency risk assessments are based largely on younger individuals in the cohort and ignore the ages at which cancer is most common.

2. The Agency uses inappropriate statistical methods for analyses of the data on lung cancer and mesothelioma. In particular the importance of duration of exposure in determining risk is ignored. In the lung cancer analysis effect modification by age, which is strongly evident in the Libby cohort, is not addressed.

3. The dataset used for estimation of RfC for the non-cancer end-point (pleural thickening) is a small subset of a cohort of workers at a vermiculite processing plant in Marysville, Ohio. There is no evidence of a monotonic increasing exposure-response relationship for pleural thickening in either the full cohort or the sub-cohort chosen for analysis by the Agency.

4. There are serious concerns regarding the statistical methods used for the analyses of pleural thickening in the Marysville cohort.

The Agency needs to undertake substantive new analyses and substantial revisions of the draft report to address the serious scientific issues raised in this review.
Exponent, Inc. has been retained by W. R. Grace & Co. to review and comment on the EPA draft risk assessment for Libby asbestos. This review will focus on the scientific aspects of the risk assessment conducted by the EPA without commenting on the specific risk numbers derived by the Agency. Specific numerical estimates of risk can be discussed meaningfully only after the major scientific issues raised in this review have been addressed. The EPA draft document addresses the risks associated with both the cancer and non-cancer health end-points resulting from inhalation exposure to Libby asbestos. Despite the considerable investment of time and effort in the current draft, there are substantial and serious deficiencies in the choice of data sets for the risk assessments and also in the choice of statistical methods for the analyses of these data sets. My concerns regarding these issues were conveyed to the Agency during the listening session held at EPA headquarters on October 6, 2011. This report provides details that could not be covered in a 30-minute presentation (Appendix A).
General Comments

1. The Agency does not provide adequate and convincing justification for its choice of data sets for the risk assessment. The cancer risk assessment is based on a small subset of the full cohort of miners at the W. R. Grace Libby mine. The choice of this data set greatly reduces the number of lung cancers and mesotheliomas available in the original cohort. The number of lung cancers available for analyses is reduced from 111 to 32. The number of mesotheliomas available for analysis is reduced from 19 to 7. Thus, the Agency retains less than one third of the available lung cancers and about one third of the available mesotheliomas for its analysis. The justification provided for this drastic reduction in the size of the original dataset is unacceptable and there are compelling reasons to base risk assessments on the original dataset. The non-cancer risk assessment is based on a cohort of workers at a Marysville, Ohio plant in which Libby vermiculite was processed. The endpoint of interest was pleural abnormalities (pleural thickening) on chest radiographs. The original data set considered by Rohs et al. (2008) consisted of 280 workers with 80 cases of abnormalities on chest radiography. The Agency assessment was based on 119 workers with 12 cases of abnormalities. Thus, the Agency discards 85% of cases for this assessment. The reasons given for this drastic reduction in the cohort size are not tenable.

2. The methods of statistical analyses are far from optimal. While the proportional hazards model used by the Agency for analysis of lung cancer in the Libby miners’ cohort is standard, EPA should have taken this opportunity to explore the impact of age on the relative risk of lung cancer, particularly in view of the fact that the Agency uses a life-table approach to derive its final cancer potency factor. I give more details below in the main body of this report. Furthermore, the model used for the mesothelioma analyses is inappropriate. The Agency rejects without adequate justification the standard model for mesothelioma based on the work of Peto and Nicholson and used in its 1986 risk assessment. Similarly, the model used for analysis of the truncated Rohs et al. (2008) data set is not adequately justified and confounding by factors that influence the appearance of pleural abnormalities was not adequately considered.

3. The report is unevenly written with critical information missing from some of the chapters. While the coverage of the literature on Libby asbestos is comprehensive, it is often
uncritically reviewed. Obvious errors in the cited literature are repeated in the report. The coverage of the general asbestos literature is spotty and many of the cited references are old and dated. In general, sufficient attention has not been paid to critical evaluation of papers. Agency documents are often used as references and it is, therefore, important that papers be critically evaluated if they are cited in the report.
Cancer Risk Assessment

Before describing the approach used by the Agency for cancer risk assessment, I discuss briefly some fundamental issues that should have been addressed by the Agency in the report. These have to do with temporal aspects of exposure and risk. Particularly important is the issue of the appropriate measure of exposure. It is often assumed that risk is determined by cumulative exposure and that pattern of exposure is relatively unimportant. This is what toxicologists call Haber’s law and, in all instances, when this law has been critically tested, it has been shown to be false. Both intensity of exposure and pattern of exposure are important in determining risk and, particularly with tumor promoters, pattern of exposure is a more important determinant of risk than intensity of exposure (e.g., Meza et al., 2008; Hazelton et al., 2005; Richardson, 2008, 2009; Peto et al., 2002). It is clear also both on theoretical grounds (e.g., Heidenreich et al., 1997; Moolgavkar, 2004; Moolgavkar and Luebeck, 2003) and on the basis of epidemiologic data (e.g., Preston et al., 1994; Richardson, 2008, 2009; Meza et al., 2008; Hazelton et al., 2005) that the risk of cancer in an exposed population declines after exposure stops. A model that uses cumulative exposure as the measure of exposure does not recognize this fundamental fact. With the relatively large cohort of Libby miners, the Agency had a real opportunity to investigate these fundamental temporal aspects of exposure and risk, but failed to do so. Particularly distressing is the Agency decision to abandon the model used for mesothelioma in the 1993 IUR estimate in favor of a Poisson regression based on cumulative exposure as the measure of exposure. The model used for mesothelioma in the 1993 IUR estimate was developed by Peto et al. (1982) and recognizes and explicitly addresses these temporal aspects of exposure and risk.

The IRIS Inhalation Unit Risk (IUR) for asbestos-associated cancer is based on combining separate slope factors for lung cancer and mesothelioma using a life-table analysis. I begin with a review of the general framework used by the Agency for the development of an asbestos cancer slope factor for the IRIS database in 1993, which was based on the risks estimated in an earlier Agency report by Nicholson (1986). This general framework has been used in the current document to develop an IUR for Libby asbestos. The details of the models and methods used to derive individual slope factors for lung cancer and mesothelioma are different, however.
In both the original 1993 IRIS file and the current document, the EPA develops an IUR for cancer in the following three steps.

1. Estimate potency for lung cancer ($K_L$) from the occupational cohort data using a relative risk (RR) model. The RR is assumed to be a function of cumulative exposure, i.e., Haber’s law is assumed to hold. Whereas the 1986 analysis was based on regressions through standardized mortality ratios (SMRs), the current Agency document uses the Cox proportional hazards model applied to a (truncated) Libby worker cohort.

2. Estimate potency for mesothelioma from the occupational cohort data using an absolute risk model. The 1986 analysis was based on a model originally developed by Petö et al. (1982) and then adopted by Nicholson, and which I call the Petö-Nicholson model. In this model, which is based loosely on ideas of multistage carcinogenesis, the hazard function for mesothelioma is a function of exposure concentration, duration of exposure, and time since exposure stopped. The model is linear in exposure concentration, but non-linear in the time variables. Therefore, this model recognizes explicitly the role of pattern of exposure in determining risk. In this model, risk cannot be expressed as a function of cumulative exposure. In its report the Agency bases its estimate of potency on a Poisson regression analysis of the same truncated data set used for the lung cancer potency estimate, using cumulative exposure as the measure of exposure. In a giant step backwards, the Agency does not recognize the important role of the time variables in determining risk. In both the 1986 and the current analyses, the background rate of mesothelioma is assumed to be 0.

3. In the final step, risk estimates for mesothelioma and lung cancer are combined in a life-table analysis to arrive at the IUR for cancer.

For its current analyses of lung cancer and mesothelioma, the Agency uses the sub-cohort of workers employed after 1959 and followed up through 2006. They give two reasons for the choice of this dataset rather than the full Libby cohort. First, they argue that exposure is better characterized\(^1\) in this sub-cohort and second, proportionality of hazards holds in this sub-cohort.

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\(^1\) The Agency repeats the old canard (page 5-78 of the report) about non-differential covariate measurement errors leading to risk estimates biased towards the null. 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,
and therefore issues of confounding and effect modification do not have to be addressed. There is some merit to the first reason, but the second reason does not stand up to scrutiny. In fact, I will argue below that effect modification by age is an important feature of many epidemiologic cohort data sets spanning several decades and should, in fact, be explicitly addressed in any risk assessments, particularly ones that rely on life table analyses as do the Agency assessments for lung cancer and mesothelioma.

There are compelling reasons to use the entire Libby cohort rather than the sub-cohort that the Agency chooses to use.

1. By discarding more than two-thirds of the lung cancers (111 in the full cohort Larson cohort followed up until 2006, 32 in the sub-cohort used by the Agency), the power to detect effect-modification by age is greatly diminished. As I will show by means of examples below, effect modification by age is an important feature of many epidemiologic data sets and age-specific relative risks should be applied in a life-table analysis. The single estimate of RR used by the Agency under-estimates risk at the younger ages and over-estimates it at the older ages (see below).

2. The sub-cohort consists of workers who entered the work force after 1959. With follow-up until 2006, there are probably very few sub-cohort members over the age of 65 by the end of the study, the age at which the incidence of lung cancer begins to increase rapidly. Therefore, the Agency potency estimates for lung cancer are based almost entirely on individuals below the age of 65. In particular, with the life-table analysis going out to age 85, it is important that lung cancer at the older ages make some contribution to the estimate of RR. In fact, as I have stated above age-specific RRs should be used in the life-table analyses.

3. By discarding more than half the cases of mesothelioma (19 in the full cohort, 7 in the sub-cohort used by the Agency), the Agency precludes the conduct of a proper likelihood-based

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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).
analysis of mesothelioma using the Peto-Nicholson model. This model was used in the original 1986 development of the IUR for asbestos and has stood the test of time. Berman and Crump (2008) show that it describes mesothelioma incidence well in multiple occupational cohort datasets. This model recognizes also the fundamental role of pattern of exposure, not just cumulative exposure, in determining the risk of mesothelioma. By jettisoning this model for one that uses cumulative exposure as the appropriate measure of exposure, the Agency has taken a giant leap backwards.
Lung Cancer

The Libby workers’ cohort is the logical choice of dataset on which to base risk estimates for lung cancer and mesothelioma. Over the years there have been numerous publications based on analyses of this cohort (Amandus et al., 1987; McDonald et al., 1986, 2002, 2004; Sullivan, 2007; Moolgavkar et al., 2010; Larson et al., 2010). As the most contemporaneous studies with the longest follow-up, the studies by Sullivan, Moolgavkar, and Larson are the most relevant to this risk assessment. Both Moolgavkar et al. (2010) and Larson et al. (2010) used the Cox proportional hazards model, as the Agency does in this report, and arrived at similar estimates of RR (~1.1 for 100f/cc-y cumulative exposure). I note here that this RR is quite a bit smaller than that estimated in other asbestos occupational cohorts. The RR associated with exposure to asbestos in the South Carolina Textile Workers’ cohort, for example, is substantially larger2 (Hein et al., 2007; Richardson, 2009). The estimation of a single RR for all ages should be interpreted as an averaging of risks over all ages and is appropriate only as a summary measure of risk in the entire cohort. When a life-table analysis is performed, however, it becomes important to investigate RR as a function of age, i.e., to investigate effect modification by age. The Agency had a great opportunity to investigate effect modification by age but went to great lengths not to do so. In fact, the Agency deliberately chose a sub-cohort for analyses in which effect-modification by age had been eliminated. I will show below that there is evidence of substantial effect modification by age in the Libby dataset and that this phenomenon is widely observed in epidemiologic data that span a wide range of ages.

In this document, the Agency used the Cox proportional hazards model for analysis of lung cancer data in a small sub-cohort of the Libby miners’ cohort. Originally proposed by Cox (1972) for the analysis of data from clinical trials, the proportional hazards model was soon adopted by epidemiologists and today provides the conceptual framework for analyses of both cohort and case-control studies. In epidemiologic studies, age is often used as the principal time axis. The main assumption of the original proportional hazards model was that the hazard ratio remained constant with time. With age as the time axis, this assumption translates into the

2 Hein et al. (2007) report an RR of about 3 associated with 100 f/cc-yr cumulative exposure as compared to an RR of about 1.11 in Libby for the same cumulative exposure.
assumption of no effect modification by age. Although the assumption of constant hazard ratios has been relaxed and methods have been devised to test this assumption in epidemiologic studies, the proportional hazards model continues to be used in its original form for analyses of epidemiologic studies with little regard for whether constancy of hazard ratios is valid in any particular data set.

Just how poor this assumption can be is seen in the series of plots shown in my presentation to the Agency at the listening session on October 6, 2011 (slides 8-10 and 14-15 in Appendix A). Slide 8 is a plot of a set of rate ratios for all-cause mortality among smokers from the first Cancer Prevention Study (CPS I) conducted by the American Cancer Society Study (ACS). The rate ratios are estimated directly from the data because the dataset is large enough to estimate rates in the smoking and never-smoking populations. The curve is a Loess smooth through the points. Slide 9 shows the rate ratios for lung cancer in the same data, but the curve is generated by a fit of the two-stage clonal expansion (TSCE), also called the MVK model to the data. The RR is estimated as the ratio of the hazard function among smokers to that among never-smokers.

The figure below is taken from Richardson’s 2009 analysis of lung cancer in the cohort of South Carolina Textile Workers using the TSCE model (also slide 10 in Appendix A). The figure clearly shows the strong effect modification of lung cancer risk by age. Richardson also performed analyses using the proportional hazards model and demonstrated strong effect modification.
Figure 1: Taken from Richardson (2009). Analysis of the South Carolina Textile Workers’ Cohort using the TSCE (MVK) model shows the strong effect-modification by age.

The Agency analyzed the sub-cohort of individuals hired after 1959, reducing the number of individuals in the entire cohort from 1871 to 880 and reducing the number of lung cancer deaths from 111 to 32. As mentioned above, two main reasons were given for the choice of this sub-cohort. First, the Agency claims that better exposure estimates were available in this sub-cohort, although it is not clear from the discussion (see, e.g., page 5-59) that exposure estimates were much better between 1960 and 1967. For reasons I have enumerated above, however, far more is lost than is gained by restricting analyses to this sub-cohort. In addition to discarding much of the data on lung cancer, much of the data on lung cancers occurring after the age of about 65 are discarded. The second justification for using the sub-cohort – that there is no confounding or effect modification by age – is not credible. As I have shown above, effect modification by age is ubiquitous in cohort data spanning a wide range of ages. The failure to detect effect
modification in the sub-cohort could simply reflect a lack of power to detect a non-monotonic departure from proportionality of hazards in the reduced dataset and/or the absence of any information on lung cancer at the older ages in the sub-cohort, where departures from proportionality of hazards are most evident. The Richardson analyses of the South Carolina cohort clearly shows substantial departures from proportionality as do analyses of the Libby cohort, as I now discuss.

I did not have access to the full data set analyzed in Larson et al. (2010). However, in Moolgavkar et al. (2010) we analyzed the Sullivan cohort with follow-up through 2002. We identified 95 lung cancers in this cohort. For this report, I extended our Cox model analyses reported in Moolgavkar et al. (2010) to model RR as a smooth function of age using natural splines. The result is shown in the figure below and in slide 14 in Appendix A.

**Figure 2.** Analysis of lung cancer in the full Sullivan cohort using natural splines to model RR as a function of age. RR on the y-axis is associated with a cumulative exposure of 1f/cc-yr. Note the similarity of the shape of this curve with figure 1 above and with slides 8 and 9 in Appendix A. A statistical test for interaction of cumulative exposure and age is statistically significant.
There are various statistical tests for departures from proportionality. One may look at the Schoenfeld residuals as shown in slides 12 and 13 in Appendix A. If proportionality holds one would expect to see a pattern of pinned random walks about a horizontal line. It turns out that, while there is clear indication of departures from proportionality in the figures, this test is not significant whereas a test for interaction between cumulative exposure and age is significant in the entire data (slide 12), but not in the sub-cohort of workers employed for more than one year (slide 13). This indicates that the interaction test has more power in this situation and also illustrates the pitfall of accepting the null hypothesis of proportionality of hazards just because a test fails to reject it. In fact, non-monotonic departures from proportionality as seen in figures 1 and 2 would be expected to be particularly difficult to pick up with conventional tests.

Note the similarity of shapes for the hazard ratios in all examples that I have shown: the hazard ratio increases with age, reaches a maximum, and then declines. This is a reflection of the fact that the denominator of the hazard ratio, namely, the hazard function in the unexposed population is increasing rapidly with age. In both the Richardson analyses shown in figure 1 and the Libby analyses shown in figure 2, the estimate of the hazard ratio associated with exposure is back to approximately 1 by age 75. Clearly, this fact must be taken into account in any life-table estimates of IUR for lung cancer in asbestos exposed cohorts.
Mesothelioma

Analyses of mesothelioma in the Agency report is based on the same sub-cohort as the lung cancer analyses. Whereas there are 19 mesotheliomas in the full cohort, there are only 7 in the sub-cohort used by the Agency. The risk estimate obtained by analysis of these 7 cases is adjusted upward to address under-ascertainment of mesothelioma cases using a method proposed by Kopylev (2011). As I discuss below, I believe this adjustment is poorly justified and ill-advised.

Agency reports are often relied on for information on a wide range of issues. It is therefore particularly important that the references be up-to-date and that papers discussed in reports be critically reviewed. The lack of critical review is particularly apparent in in the mesothelioma section of the Agency report. For example, the Agency cites a single paper by Hillerdal (1983) to support the statement that mesothelioma is extremely rare without asbestos exposure. However, Hillerdal did not base his conclusion on data, but on opinion. He did not have the data in 1983 to estimate the fraction of mesotheliomas that occur without asbestos exposure.

Spirtas et al. (1994) undertook a formal analysis to estimate the fraction of mesothelioma cases that could be attributed to asbestos exposure. They concluded that, in their study, among men, 88% of pleural mesotheliomas and 58% of peritoneal mesotheliomas could be attributed to asbestos exposure. Among women, they could not estimate the population attributable fraction (PAF) separately for pleural and peritoneal mesotheliomas, but reported that only 23% of all mesotheliomas were attributable to asbestos exposure. This study provides strong evidence that both pleural and peritoneal mesothelioma can occur without asbestos exposure and that the fraction of peritoneal mesothelioma occurring without asbestos exposure is larger than the fraction of pleural mesothelioma occurring without asbestos exposure. A recent large case-control study of mesothelioma in Great Britain (Rake et al., 2009) concludes that 86% of male and 38% of female cases were attributable to either occupational or domestic asbestos exposure. Price and Ware (2009) estimate that approximately 70–75% of mesotheliomas among males and only 3–10% of mesotheliomas among females in the U.S. in 2008 were attributable to asbestos exposure. Aguilar-Madrid et al. (2010) conclude that only 44% of cases of pleural
mesothelioma in Mexico over the period 2004–2006 were attributable to occupational asbestos exposure. Lacourt et al. (2010) show that control selection can have a substantial impact on estimates of PAF from case-control studies, but conclude that the PAF for mesothelioma, i.e., the fraction of cases attributable to asbestos exposure, in France was between about 50% and 70%. Mesothelioma has also been reported to occur in young children and even congenitally (World Trade Organization [WTO], 2000; Huncharek, 2002). Such cases are manifestly not associated with asbestos exposure. Thus, mesothelioma can clearly occur idiopathically.

A recent analysis of the Surveillance, Epidemiology and End Results (SEER) data (Price and Ware, 2004) indicates that the background (spontaneous) rate of mesothelioma (pleural and peritoneal combined) in the United States is between 2 and 4 cases per million individuals per year and that the lifetime risk of spontaneous mesothelioma is between 2 and 4 per 10,000 individuals. Price and Ware (2004) do not provide separate estimates for pleural and peritoneal mesothelioma. In an updated analysis of the SEER data, Moolgavkar et al. (2009) estimate that the background rate of peritoneal mesothelioma in the U.S. is approximately 1 per million per year and that the lifetime risk of spontaneously occurring peritoneal mesothelioma is approximately 1 in 10,000. For pleural mesothelioma, Moolgavkar et al. (2009) estimate that background rates are between 2 and 3 per million individuals per year and the lifetime probability is approximately 3 per 10,000 individuals. A recent large case-control study of mesothelioma (Rake et al., 2009) in the U.K. estimated a lifetime risk of mesothelioma (pleural and peritoneal combined) among individuals not exposed to asbestos of about 1 in 1,000, approximately three times that estimated by Moolgavkar et al. (2009) in the U.S.

Clearly, the issue of non-asbestos-associated mesothelioma cannot be dismissed in a single sentence as done in the Agency report.

The report also mischaracterizes the analysis of mesothelioma deaths in Moolgavkar et al. (2010) and McDonald et al. (2004). Neither analysis is based on Poisson regression. The analysis in Moolgavkar et al. is a full likelihood-based time-to-tumor analysis using the Peto-Nicholson model. The estimate of $K_M$ for Libby asbestos was $0.5 \times 10^{-8}$, half the $K_M$ used by the

The Agency states that the Peto-Nicholson model was tried, but did not describe the data as well as the Poisson model that it ultimately used. It is not clear, however, that the Peto-Nicholson model was tested appropriately. The version of the model used by Berman and Crump (2008), which accommodates time-varying exposure concentrations, should have been used and a full likelihood time-to-tumor analyses performed to estimate not only $K_M$, but also the exponent$^3$ of the duration of exposure. With only 7 cases, such an analysis is probably not feasible. In my opinion, the full Larson data set should be analyzed using the Peto-Nicholson model. With the Poisson regression adopted by the Agency, all information about time-to-tumor is lost. It is also not clear from the description provided in the report how the Poisson regression was performed. For example, the report should state clearly what contribution each individual in the cohort made to the expectation of the Poisson model. Even if Poisson regression is used for these analyses, it is not clear why it is necessary to use Bayesian MCMC methods. Likelihood-based analyses using generalized linear models appear to be straightforward. The numerous analyses performed and reported on would appear to be overkill. How can one discriminate among the many models used with only 7 cases of mesothelioma in the dataset? Small differences in the deviance information criterion (DIC), or whatever criterion is used to measure relative fits, are hardly informative with this small dataset.

Finally, the Agency used a method proposed by Kopylev (2011) to adjust risk upward by a factor 1.39 to compensate for under-ascertainment of mesothelioma deaths in the sub-cohort. I believe this adjustment is ill-advised for the following reasons. First, the under-ascertainment of exposure asbestos from other sources should be considered before any adjustment is made for under-ascertainment of mesothelioma (or any other) deaths. Many of the workers at the Libby mines worked there only for short periods of time. A substantial number in the full Libby cohort were employed there for less than one year. It is clear from the data in Peipins et el. (2003) that residents of Libby were employed in other jobs that could have exposed them to asbestos. It is

$^3$ Moolgavkar et al. (2009) could not estimate the exponent because they had information only on the number (15) of mesotheliomas in the Sullivan cohort, but not on which individuals had the disease. With this information, only $K_M$ can be estimated.
therefore highly likely that exposure to asbestos is under-estimated in the cohort, particularly among short-term workers. This is not a problem peculiar to Libby. It is ubiquitous with occupational cohort studies and the only way to get around it is to perform a case-control study nested within the cohort. Second, I do not believe that the data on under-ascertainment used for estimating the adjustment factor is reliable. Third, the adjustment factor is based on a Poisson regression analysis and it is not clear that the same Poisson models were used in the report and in Kopylev et al. (2011). The adjustment factor using a proper likelihood based analysis using the Peto-Nicholson model would likely be different. Finally, the adjustment factor applied in the Agency report is the one derived by Kopylev et al. (2011) based on the full dataset. It is not clear that the same adjustment factor would be obtained if the method were applied directly to the sub-cohort.

**Treatment of half-life is inappropriate for mesothelioma**

The lung cancer and mesothelioma models used by the Agency modify exposure by an exponential decay term to represent the gradual clearance of asbestos fibers from tissues. This approach has been suggested by some authors, but a moment’s reflection makes it clear that biological half-life cannot be used in this fashion in an analysis of mesothelioma. This is another example of the Agency adopting an approach without critical assessment. If deposition in the tissue is proportional to exposure concentration (c) and deposited fibers are eliminated with linear kinetics (constant rate k), both reasonable assumptions for deposition and clearance of fibers from the lung, then a simple calculation\(^4\) shows that on a time interval with constant exposure concentration

\[
CD(t) = \text{constant} \times \frac{c}{k} \left(1 - \exp(-kt)\right)
\]

(where CD(t) is cumulative tissue dose).

With piecewise constant exposure concentrations, the cumulative tissue dose is a sum of terms of the type given above plus terms that track the decay of fibers from asbestos accumulated during previous time intervals. Equation 5-3 on page 5-67 in the report is a discrete approximation to this expression for cumulative dose or fiber burden as a function of time. In

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\(^4\) Requires the solution of an ordinary differential equation.
view of this fact, the appropriate way to model clearance in the lung would be to replace cumulative exposure by cumulative dose in the Cox proportional hazards model or the fiber concentration term by the cumulative dose in the hazard function of a multistage model.

The deposition and clearance of fibers in the pleura or peritoneum cannot be modeled in this simple fashion because fibers must go through the lung to reach these tissues. The simplest model would posit constant deposition in the lung and clearance with linear kinetics into one of three compartments: removal by the defense mechanisms of the body, migration into the pleura, or migration into the peritoneum. Fibers migrating into the pleura or peritoneum could be eliminated with linear kinetics. Even this simple model for the deposition and clearance of fibers in the pleura or the peritoneum is much more difficult to incorporate into epidemiologic analyses than the lung model. The model used by the Agency and, therefore the estimate of half-life in the pleura has no obvious interpretation. Clearly, if the half-life as estimated from the epidemiologic data is meant to be a measure of the time from exposure to asbestos fibers to clearance from tissues, then the half-life in the pleura or peritoneum must be longer than that in the lung, contrary to the result in the current Agency report.
Non-Cancer Risk Assessment

The Agency bases its risk assessment for non-cancer end-points on a cohort of workers involved in the processing of vermiculite at a plant in Marysville, Ohio, and analyzed by Lockey et al. (1984) and Rohs et al. (2008). The Agency risk assessment is based on a sub-cohort of the cohort analyzed by Rohs et al. (2008). The end-point of interest for the analyses is localized pleural thickening. The Rohs et al. cohort consists of 280 individuals with 80 cases of pleural thickening. The sub-cohort chosen by the Agency includes 119 participants with 12 cases of pleural thickening. Therefore, as is the case for lung cancer and mesothelioma, the Agency discards much of the data for the analyses in this report.

The Agency says, “…more accurate exposure data are considered to be those from 1972 and later, as these data were based on analytical measurements.” Based on these considerations, the Agency chose from the Rohs cohort the sub-cohort consisting of workers who began work in 1972 or later. The radiographic examination of these workers was conducted over the period 2002-2005. However, in their paper, Rohs et al. identified 1973, not 1971, as the year after which “…more comprehensive environmental exposures were available…” The sub-cohort of workers hired after 1973 consists of 94 individuals with 10 cases of pleural abnormalities. I have the Rohs database and it includes an identifier for workers hired after 1973 but not for those hired after 1971. The report does not explain this discrepancy.

I have analyzed the full Rohs dataset using logistic regression and spline smoothers to explore exposure-response relationships. The results are shown in slide 24 of Appendix A. The figure shows that most of the exposure data (the thickness of the rug at the bottom of the figure reflects the number of data points) lies in the range of 0-3 f/cc-yr. In this range of exposure, the flexible exposure-response model does not support a monotonic increasing exposure-response relationship. While the exposure-response relationship is consistent with linearity above 3 f/cc-yr, it is statistically insignificant in this range, possibly because of the paucity of data.

I analyzed the data in the sub-cohort of individuals in the Rohs cohort who were first employed after 1973. With flexible spline smoothers there is little evidence of a monotonic increasing
exposure-response relationship, in agreement with the finding for the full Rohs cohort. With the usual assumption of a logit-linear relationship between exposure and response in the logistic model, the coefficient for cumulative exposure is statistically significant at the 0.05 level of significance. If, however, either age or body mass index (BMI) are considered as confounders in a joint analysis, the coefficient for cumulative exposure becomes insignificant. One of the important criteria enunciated by the Agency for study selection for non-cancer risk assessment is that the exposure-response relationship be robust to adjustment for potential confounders. Thus, on page 5-11, the report states, “Amandus et al. (1987b) report that although cumulative exposure and age are both significant predictors of small opacities, cumulative exposure was not significantly related to pleural abnormalities when age is included in the model, thus limiting the usefulness of these data for RfC derivation based on pleural abnormalities.” In listing the advantages of the Rohs sub-cohort the Agency used, the report on page 5-14 (number 6) clearly states that it considers the absence of any evidence of confounding in this dataset a distinct advantage. I do not have access to the exact data used by the Agency, but I have analyzed a closely related dataset as described above and there is strong evidence of confounding by both age and BMI. By its own criteria, the Agency should not be using this dataset for derivation of an RfC.

Finally, the Agency uses various lags in the analyses of the sub-cohort. The use of lags for the analyses of pleural abnormalities makes no sense. Lags, although I do not generally favor them, can be used in analyses of hazard or incidence functions when the diagnosis of an end-point, such as cancer, is made at a well-defined point in time. It makes absolutely no sense to use lags in the analyses of prevalent conditions, which could have occurred many years before the condition was noted. In the Rohs database all radiography was performed between 2002 and 2005 when pleural abnormalities were noted. These could have occurred many years before the radiography was done. What is the interpretation of a lag in this situation?
Other Issues

I have given examples above of the generally incomplete and uncritical review of the literature on asbestos-associated disease in the Agency report. I give some other examples here. The re-analyses of the Sullivan data by Moolgavkar et al. (2010) is given short shrift in chapter 4 on risk characterization, while it is discussed in some detail in chapter 5 for the cancer end-points, but again ignored in the discussion of the cancer end-points. The results in Larson et al. (2010) are uncritically accepted despite obvious inconsistencies. As an example, I show below table 4-5 from the report showing the main results from the Larson analysis of mesothelioma.

Table 4-5. Mesothelioma mortality risk based on studies of the vermiculite mine workers in Libby, MTa (continued)

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>Inclusion criteria and design details</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larson et al. (2010a)</td>
<td>Inclusion criteria not described (n = 1,862); follow-up through 2006; 952 deaths (80% with known cause of death). Median duration: 0.8 years; Median fibers/cc-yr = 4.3.</td>
<td>19 mesothelioma deaths observed&lt;br&gt;SMR: 94.8 (95% CI: 57, 248)</td>
</tr>
<tr>
<td></td>
<td>20 year exposure lag: Cumulative Exposure</td>
<td>RR (95% CI)&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>&lt;1.4 fibers/cc-yr</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1.4 to &lt;8.6 fibers/cc-yr</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>8.6 to &lt;440 fibers/cc-yr</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>≥440 fibers/cc-yr</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>per 100 fibers/cc-yr increase</td>
<td>1.15 (1.03, 1.28) (p = 0.0134)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Includes miners, millers, and processors; workers in the screening plant, loading docks, and expansion plants; and office workers.

<sup>1</sup>In McDonald et al. (2004), the RR is based on Poisson analysis using an internal referent group.

<sup>2</sup>In Larson et al. (2010b), the RR is based on Cox proportional hazards modeling using an internal referent group.

SMR = standardized mortality ratio, CI = confidence interval, SRR = standardized rate ratio, RR = relative risk.

Note that Larson et al. (2010) present RRs both in categories of exposure and as a continuous function of cumulative exposure based on a Cox proportional hazards model analysis. The RR based on the latter analysis is 1.15 per 100 f/cc-yr cumulative exposure. In the categorical analysis, the RR associated with an exposure between 8.6 and 44 f/cc-yr is 4.5. Thus the results of the two analyses are clearly highly inconsistent. Yet the Agency presents them together without comment.
Conclusions and Recommendations

1. Risk assessments for both cancer and non-cancer end-points are based on severely and inappropriately restricted datasets.

2. The model for mesothelioma is a giant step backwards because it ignores the important role played by pattern of exposure in determining risk, which was recognized by the Agency in its earlier 1993 IRIS document. I recommend that the Agency explore a likelihood-based time to tumor analysis on the full Libby dataset using the Peto-Nicholson model.

3. The model for lung cancer should be extended to examine both the role of pattern of exposure in determining risk and effect modification of RR by age. Age-specific RRs should be used in the life-table analyses.

4. The analysis of the sub-cohort of the Rohs cohort is particularly simplistic. The use of lags for prevalent conditions is inappropriate. There may not be a suitable data set for the derivation of an RfC based on pleural thickening.

5. In summary, I recommend that the Agency undertake substantive new analyses and a complete and thorough revision of the report.
References


Thomas DC. Re: "When will nondifferential misclassification of an exposure preserve the direction of a trend?". Am J Epidemiol 1995;142(7):782-4.


Appendix A

Comments on the EPA draft risk assessment for Libby asbestos – PowerPoint presentation by Suresh H. Moolgavkar on October 6, 2011
Comments on the EPA draft risk assessment for Libby asbestos – October 6, 2011

Suresh H. Moolgavkar, M.D., Ph.D.
Exponent, Inc.
General Comments

- Clear that considerable time and effort has been devoted to this comprehensive report.

- Report is unevenly written and certain chapters omit critical information. For example, the Moolgavkar et al. (2010) study is given short shrift in chapter 4 on risk characterization, while it is discussed in some detail in chapter 5 for the cancer end-points, but ignored in the discussion of non-cancer end-points.

- Literature review is uneven and references are dated.

- Sufficient attention has not been paid to critical evaluation of papers. Examples later.
General Comments

- Extensive new analyses have been performed by EPA in this report. These, to the best of my knowledge, have not been peer-reviewed. Some of these are ill-conceived and yield biologically implausible results. Examples later.

- Important analyses to investigate temporal aspects of asbestos-associated lung cancer and mesothelioma risk not undertaken.

- Sufficient justification not provided for the new and unpublished data sets used for assessment of cancer and non-cancer risks.
Fundamental Issues

- Temporal aspects of exposure and risk

1. How does pattern of exposure to a carcinogen determine risk?
   - Is the risk determined by cumulative exposure (Haber’s law)?
   - Or are patterns of exposure (age at start and stop, intensity of exposure) important?

2. How does risk evolve with time since start of exposure? How long does the memory of exposure last? What is the temporal pattern of risk after exposure stops?
Fundamental Issues

- Haber’s law is false. Cumulative exposure is generally a poor determinant of carcinogenic risk, but is often used as a measure of exposure because it is easily understood.
- Cancer risk depends on entire temporal history of exposure to carcinogen.
- For most carcinogens, ‘memory’ of exposure fades with time.
- Currently used statistical methods for analyses of epidemiologic data, based on the Cox proportional hazards model, are not well-suited to investigating temporal aspects of exposure and risk. Epidemiologic studies only rarely address these issues.
- Methods based on biological ideas of multistage carcinogenesis are better suited to studying temporal aspects of cancer risk.
- Because the IUR for Libby asbestos is ultimately based on a life-table calculation it is important that temporal aspects of risk, e.g., changing RR with age be addressed.
EPA’s 1986 IRIS Slope Factor for Asbestos

- Hybrid approach based on consideration of mesothelioma and lung cancer.
- Mesothelioma model – Absolute risk model: Hazard function is modeled explicitly as a function of both intensity of exposure and duration of exposure. Model is linear in concentration but non-linear in duration of exposure. Peto based the model on ideas of multistage carcinogenesis. In this model, risk CANNOT be expressed as a function of cumulative exposure.
- Lung cancer model – Relative risk model: Relative risk modeled as a linear function of cumulative exposure (Haber’s law!).
- In the final step risk estimates for mesothelioma and lung cancer are combined in a life-table analysis to arrive at the IRIS Inhalation Unit Risk (IUR) for cancer.
- The 2008 EPA OSWER directive essentially endorsed the use of this approach with some refinements for exposure assessment.
Lung Cancer - Cox Proportional Hazards Model

- Introduced in 1972 for analyses of clinical trials data. Trials rarely last more than a few years. Has now been widely adopted for analyses of epidemiologic studies spanning decades. Proportionality of hazards cannot be expected to hold over this long time period and is clearly often violated.

- EPA treats proportionality of hazards as a ‘law of nature’ and goes to great lengths (pages 5-76 – 5-77) to explain why this ‘law’ is violated for lung cancer in the full Libby cohort. This is a principal reason given by EPA for choosing a sub-cohort for lung cancer risk assessment.

- EPA wrongly believes that proportionality holds in the sub-cohort. Failure to reject proportionality is probably a power issue (number of lung cancer cases reduced from ~95 to 32).
Rate ratios for all-cause mortality among smokers with a two-pack a day habit as a function of age. Rate ratios are from the Cancer Prevention Study I (CPS I) cohort (Burns et al., 1997). The line is a smoother through the observed rate ratios.
Rate ratios for lung cancer among smokers with a two-pack a day smoking history in the CPS I cohort (Burns et al., 1997). The line represents the predicted relative risks from a fit of the TSCE model to the data (Hazelton et al. 2005).
Table 5  Estimated excess relative risk per fiber-year/ml (and associated 95% CI) for lung cancer mortality obtained via proportional hazards regression analysis. Lifetime cumulative exposure under a 10-year lag and within time-windows defined by attained age. White male asbestos textile workers, South Carolina, 1940–2001

<table>
<thead>
<tr>
<th></th>
<th>ERR fiber-years/ml (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative exposure</td>
<td>0.015 (0.007, 0.028)</td>
</tr>
<tr>
<td><strong>Attained age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>0.053 (0.023, 0.124)</td>
</tr>
<tr>
<td>65 or more years</td>
<td>0.003 (nd, 0.012)</td>
</tr>
<tr>
<td><strong>Test of heterogeneity</strong></td>
<td></td>
</tr>
<tr>
<td>LRT, 1 d.f.</td>
<td>14.0</td>
</tr>
<tr>
<td>p-Value</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

\( ^a \) LRT comparing a model with two exposure terms to a model with one term for lifetime cumulative exposure

Schoenfeld residuals – Libby lung cancer. P = 0.1, N = 95
Cum.exp:age interaction, p = 0.048
Schoenfeld residuals – Libby lung cancer among those employed more than 1 year. P = 0.3, N = 53
Cum.exp:age interaction, p = 0.086
Libby Lung Cancer – Full Data
95 lung cancers. RR associated with 1 f/ml-yr.

RR if proportionality holds
Libby Lung Cancer – Employed longer than 1 year
53 lung cancers. RR associated with 1 f/ml-yr

RR if proportionality holds
Mesothelioma

- References outdated. Hillerdal (1983) is really dated and based on opinion, not data. Background rates have been estimated in more contemporary references (Price & Ware, 2004; Moolgavkar et al, 2009). Substantial fraction of mesotheliomas not attributable to asbestos exposure (numerous references will be provided in written comments).


- Even if Poisson regression is used, why is it necessary to use Bayesian MCMC methods? Likelihood analyses appear to be straightforward. In either case, CIs are unlikely to be particularly informative with only 8 cases of mesothelioma.

- Performing the multiple analyses reported in this document with only 8 cases of mesothelioma is overkill.
Mesothelioma – contd.

- Clear for most carcinogens (in fact, ALL carcinogens I am aware of) that risk depends both upon concentration and on duration of exposure independently. The Peto-Nicholson model used in 1986 EPA document acknowledges this fact. Berman & Crump (2008) showed that the Peto-Nicholson model does a satisfactory job of describing mesothelioma mortality in many occupational cohorts.

- Not clear that the Peto-Nicholson model was appropriately applied (equation 5-5) to the Libby data. The version with time-varying exposure concentration as in Berman & Crump (2008) should have been applied. Maximum likelihood estimate of $K_M$ (Moolgavkar et al. (2010)) should have been obtained. The exponent for duration of exposure (fixed at 3) could also have been estimated. {Moolgavkar et al. could not estimate the exponent because they had no information on which specific individuals actually had pleural cancer/mesothelioma.}

- By reverting to some measure of cumulative exposure without a proper exploration of the Peto-Nicholson model, the current EPA analysis takes a giant step backwards. Jettisoning the full Libby data set in favor of a smaller data set because the full data do not find a significant effect of concentration after taking duration into account on basis of the Poisson analysis is unwarranted. The sub-cohort used for this analysis reduces the number of mesotheliomas from ~15 to 8.

- The adjustment made for alleged under-estimation of mesothelioma in the cohort is inappropriate. Details in written report.
Not at all clear that the risks reported in the last column are comparable. Moolgavkar et al. estimated $K_M$ from the Peto-Nicholson model, whereas the current risk assessment reports risk associated with lagged cumulative exposure.
Table 4-5. Mesothelioma mortality risk based on studies of the vermiculite mine workers in Libby, MTa (continued)

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>Inclusion criteria and design details</th>
<th>Results</th>
</tr>
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</table>
| Larson et al. (2010a) | Inclusion criteria not described \((n = 1,862)\); follow-up through 2006; 952 deaths (80% with known cause of death). Median duration: 0.8 years; Median fibers/cc-yr = 4.3. Immediate and underlying cause of death data (i.e., multiple causes of death) from death certificates or National Death Index-Plus. | 19 mesothelioma deaths observed  
SMR: 94.8 (95% CI: 57, 248)  
20 year exposure lag:  
Cumulative Exposure  

| &lt;1.4 fibers/cc-yrs  
1  
RR (95% CI)\(^c\)  
1.0 (referent) | 2  
1.9 (0.31, 13.6)  
8.6 to &lt;440 fibers/cc-yrs  
5  
4.5 (0.8, 24.6)  
\geq44.0 fibers/cc-yrs  
11  
17.1 (3.7, 78.1)  
per 100 fibers/cc-yrs increase  
1.15 (1.03, 1.28)  
\((p = 0.0134)\) |

\(^a\)Includes miners, millers, and processors; workers in the screening plant, loading docks, and expansion plants; and office workers.  
\(^b\)In McDonald et al. (2004), the RR is based on Poisson analysis using an internal referent group.  
\(^c\)In Larson et al. (2010b), the RR is based on Cox proportional hazards modeling using an internal referent group.  

SMR = standardized mortality ratio, CI = confidence interval, SRR = standardized rate ratio, RR = relative risk.
Treatment of half-life is inappropriate

- What is the interpretation of half-life in this report?
- If deposition in the tissue is proportional to concentration (c) and deposited fibers are eliminated with linear kinetics (constant rate k). Then,
  \[ CD(t) = \text{const.} \times \frac{c}{k} \left(1 - \exp(-kt)\right) \]  (CD = cumulative tissue dose)
- The appropriate way to model clearance would be to replace cumulative exposure by cumulative dose (CD) above in the Cox model or the hazard function of a multistage model.
- Just because half-life, as used in this report, has been used in previous publications does not mean its use is justified (literature should be critically reviewed).
- The estimated half-lives (10 years for the lung cancer model and 5 years for the mesothelioma model) appear to be far too short.
- That the half-life in the pleura is much shorter than in the lung is biologically implausible.
### Table 5-3. Distribution of cases and time from first exposure ($T$) for cohort of Marysville workers

<table>
<thead>
<tr>
<th></th>
<th>All participants</th>
<th>First exposed before 1972</th>
<th>First exposed 1972 or later</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases/Total</td>
<td>Range of $T$</td>
<td>Cases/Total</td>
</tr>
<tr>
<td>Examined 1980 (Lockey et al., 1984)</td>
<td>5/434</td>
<td>0.42–23.43</td>
<td>4/236</td>
</tr>
<tr>
<td>Marysville cohort ($n = 434$, examination in either 1980 or 2002–2005)</td>
<td>61/434</td>
<td>0.42–47.34</td>
<td>48/236</td>
</tr>
</tbody>
</table>

*The 252 individuals examined in 2002–2005 were also examined in 1980. Note that 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 Rohs et al. (2008) cohort.

Source: Rohs et al. (2008) and Lockey et al. (1984).
Non-cancer end-points

- Based on the Rohs et al. (2008) data. Localized pleural thickening taken as end-point of interest.

- Again, as is the case for cancer end-points, this EPA analysis discards most of the data from the Rohs data set and restricts analyses to workers with ‘good’ exposure data (57 cases among 250 participants reduced to 12 among 119 participants).

- These numbers are at odds with those reported by Rohs et al., which reports 80 cases among 280 participants total (first discrepancy) and 10 cases among 90 participants with ‘good’ exposure data (second discrepancy).

- The reasons for these discrepancies are not clear. Rohs reports ‘good’ exposure estimates after 1973; this report says ‘good’ exposure estimates were available after 1971. May explain second discrepancy.
Non-cancer end-points – contd.

- The Agency fits numerous parametric models to the data with various lag structures, while failing to check whether a monotone increasing function of cumulative exposure is appropriate.

- Since the Rohs study reports on the prevalence of pleural abnormalities, the use of lags is totally inappropriate. There is NO information in the data on when the abnormality first appeared.
Exposure Response for Pleural Abnormalities in Rohs et al. (2008) data

- Non-statistically significant dose-response relationship
- Interstitial Fibrosis and Diffuse Pleural Thickening NOT statistically significant when age considered

**Response (beta for pleural abnormalities)**

**Cumulative Exposure**

- 3 f/cc-yr
CONCLUSIONS

- Risk assessments for both cancer and non-cancer end-points based on severely and inappropriately restricted data sets.
- Mesothelioma model is a giant step backwards because it ignores the important role played by pattern of exposure, rather than just cumulative exposure, in determining risk. Peto-Nicholson model should be more thoroughly explored.
- Lung cancer model should have been extended to examine the role of pattern of exposure, rather than just cumulative exposure. Proportionality of hazards is not a ‘law of nature’; nor does it have any intrinsic biological justification.
- Treatment of half-life is unrealistic.
- The analysis of the Rohs data set is particularly simplistic. The use of lags for prevalent conditions is totally inappropriate.
- Detailed comments on these and other issues will be provided in the written document.