Appendix F

Observer Post-Meeting Comments

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Betty Anderson

The quantitative aspect of carcinogen risk assessment is included here because it may be of use in the regulatory decision-making process, e.g., setting regulatory priorities, evaluating the adequacy of technology-based controls etc. However, it should be recognized that the estimation of cancer risks to humans at low levels of exposure is uncertain. At best, the low-dose linearity extrapolation model used here provides a rough but plausible estimate of the upper limit of risk; i.e., it is not likely that the true risk would be much more than the estimated risk, but it could very well be considerably lower. The risk estimates presented below should not be regarded as accurate representations of the true cancer risks even when the exposures are accurately defined. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper risk limits is found to be useful.

There is no solid scientific basis for any mathematical extrapolation model that relates carcinogen exposure to cancer risks at the extremely low concentrations that must be dealt with in evaluating environmental hazards. For practical reasons such low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. We must, therefore, depend on our current understanding of the mechanisms of carcinogenesis for guidance as to which risk model to use. At the present time the dominant view of the carcinogenic process involves the concept that most cancer-causing agents also cause irreversible damage to DNA. This position is reflected by the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that the quantal type of biological response, which is characteristic of mutagenesis, is associated with a linear non-threshold dose-response relationship. Indeed, there is substantial evidence from mutagenesis studies with both ionizing radiation and a wide variety of chemicals that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at higher doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The low-dose linearity and nonthreshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aftatoxins in the diet). There is also some evidence from animal experiments that is consistent with the linear nonthreshold model (e.g., the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because its scientific basis, although limited, is the beat of any of the current mathematical extrapolation models, the linear nonthreshold model has been adopted as the primary basis for risk extrapolation to low levels of the dose-response relationship.

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Comments on Technical Support Document for a Protocol to Assess Asbestos-Related Risk
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GENERAL COMMENTS

I would like to commend Drs. Berman and Crump for taking on the formidable task of reviewing and synthesizing the vast literature on asbestos. Asbestos is one of the few agents for which extensive epidemiological data are available allowing risk assessments to be based largely on these data, with ancillary and supporting information derived from experimental studies. Drs. Berman and Crump have appropriately chosen to use this approach in their proposed revision of the current EPA approach to assessing the carcinogenic risk posed by exposure to asbestos. I believe, however, that the charge questions that the Expert Panel and the Observers have been asked to address are too narrowly framed. The current EPA approach to risk assessment for asbestos is based on a document that appeared in 1986. Given that almost 20 years have elapsed since that risk assessment, there are clearly important fundamental issues that need to be thoroughly addressed in the current document.

The first of these issues is reanalyses of the epidemiological data and, particularly, a thorough reassessment of the exposure-response relationships for lung cancer and mesothelioma with the different asbestos types. Such reanalyses would explore various models and functional forms for asbestos-induced lung cancer and mesothelioma. Disappointingly, Drs. Berman and Crump choose to use only minor extensions of the models and methods used in the 1986 EPA document. Although they also attempt to use models based on ideas on multistage carcinogenesis, this section of the document has some technical problems (detailed below). In any case, this attempt is soon abandoned for lack of time. A question of some importance is the differential potencies of the various kinds of asbestos fibers. There is considerable evidence from the experimental literature that for fibers in a given size class carcinogenicity is largely determined by tissue burden which, in turn, is determined by the biopersistence. Analyses of several long-term rat bioassays for many of the man-made fibers are consistent with this hypothesis (Moolgavkar et al., 2000, 2001a,b). This observation could help explain not only the vastly different potencies of amphiboles and chrysotile in causing lung cancer and mesothelioma in humans, but also the different temporal patterns of risk after exposures to these agents end. A careful analysis of the epidemiological data sets currently available could be used to address this issue. I would encourage further more detailed analyses to address this issue because it is clearly important in the understanding of the temporal evolution of risk, particularly after exposure stops. If possible other data sets with individual-level information should be obtained for analyses. Where possible these data sets should be analyzed without collapsing the data into cross tabulations, which can lead to considerable loss of information. Dr. Leslie Stayner suggested that the Quebec and Libby

data sets be obtained and analyzed in addition to the Wittenoom and South Carolina data sets that Drs. Berman and Crump already have.

Although I believe that the main focus of any reassessment of asbestos risk should be reanalyses of epidemiology studies, and a number of pages in this document are devoted to such reanalyses, the *raison d'être* of this assessment appears to be the introduction of a new exposure index for asbestos. This exposure index, which is based on the counting of fibers by TEM, is justified largely on experimental grounds. Clearly, in order to use this new index of exposure there should be a method of establishing congruence between the new index and the old one based on PCM measurements which were used in most of the epidemiological studies. Drs. Berman and Crump attempt to set up such a relationship. While I found their argument virtually impossible to follow in the written report. Their presentation at the workshop was much clearer.

DETAILED COMMENTS

Epidemiology Studies

I believe that any reanalyses of the epidemiology studies should focus on the following issues.

I. A thorough reevaluation of the exposure-response relationships for lung cancer and mesothelioma for the various types of asbestos fibers. Questions of interest include the choice of a suitable metric of exposure (cumulative exposure versus separate consideration of intensity and duration of exposure) and evolution of risk after exposure to asbestos stops. If, as Drs. Berman and Crump point out, asbestos fibers act mainly as 'promoters' in the carcinogenic process, then one would expect (as with cigarette smoke) duration of exposure to be much more important than intensity of exposure in determining risk and cumulative exposure would be a poor metric. There is considerable evidence that after exposure to cigarette smoke or ionizing radiation stops, the risk among the exposed drops and eventually approaches the risk in the non-exposed. A similar phenomenon appears to be observable with chrysotile, but not amphibole, exposure, probably reflecting the long biological half-lives of the amphiboles. Thus, a careful evaluation of temporal evolution of risk is an integral part of any asbestos risk assessment.

II. To the extent possible, an assessment of the joint roles of asbestos and cigarette smoking in determining the risks of lung cancer and mesothelioma.

III. Comparison of the results of these analyses with other recently published syntheses of the epidemiology literature.

I consider each of these issues in more detail below.

Exposure-response relationships

For the most part, for analyses of lung cancer, Drs. Berman and Crump have used the excess relative risk (ERR) model used in the 1986 EPA document or an extension of it that incorporates a baseline multiplicative factor for lung cancer. The outputs of the analyses applied to the various occupational cohorts are presented in tables. When the values of the multiplicative factor (α) are significantly different from 1, these should be presented in the tables. They currently are not. There is little justification for taking the geometric mean of estimates when α is close to significant. These analyses also introduce a number of 'uncertainty factors' that are used to adjust the confidence intervals for the potencies. These 'uncertainty factors' are clearly subjective (as acknowledged by the authors) and no justification or rationale is given for the choice of one number or another for any particular data set. It would be helpful to have at least a qualitative discussion of the considerations that went in to the choices for any specific data. Moreover, there appears to be no justification for using these factors to inflate the confidence intervals. At least some of these uncertainty factors could be replaced by more rigorous approaches to analyses of uncertainties. For example, there is a rich literature on the incorporation of exposure uncertainties in to statistical analyses. Some of these methods could be exploited.

Even with the simple linear ERR model chosen for analyses of these data, several choices of approach are possible that could quite significantly affect the parameter estimates. First, the approach evidently used in the 1986 EPA document could be used, i.e., the potency K_L could be estimated by a linear regression of ERR against cumulative asbestos exposure. A slight modification of this procedure would use a weighted linear regression. This procedure, while having the virtue of simplicity, ignores the Poisson nature of the observed data. A better approach would be to acknowledge explicitly that the data are Poisson, as Drs. Berman and Crump do, and use the linear form for ERR. This procedure is tantamount to doing a general linear model (GLM) analysis with Poisson variance, the identity link function and offset given by the expected numbers in each bin. However, the natural link for Poisson regression is not the identity but the log. Hence a third approach would be to use the log link, which would make the ERR log linear. It is possible that the extra parameter α may not be required with this form of the ERR. Other functional forms for exposure-response, such as a linear-quadratic model, could be used as well for analyses of these data.

Drs. Berman and Crump report the results of their analyses in a series of tables. Some of these results are puzzling. For example, tables 14 and 15 in Appendix A (labeled figures 14 and 15) report the results of reanalyses of the cohorts of Amandus and McDonald. Both cohorts are drawn from vermiculite miners in Libby, Montana and there is considerable overlap among the cohorts. Despite this, the potencies (with $\alpha = 1$) differ by a factor of 2. Amandus and Wheeler do not report either average or median cumulative exposures in any of their exposure bins. So clearly, Drs. Berman and Crump had to make a choice of a summary exposure metric in each

exposure bin. Their choices may or may not be reasonable, but they can clearly affect the results, particularly when the bins are broad, as is the case here. For example, in the exposure bin 25-200 (f/ml).yr McDonald et al. report an average cumulative exposure of 77.3 (f/ml).yr. In (virtually) the same cohort the authors use a cumulative exposure of 75 (f/ml).yr in the bin 50-99 (f/ml).yr, which would appear to be too high to be either the mean or the median. When such choices have been made this should be clearly indicated in the table.

With respect to exposure-response analyses for mesothelioma, the authors use a functional form that is virtually identical to that used in the original EPA 1986 document. It is not clear whether other functional relationships were tried. I would like to direct the attention of Drs. Berman and Crump to a recent paper by Berry (1999) that proposes various functional forms for an exposure-response relationship for asbestos-induced mesothelioma. Berry also considers elimination kinetics in this paper and the incidence of mesothelioma after exposure to asbestos stops. He applies the model to the Wittenoom data, which is one of the data sets examined in detail by the authors of this report.

When individual level, rather than grouped, data are available other methods of analyses than the ones described above can be used. Evidently the authors had individual level data from cohorts in South Carolina (exposed mainly to chrysotile) and Wittenoom (exposed to crocidolite). In this case, proportional hazards regression (Cox regression) and methods based on hazard functions derived from considerations of multistage carcinogenesis can be used. Drs. Berman and Crump do not use Cox regression, but they do attempt to analyze the data using hazard functions derived from the two-stage clonal expansion (TSCE) model. In my view this is probably the best approach to understanding the distinct roles of intensity and duration of exposure and the temporal evolution of risk, particularly the behavior of risk after exposure ends. Although Drs. Berman and Crump present some analyses of South Carolina and Wittenoom cohorts using the TSCE model, these analyses appear to be technically flawed and were abandoned for lack of time.

I detail my concerns here regarding the analyses based on the TSCE model. As Drs. Berman and Crump assert, not all parameters of the TSCE model are mathematically identifiable from the hazard function alone. However, identifiable combinations of biological parameters can be readily constructed. These parameters, and not the biological parameters, should be used in the construction of the hazard function and the likelihood. Thus, I would not express the exposure-response relationships as presented by Drs. Berman and Crump on page 6-19 in terms of the biological parameters. Rather, these should be expressed in terms of a set of identifiable parameters. Second, for each individual in the cohort, the hazard function depends explicitly on at least four distinct time intervals, the time between birth and beginning of employment (age at first exposure), the time period after beginning of exposure over which asbestos concentrations in the tissues reach equilibrium, the period of time during which asbestos concentrations remain constant, and the period after exposure stops when tissue concentrations may decline. While in epidemiology studies such information may not be directly available, approximations can be made based on deposition and clearance rates for specific types of asbestos. For example, a

recent paper (Finkelstein and Murray, 1999) reports that the half-life of chrysotile fibers longer than 10 microns is about 8 years. While the authors appear to have taken account of the time-dependent decrease in asbestos concentrations after exposure stops, it is not clear to me that they have explicitly considered some of the other time intervals. The authors also attempt to estimate the half-lives of chrysotile and crocidolite from the incidence data in some of their analyses. I believe this is misguided. On the other hand, the authors assume a constant lag (or latency) period of 4 years. I believe that this period should actually be estimated from the data, either as a constant or as a distribution of lags (gamma distribution, for example).

There are other serious problems with the procedures used for data analyses using the TSCE model. The authors state on page 6-20 that "either α or β was fixed at zero, because, when the mortality rate is low, h(t) is practically a function of the difference between the two parameters." This is simply not true. First, setting $\alpha = 0$ leads to a nonsensical result because it makes β the rate of apoptosis negative, which is absurd. Second, in particular when the agent under consideration is a promoter as Drs. Berman and Crump believe to be the case with asbestos, both α and β are independently important in determining the hazard. Furthermore, these two parameters are independently important in determining the temporal evolution of risk after exposure stops. If identifiable parameters are used to construct the hazard function it is unnecessary to use simplifying assumptions setting one of the biological parameters to zero. Finally, the authors report results that are patently absurd. They report on page 6.26 that each of the 'mutation rates' from the South Carolina cohort are 250 times larger than the rates estimated from the Wittenoom cohort. This would imply, other parameters being approximately equal, that the background lung cancer rates in South Carolina are 62,500 times higher than the rates in Wittenoom! I have had considerable experience over many years fitting the TSCE model to large and complex occupational cohort data, and I have never encountered results of this type.

The analyses of data with individual-level information offers the best potential for understanding the temporal evolution of risk and the relative roles of intensity of exposure and duration of exposure in asbestos-induced carcinogenesis. Therefore, the Wittenoom and South Carolina data sets should be carefully analyzed. If other data sets, such as Libby and Quebec, can be obtained these should be analyzed in detail as well.

Clearly, the TSCE model analyses need to be redone with proper account taken of the considerations outlined above. In fact, I would be happy to help with such reanalyses.

Consideration of other Carcinogens

To the extent possible it would be of interest to reassess the joint roles of cigarette smoking and asbestos in lung cancer and mesothelioma. Conventional wisdom, going back to Hammond in the seventies, has it that relative risk for lung cancer with joint exposure is multiplicative. There are more recent analyses, by Little and Armstrong for example, that suggest that the risk may be closer to additive. Thus, clearly this issue needs to be addressed, if possible. Current risk projection methods are based on the assumption that the risk of asbestos exposure

multiplies the risk of smoking. Such projections could be quite misleading if this assumption does not hold. There might be information on cigarette smoking in some of the cohorts that would allow this issue to be addressed. For example, if smoking information is available on a subcohort it may be possible to conduct case-cohort analyses to explore this issue. Similarly, a number of the cohorts might have been exposed to other potential lung carcinogens. For example, the mining cohorts might have been exposed to radon and/or diesel exhaust. This is a long shot, but, if possible, these exposures should be investigated.

Comparison with other Recent Studies

A recent comprehensive review of the epidemiology literature by Hodgson and Darnton, referenced by Drs. Berman and Crump, presents detailed tables of the carcinogenic risk posed by various forms of asbestos. It would be useful to have a comparison of the risks presented in that review with those derived by Drs. Berman and Crump in this document.

New Exposure Index for Asbestos

The main goal of this document appears to be to propose a new index or metric of exposure to asbestos fibers. This exposure index would count asbestos fibers using TEM and give appropriate weight to the longer fibers, which are believed to be more toxic. The weights were apparently estimated on the basis of an analysis of experimental data by Berman and Crump in 1995. While the general principle that the longer fibers are more toxic appears to be generally accepted and sound, the cut-off at 10 microns proposed in this document is arbitrary. The experimental data suggest a cut-off at 40 microns. However, because of differences in airway anatomy, which affects deposition of fibers, and in clearance of fibers from the lung, it is difficult to infer from these experiments where the cut-off in humans should be. While any new index, whether or not based on TEM, should be risk-neutral on the existing epidemiological data sets, it is not clear what structures should be actually counted in any practical use of the new method. For example, there is considerable debate as to whether cleavage fragments of similar dimensions as fibers pose the same, or any, carcinogenic risk. Clearly this issue needs to be addressed before the new index can be used for risk assessment.

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