Historical Perspective

Developments in Asbestos Cancer Risk Assessment

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Background *Efforts have been made for 25 years to develop asbestos risk assessments that provide valid information about workplace and community cancer risks. Mathematical models have been applied to a group of workplace epidemiology studies to describe the relationships between exposure and risk. EPA's most recent proposed method was presented at a public meeting in July 2008.*

Methods *Risk assessments prepared by USEPA, OSHA, and NIOSH since 1972 were reviewed, along with related literature.*

Results and Conclusions *None of the efforts to use statistical models to characterize relative cancer potencies for asbestos fiber types and sizes have been able to overcome limitations of the exposure data. Resulting uncertainties have been so great that these estimates should not be used to drive occupational and environmental health policy. The EPA has now rejected and discontinued work on its proposed methods for estimating potency factors. Future efforts will require new methods and more precise and reliable exposure assessments. However, while there may be genuine need for such work, a more pressing priority with regard to the six regulated forms of asbestos and other asbestiform fibers is to ban their production and use.* Am. J. Ind. Med. 2009.

KEY WORDS: asbestos; lung cancer; mesothelioma; risk assessment; chrysotile; amphiboles; EPA; NIOSH; OSHA

INTRODUCTION

Asbestos, in its various forms, is perhaps the most thoroughly researched and best characterized occupational and environmental health hazard. Nevertheless, knowledge gaps persist and continue to generate scientific interest and policy concerns. Issues that continue to draw attention include:

- The relative potencies of asbestos fiber types, given that all types are known to cause both lung cancer and mesothelioma.
- The health effects of various non-asbestiform fibers, cleavage products and unregulated fibers with asbestiform habits.

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Conflict of interest: Each of the authors has provided expert witness testimony and/or reports in litigation where issues regarding the carcinogenic potency of asbestos have been raised.

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- The roles of fiber dimension (length, diameter, and aspect ratio), surface properties, chemical composition, biopersistence, and other physicochemical characteristics in determining toxicity.
- The need for standardization of sampling and analytical methods to improve specificity, precision, and reliability in the measurement of biologically meaningful fiber parameters.

For more than 25 years efforts have been made to develop asbestos risk assessment methods that provide reasonably valid and reliable information about workplace and community cancer risks. Increasingly sophisticated mathematical techniques have been used to fit data from workplace epidemiology studies into statistical models to shed light on the relationships between asbestos fiber types and dimensions and the risk of lung cancer and mesothelioma. However, none of these efforts have been able to overcome a fundamental hurdle recognized as early as 1972 by the National Institute for Occupational Safety and Health (NIOSH): ''The environmental samples were expressly collected in many cases for control purposes rather than for research and, as a result, meaningful evaluations cannot be made'' [NIOSH, 1972].

EPA's most recent asbestos cancer risk assessment proposal [Brattin, 2008] has now been formally rejected by the agency following a public meeting of its Scientific Advisory Board Asbestos Committee July 21–22, 2008 [Johnson, 2008]. The dismissal of this proposal has demonstrated that mathematical brute force cannot turn a meta-analysis into a believable guide for public policy when sufficiently detailed and reliable exposure and disease information is just not available to support the approach.

BACKGROUND

The methods used by the U.S. Environmental Protection Agency (EPA) and Occupational Safety and Health Administration (OSHA) for assessing the risks of lung cancer and mesothelioma from asbestos exposure originated more than 20 years ago. Based on an approach developed in the early 1980s [Nicholson, 1983] these risk assessment methods have shared several key features:

- Data on asbestos exposures and cancer outcomes are drawn from a set of occupational epidemiology studies, many having large data gaps and misclassifications that are discussed below.
- A mathematical model is used to describe the relationship between dose and response in each study, with a potency factor (essentially the slope of the dose–response relationship) being a dependent variable. This is done separately for lung cancer and mesothelioma, generating a potency factor for each (K_L for lung cancer and K_M for mesothelioma) with a range of uncertainty.
- The individual potency factors are mathematically combined (usually some form of weighted average) into composite potency factors with ranges of uncertainty.
- A dose–response model is used again, this time with the composite potency factors and known or estimated asbestos exposure data being independent variables. The dependent variables (risk ratios for lung cancer and cancer rates for mesothelioma) are calculated and expressed as estimates of individual or population risk with ranges of uncertainty.

The 1983 Nicholson dose–response model assumed the following: Equal potency for chrysotile and the amphiboles; equal potency for all fibers longer than 5 μm; no threshold exposure level for carcinogenicity; a multiplicative interaction between asbestos exposure and cigarette smoking for lung cancer; relative risks for lung cancer that vary linearly with cumulative exposure lagged by 10 years; and death rates for mesothelioma that vary as a linear function of concentration and a cubic function of time since first exposure.

OSHA and EPA have used this model for more than 25 years, with periodic efforts to modify it to address questions about the way fiber type, fiber dimensions, industrial process, or other exposure characteristics affect cancer outcomes. These efforts have differed in their assumptions about relative potency, choice of studies assessed, mathematical models for point estimate and uncertainty calculations, sub-grouping of studies for meta-analysis, and techniques for estimating exposures. For example, OSHA's 1983 assessment used data from eleven epidemiology studies to estimate lung cancer potency factors and four studies for mesothelioma [Nicholson, 1983]. During rulemaking in 1986 OSHA used the same model, but applied it to only eight studies for lung cancer, excluding three studies of mining and/or milling it had included in 1983. OSHA's reasoning was that it had no jurisdiction over mining operations and that ''there is some evidence that risks in the asbestos mining–milling operations are lower than other industrial operations due to differences in fiber size. . .Thus, in determining the best overall value for K_L for the final rule, the data from mining and milling processes were not considered'' [OSHA, 1986]. Testifying on behalf of the Asbestos Information Association of North America Dr. Kenneth Crump argued for additional exclusions: ''I believe there is considerable data to indicate that chrysotile is less risky [than the amphiboles]. OSHA has already omitted from its risk calculation data from mining and milling operations, on the grounds that these exposures are not representative of those in the populations of workers OSHA has responsibility to protect. I believe this principle should also be applied to the chrysotile–amphibole question, and that risk to modern day

workers, who are exposed almost exclusively to chrysotile, should be estimated from studies in which chrysotile exposures predominate'' [Crump, 1984].

Since 1986 the EPA has proposed several times to modify its risk assessment method to include estimates of potencies by fiber type and dimension [USEPA, 1986]. The agency noted in 1986 ''whether there is a different carcinogenic response according to fiber type or industrial process is an issue of increasing concern. . .'' Applying the 1983 model to 14 lung cancer studies, including mining and milling, EPA considered geometric mean potency factors for groups of studies by industry and fiber type. However, while EPA noted possible evidence of differential potency, the wide variation and inconsistencies among studies limited the ability to draw conclusions and EPA decided to continue its practice of presenting overall values for K_L and K_M, as it had in 1983.

In 1993 EPA adopted its current official agency policy on asbestos, Carcinogenicity Assessment for Lifetime Exposure, published in its Integrated Risk Information System (IRIS) [USEPA, 1993]. Once again the basic 1983 model was used, but this time 11 lung cancer and 4 mesothelioma studies were included and 3 mining and milling cohorts were excluded. EPA acknowledged ''some evidence which suggests that different types of asbestos fibers vary in carcinogenic potency'' but settled on a composite risk estimate that did not distinguish fiber types because ''the evidence is limited by the lack of information on fiber exposure by mineral type.'' EPA's 1993 IRIS assessment restated the earlier caution that ''the quantitative estimate is limited by uncertainty in the exposure estimates, which results from a lack of data on early exposure in the occupational studies and the uncertainty of conversions between various analytical measurements.''

In the mid 1990s EPA's Office of solid waste and emergency response (OSWER) began a more deliberate and systematic effort to estimate specific potency factors for different fiber types and dimensions. This effort produced a 1999 draft method [Berman and Crump, 1999], a 2001 draft report [Berman and Crump, 2001] and, following comments from an EPA expert panel [Eastern Research Group, 2003], a 2003 final report [Berman and Crump, 2003] that was submitted to OSWER but never adopted as policy by the EPA.

The Berman and Crump models used the Nicholson method with six significant modifications: First, 20 studies were considered for lung cancer and 14 for mesothelioma. Second, chrysotile and amphibole potency factors were estimated separately, both for lung cancer and mesothelioma. Third, new fiber dimension categories were used. Fourth, correction factors were applied to historic fiber counts based on selected and limited transmission electron microscopy (TEM) results. Fifth, a new parameter was added to the lung cancer model, to account for the possibility that the background lung cancer mortality rate in the asbestos-exposed cohort differs from the rate in the control population. Sixth, models for calculating uncertainty ranges addressed uncertainties in exposure data as well as statistical variation.

The 2001 draft estimated that chrysotile is only 20% as potent as amphiboles for lung cancer. Because these differences were not statistically significant the draft left open the possibility that chrysotile and the amphiboles are equally potent. The estimate for mesothelioma was that chrysotile was only 0.2% as potent as the amphiboles. The revised risk assessment in 2003 increased the relative chrysotile potency for lung cancer to 27% of the amphibole potency. Again, these differences were not statistically significant and the new report again left open the possibility of equal potency. The chrysotile potency for mesothelioma was reduced to only 0.13% of the amphiboles, with the added suggestion that chrysotile might not cause mesothelioma at all.

The 2003 report repeated earlier cautions that grossly imperfect exposure characterization in the epidemiology studies creates substantial uncertainties in the estimation of potency factors, including both random and systematic biases. Among the specific data flaws mentioned were unrepresentative sampling strategies, use of surrogate measures in the absence of actual asbestos measures, lack of data from earlier time periods, and reliance on area samples rather than personal breathing zone measures. Concerns were raised by members of the 2003 expert panel convened by the EPA that the epidemiologic exposure data underlying the risk assessment models was inadequate, particularly for estimating fiber size specific risk estimates. It was also noted that the results for lung cancer were unstable and highly dependent on which studies were included. Sensitivity calculations by one reviewer, Dr. Leslie Stayner, found that when the Quebec miners and millers were excluded chrysotile had twice the potency of amphiboles, but when the South Carolina textile workers were excluded the amphiboles had ten times the potency of chrysotile [Eastern Research Group, 2003; L. Stayner, personal communication].

The 2003 report was never published or formally adopted by EPA, but Dr. Berman and Dr. Crump, the consultants on that risk assessment, have recently published two articles based on this work [Berman and Crump, 2008a,b]. While these articles repeat most of the 2003 conclusions, the analysis was expanded to examine potency by several categories of fiber type and size and the authors argue more strongly than previously that chrysotile may have zero potency for mesothelioma and that short fibers may be non-potent for both lung cancer and mesothelioma.[1] The

[1] Berman and Crump [2008b, pp. 63–64]. Using ''conventional levels'' of significance ''the hypothesis that chrysotile does not cause mesothelioma could not be rejected in any analysis that allowed at least some amphibole contaminations in locations where exposures were principally to chrysotile. . .Also. . .the test of equal potency for the shorter and longer fibers. . .is rejected for the width $<0.4\,\mu m$ metric fit to the lung cancer data and nearly rejected for the 'all widths' metric fit to lung cancer and both metrics fit to mesothelioma ($P < 0.09$).''

best estimate of chrysotile's lung cancer potency relative to the amphiboles was reduced from 27% in the 2003 draft to 11% in the 2008 articles. While the authors largely ignore the problems with exposure misclassification that many others have noted, they do acknowledge, for example, that ''a major obstacle. . .is the lack of data for characterizing the types of fibers and distribution of fiber sizes. They do caution that their findings should be considered ''a proof of concept more than a final result.''

In 2003 OSWER awarded a contract to develop a further modification of the ''multi-bin'' approach begun in 2003, intending to apply new cancer potency factors in risk assessments of Superfund sites. The new proposed risk assessment model was completed on April 23, 2008 [Brattin, 2008]. EPA's Science Advisory Board (SAB) appointed an expert Asbestos Committee to review the proposal, announced a public meeting of this Committee for July 21–22, 2008 and released the proposal for public comments. The 2008 proposal adapted the 1986, 1993, and 2003 risk models to estimate cancer potency for each of 20 ''bins'' consisting of different combinations of asbestos fiber types and dimensions. A new Bayesian Markov Chain Monte Carlo method was adopted as the statistical approach for fitting the risk models to the epidemiological data. A set of 23 studies was chosen for lung cancer analysis and 8 for mesothelioma. A noteworthy change from the previous assessments was the exclusion from the mesothelioma analysis of the Selikoff insulation worker cohort and the de Klerk crocidolite miners' cohort, containing more than 80% of all mesothelioma deaths in the 2008 database [Selikoff et al., 1979; de Klerk et al., 1989; Selikoff and Seidman, 1991]. The Selikoff data were excluded because ''the study population was not exposed at a single location... increasing the likelihood that different workers were exposed to differing types of insulation'' and because ''individuals who were exposed early in the study period would have been exposed to a differing mixture of asbestos individuals exposed later'' [Brattin, 2008, p. 69]. The de Klerk cases were excluded because there was no data on mesothelioma incidence [Brattin, 2008, p. A14-4].

After reviewing the 2008 OSWER proposal, the SAB Asbestos Committee ''generally agreed that the scientific basis as laid out in the technical document in support of the proposed method is weak and inadequate. A primary concern is the lack of available data to estimate the TEM specific levels of exposure for the epidemiological studies utilized in this analysis'' [Kane, 2008]. In response to these concerns EPA Administrator Stephen Johnson accepted the Committee's conclusion ''that the quality of the available exposure data was generally insufficient to support the effort EPA proposed'' and announced that the proposed risk assessment would not be pursued further [Johnson, 2008].

SOURCES OF UNCERTAINTY IN ASBESTOS CANCER RISK ASSESSMENT

All asbestos cancer risk assessment methods proposed since 1972 have been statistical models with point estimates surrounded by ranges of uncertainty. While estimates and uncertainty are not by themselves barriers to good occupational and environmental health policy, policy makers should proceed with caution when the risk estimates have broad zones of uncertainty and low degrees of reliability. For the following reasons the EPA's 2003 and 2008 models were highly uncertain, and the data limitations could not be overcome by statistical modeling.

Exposure misclassification in epidemiological studies can make it difficult or impossible to find true associations between exposure and effect. Systematic misclassifications will create falsely high- or low-risk estimates while random misclassification may mask true associations altogether. About 30 occupational epidemiology studies have had enough asbestos exposure data to have been considered seriously for use in risk assessments. Most of these studies have had one or more of the following problems:

- Phase contrast microscopy (PCM), the most common method for counting asbestos fibers since the late 1960s, measures only those fibers >5 μm in length and does not have the resolution needed to identify fibers <0.25 μm in diameter [Dement et al., 2008]. Extensive toxicologic [Stanton et al., 1981] and limited epidemiological data [Stayner et al., 2008] demonstrate that thin fibers are more carcinogenic than thick fibers. Undercounting of thin chrysotile fibers could inadvertently lead to the incorrect attribution of observed risks to the thicker measurable fiber types and result in an overestimate of dose–response relationships.
- Workers are not exposed to fibers of a single dimension but to a full distribution and there is a strong correlation between exposures by size. The statistical models that have attempted to look at size-specific risks have not been capable of disentangling this correlation [Stayner et al., 2008]. These correlations were not addressed by Berman and Crump [2008a,b] but may well have influenced their fiber size-specific risk estimates.
- PCM fiber counts vary between microscopes and differences may be related to the type and dimensions of asbestos. Resulting misclassification would reduce the ability to find true dose–response relationships if samples with actual differences in fiber count were mistakenly considered equivalent [Dement et al., 2008; NIOSH, 2008].
- According to Dodson and Hammar [2006], ''There are over 30 different 'standard' methods available for the analysis of asbestos in a variety of media.'' Berman and Crump [2003] state ''Measurements. . .derived

using different analytical techniques and methods can vary substantially and are not comparable. In fact, results can differ by two or three orders of magnitude.'' The National Voluntary Laboratory Accreditation Program, which provides standards for testing and measurement of asbestos samples, was not created until 1976. Almost all the asbestos exposures experienced by workers in each of the risk assessments described here took place prior to 1976, and so lack of reliable and consistent quality control for laboratory performance could also cause exposure misclassification.

- Use of area samples to estimate personal exposures may result in underestimates or overestimates of true exposures. For example, ''stationary air monitors were used at the Ontario asbestos-cement plant until 1969... the use of stationary air monitors may tend to underestimate the true exposure level of workers...'' [Brattin, 2008, p. A4–6]. Lack of data on respiratory protection, local exhaust ventilation, and other control technologies also limits greatly the reliability of area sampling.
- Use of data collected on one shift, job or time period to estimate values for other shifts, jobs or times increases uncertainty. For example, ''environmental hygiene surveys started in the mid 1950s... For earlier periods dust levels were estimated by the company industrial hygienist based on knowledge of past plant operations and conditions....'' [Brattin, 2008, p. A3–4].
- Incomplete or misclassified work histories. For example, ''unrecorded movement of personnel between the mine and mill and the factory in Asbestos, Quebec was reported by Liddell et al. [1997] to occur frequently. This effect makes the exposure estimates more uncertain and may lead to exposure misclassification'' [Brattin, 2008; referencing Liddell et al., 1997].

Efforts to correct for these deficiencies have added additional uncertainties. For example, where relative amounts of chrysotile and amphiboles in the air were not known the proposed 2008 OSWER model sometimes used the relative amounts purchased or processed as a proxy for amounts in the air. This model also assumed that all chrysotile is contaminated with amphiboles based on a 1990 study in which 28/81 or 35% of chrysotile samples were found to have trace tremolite [Brattin, 2008, referencing Addison and Davies, 1990]. Berman and Crump [2008b] used the results of air samples from narrow time ranges to represent fiber size distributions throughout much longer exposure periods.

Another attempt to address the weaknesses in the exposure data has been conversion of historic sampling data to new values as if the samples had been analyzed with more modern equipment. Two conversions have been used. First, many of the old studies used midget impingers and counted dust particles. Since the early 1970s several comparisons of midget impinger dust counts with phase contrast microscope (PCM) fiber counts have been used to generate multipliers for the conversion of dust counts to fiber counts. Hodgson and Darnton [2000], for example, used such multipliers, assuming for most studies that 1 mppcf = 3 f/ml. However, EPA's 1986 risk assessment found ''poor correlations'' in two studies [USEPA, 1986 citing Ayer et al., 1965 and Gibbs and Lachance, 1974]. Brattin considered six additional comparisons that generated conversion factors ranging from 0.1 to 52 and then used a value of 3, but acknowledged, ''it is evident that the use of this default factor is associated with substantial uncertainty'' [Brattin, 2008, p. C-6]. NIOSH had recognized 35 years earlier that ''the conversion of data from million particles per cubic foot (mppcf) to fibers/ml in all asbestos operations can only be done with considerable risk to the validity of the results'' [NIOSH, 1972, p. V-5].

Second, efforts have been made to convert total fiber counts to counts of specific fiber types, lengths, and diameters based on data in the late 1970s and early 1980s in which samples were analyzed with TEM [Brattin, 2008 Appendix B, citing Dement and Harris, 1979, Gibbs and Hwang, 1980, Hwang and Gibbs, 1981, and Sebastian, 1983]. This requires a judgment that workplaces where early epidemiology studies were done were comparable in exposure patterns to those where the later TEM measures were made. However ''it is apparent that use of TEM data measured in one location to represent the particle size distribution in another location is a source of uncertainty'' [Brattin, 2008, p. 76].

Even if exposure conditions in one time and place could be accurately matched to conditions in other times and places, the conversion from PCM fiber data to TEM exposure bins can introduce error. Comparing PCM and TCM measurements on historic samples from three industries using chrysotile asbestos in the 1960s, Dement and Wallingford found that PCM was ''a good measure of fibers $>5\,\mu m$ but not total airborne fiber,'' an important finding because the ratio of total fibers to those longer than $5\,\mu m$ varied from 2 to more than 130 [Dement and Wallingford, 1990]. Since TEM shows substantial variations in fiber size distributions between industries and among different operations in the same industry, one cannot apply a single correction factor to PCM measures. Dement and colleagues have recently shown that it is possible to determine a specific PCM correction factor for a specific uniform job category (UJC) only if TEM analysis of samples from that UJC provides data on size-specific fiber distributions [Dement et al., 2008]. They conclude, ''the PCM method is relatively insensitive to differences in airborne fiber characteristic across and within industries and does not allow for analyses of fiber-specific risks.'' OSHA has concluded, ''PCM and TEM results do not correlate well, and no generally applicable conversion factor exists between the two measurement techniques'' [Snare, 2005].

In addition to exposure misclassification additional problems arise when epidemiologic measures of effect (in this case cancer deaths) are subject to error or bias. Given the small numbers of mesotheliomas available across all studies, several limitations commonly seen in epidemiologic studies are particularly important in asbestos-exposed cohorts. For example, many cases of mesothelioma have historically been misdiagnosed and death certificates have been notably unreliable. The International Classification of Diseases (ICD) prior to the 10th edition (1999) did not classify mesothelioma separately, and cases were generally coded as ''pleural cancer.'' Few studies have gone to the lengths taken by Selikoff who obtained medical records and tissue specimens for review in a great majority of deaths in the insulators' cohort. Also, when most of the studies in the OSWER proposal were completed a majority of cohort members were still alive and in many cases only 20–40% were deceased. As discussed by Selikoff and Seidman [1991] ''Asbestos insulation workers beginning employment at the ages of 18, 20, and 22, for example, did not die of asbestos-associated cancers or asbestosis until they were 40, 50, 60 years of age or older.'' Mesotheliomas continued to appear as the group of New York and New Jersey insulators aged until 1992 when 95% were deceased [Landrigan et al., 1999]. Thus if studies do not follow these cohorts until they have reached such maturity the relative risk for some diseases may be underestimated. Assuring that sufficient latency is represented within the cohort is very important to show the full impact of disease categories.

Asbestos risk assessments have also been exquisitely sensitive to small changes in decisions about which data to include or exclude. When the sensitivity analysis in the 2003 EPA model found the relative potency of chrysotile and amphibole fibers to be highly sensitive to whether single studies were omitted one expert panelist became ''more skeptical about whether the increased potency of amphibole fibers is a robust finding. . .'' [Eastern Research Group, 2003].[2] The 2008 OSWER proposal again excluded cases or studies in an attempt to use only those that could be classified as being exposed to a specific fiber type, or which had other data required by the model. It excluded 769 deaths from the follow-up study of friction products workers by Newhouse and Sullivan [1989], 162 deaths from the Enterline et al. [1987] asbestos products cohort (including, as many as 8 mesothelioma deaths) and 25 mesothelioma deaths from the McDonald et al. [1993] Quebec mine and mill cohort [Brattin, 2008]. It also excluded data on the Selikoff et al. [1979] insulation worker cohort with more than 400 mesothelioma deaths [Brattin, 2008]. OSHA had considered doing this in 1986 but did not, stating, ''excluding this study would mean excluding 45% of all the asbestos-related lung cancer deaths and 84% of all the mesothelioma deaths from the overall analysis. OSHA believes it would be a serious error to eliminate such a large portion of the available data, when appropriate estimates of the exposure levels of these workers are available'' [OSHA, 1986 preamble]. The 2008 OSWER proposal also excluded studies of Texas insulation workers [Levin et al., 1998], Swedish cement workers [Ohlson and Hogstedt, 1985], and Italian textile workers [Pira et al., 2005].

These problems have been identified by the authors and reviewers of each asbestos risk assessment since NIOSH's 1972 criteria document, along with strong notes of caution. EPA's 1986 assessment, for example, notes ''current health effects are the result of exposures to dust in previous decades when few and imperfect measurements of fiber concentrations were made. Current estimates of what such concentrations might have been can be inaccurate. . .'' [USEPA, 1986, p. 43]. Also, these problems are ''exacerbated by sampling limitations in determining individual or even average exposures. . .only few workmen at a worksite are monitored, and then only occasionally. Variability in work practices, ventilation controls, use of protective equipment, personal habits, and sampling circumstances add considerable uncertainty to our knowledge of exposure'' [USEPA, 1986, p. 45–46]. More than 20 years later OSWER acknowledged the same concerns: ''It is very clear that there are errors in the cumulative exposure values. . .and that these errors may be substantial'' [Brattin, 2008, p. 50] and ''it is necessary to extrapolate from the original estimates of concentration or cumulative exposure to the corresponding bin-specific values based on data from studies at other locations. It is important to emphasize that this is a substantial obstacle and source of uncertainty in the development of bin-specific potency factors'' [Brattin, 2008, p. 73].

The potential consequences of these technical problems have been evident: when the 2003 model was used the lung cancer potency factors for 15 epidemiology studies varied by a factor of 50, even after adjusting for fiber type and size. The range of uncertainty calculated around each study specific potency factor was from 6- to over 175-fold and the 90% confidence intervals varied from 2- to over 18-fold. For mesothelioma the estimated potency factors varied by a factor of 30 after taking fiber type and size into account. The uncertainty around each potency factor ranged from 5- to over 400-fold and the 90% confidence intervals varied from 1.5- to over 35-fold [Berman and Crump, 2003, p. 7.60 and Tables 7-6 and 7-9].

WHAT NEXT?

The history of asbestos cancer risk assessment illustrates the point that elegant mathematics does not ensure good public policy. Trying to turn fundamentally unreliable data

[2] Similar sensitivity analyses have not, to our knowledge, been done for mesothelioma. Given the fact that most of the cases come from a very small number of studies, this type of analysis should accompany any future cancer risk assessment.

into valid and reliable output is statistical alchemy, no matter how sophisticated and complex the mathematical models. The repeated efforts by the EPA to characterize the relative cancer potencies for different asbestos fiber types and sizes have not been able to overcome the limitations of the exposure data in the epidemiological studies, and the resulting problems with the 2008 model led EPA to conclude that it could not be used to make public policy decisions [Johnson, 2008].

Uncertainty does not need to be a barrier to good occupational and environmental health policy. Indeed scientists and policy makers often must take definitive action in the face of uncertainty in order to protect the public health and welfare. Retrospective exposure assessments in connection with epidemiological investigations have proven useful public policy tools when the exposure data have been sufficiently informative and when investigators and policy makers have adequately considered the strengths and weaknesses of specific studies. The epidemiologic evidence on asbestos exposure and health outcomes is limited in important ways that render a *fiber specific* asbestos risk assessment troublesome. Our criticism of the EPA asbestos risk assessments should not be generalized to all epidemiology, and is not a blanket rejection of all asbestos risk assessments for public policy purposes. We view Dr. Nicholson's 1983 approach as a valid basis for certain types of decision-making, despite its uncertainties and reliance on imperfect exposure data, and we believe that it remains useful to this day. OSHA rulemaking follows the statutory direction given to the agency to take protective action based on the ''best available evidence'' and guidance from the U.S. Supreme Court's ruling that ''the Agency has no duty to calculate the exact probability of harm'' and ''so long as they are supported by a body of reputable scientific thought, the Agency is free to use conservative assumptions in interpreting the data. . .risking error on the side of overprotection rather than under-protection'' [U.S. Supreme Court, 1980]. Dr. Nicholson made appropriately conservative assumptions in estimating the risk for asbestos across all fiber types, for example, in assuming equal potency and not attempting to determine exact risks for subgroups of fiber types. The limitations we describe are with the attempt to parse out risk by exposure subgroups when these groups cannot be accurately identified and when there are multiple exposures that are inextricably intertwined.

We recognize the need for developing better analytic methods and more precise exposure data to aid in addressing several important scientific questions and policy challenges concerning occupational and environmental exposures to mineral fibers. These include differences in risk by fiber type, dimension, and other physico-chemical characteristics; risks from exposure to cleavage fragments and other non-asbestiform mineral fibers; and risks from exposure to nanotubules. While we recognize the value of a research agenda that addresses questions like these, we also believe that scientific inquiry should not stand in the way of a public health intervention for which there is already ample justification. As expressed by Bradford-Hill [1965], ''All scientific work is incomplete. . . That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.''

In this regard, we believe the most important public and environmental health priority concerning the six forms of asbestos regulated by OSHA and other asbestiform mineral fibers is to ban their production and use. There is ample reason to do this without waiting for more evidence on the precise relative potency of chrysotile versus the five regulated amphibole asbestos minerals. The World Health Organization's (WHO) International Agency for Research on Cancer (IARC) has recently re-affirmed its conclusion that all forms of asbestos including chrysotile cause mesothelioma as well as cancers of the lung, larynx, and ovary [Straif et al., 2009]. The WHO has called for a worldwide ban on all asbestos use [WHO, 2006]. In 1999, the European Union directed member states to cease using all types of asbestos, including chrysotile, by 2005 [EU, 1999]. Forty-three countries now have national asbestos bans in place. A recent editorial in The Lancet [2008] stated, ''Less hazardous alternatives have now been found for virtually every use of asbestos and poverty is no longer an excuse. . .All countries should listen to WHO's advice: the only way to eliminate asbestos-related disease is to stop the use of all types of asbestos, all over the world.'' We agree.

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This article shares and builds upon a number of points made in comments submitted to the EPA by the 3 authors and 80 other scientists in July 2008 on EPA-OSWER's proposed approach to asbestos cancer risk assessment. Those comments and the full list of signers can be found at http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/CDFC688FB693B6EC8525741E0047E19B?OpenDocument. The Editor-in-Chief has provided expert witness testimony in litigation involving individuals with asbestos-related cancers.

REFERENCES

Addison J, Davies L. 1990. Analysis of amphibole asbestos in chrysotile and other minerals. Br Occup Hyg Soc 34(2):159–175.

Ayer HE, Lynch JR, Fanney JH. 1965. A comparison of impinger and membrane filter techniques for evaluating air samples in asbestos plants. Ann NY Acad Sci 132:274–287.

Berman DW, Crump KS. 1999. Methodology for conducting risk assessments at asbestos superfund sites; part 1: Protocol. Final

Draft. Prepared for U.S. Environmental Protection Agency. February 15, 1999.

Berman DW, Crump KS. 2001. Technical support document for a protocol to assess asbestos-related risk, final draft. Final Draft. Prepared for U.S. Environmental Protection Agency and U.S. Department of Transportation. September 4, 2001.

Berman DW, Crump KS. 2003. Final draft: Technical support document for a protocol to assess asbestos-related risk. Prepared for EPA Office of Solid Waste and Emergency Response. EPA #9345.4-06, October 2003.

Berman DW, Crump KS. 2008a. Update of potency factors for asbestos-related lung cancer and mesothelioma. Crit Rev Toxicol 38(S1):1–47.

Berman DW, Crump KS. 2008b. A meta-analysis of asbestos-related cancer risk that addresses fiber sixe and mineral type. Crit Rev Toxicol 38(S1):49–73.

Bradford-Hill A. 1965. The environment and disease: Association or causation? Proc R Soc Med 58:295–300.

Brattin WJ. 2008. Proposed approach for estimation of bin-specific cancer potency factors for inhalation exposure to asbestos. U.S. EPA, Office of Solid Waste and Emergency, Contract GS-00F-0019L, April 23, 2008.

Crump K. 1984. OSHA asbestos rulemaking docket H033C, Exhibit 237A, p. 47. 5/15/1984.

de Klerk N, Armstrong B, Musk A, Hobbs M. 1989. Cancer mortality in relation to measures of occupational exposure to crocidolite at Wittenoom Gorge in Western Australia. Br J Ind Med 46:529–536.

Dement JM, Harris RL. 1979. Estimates of Pulmonary and Gastro-intestinal Deposition for Occupational Fiber Exposure. NTIS PB80-149644. U. S. HEW Contract #78-2438.

Dement J, Wallingford K. 1990. Comparison of phase contrast and electron microscopic methods for evaluation of occupational asbestos exposures. Appl Occup Environ Hyg 5:242–247.

Dement J, Kuempel E, Zumwalde R, Smith R, Stayner L, Loomis D. 2008. Development of a fibre size-specific job-exposure matrix for airborne asbestos fibres. Occup Environ Med 65:605–612.

Dodson RF, Hammar SP, editors. 2006. Asbestos: Risk assessment, epidemiology and health effects. Boca Raton, FL: Taylor & Francis Group, LLC.

Eastern Research Group. 2003. Report on the peer consultation workshop to discuss a proposed protocol to assess asbestos-related risk. EPA Contract No. 68-C-98-148. Final Report May 30, 2003.

Enterline P, Hartley J, Henderson V. 1987. Asbestos and cancer: A cohort followed up to death. Br J Ind Med 44:396–401.

European Union (EU) Council. 1999. Annex 1 of Council Directive 76/769/EEC as amended 12/31/1991 and 8/6/1999.

Gibbs GW, Hwang CY. 1980. Dimensions of airborne asbestos fibers. In: Wagner JC, editor. Biological effects of mineral fibers. Lyon, France: IARC Scientific Publication. p 69–78.

Gibbs G, Lachance M. 1974. Dust-fibre relationship in Quebec chrysotile industry. Arch Environ Health 28:69–71.

Hodgson J, Darnton A. 2000. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg 44(8):565–601.

Hwang CY, Gibbs GW. 1981. The dimensions of airborne asbestos Fibres—I. Crocidolite from Kuruman Area, Cape Province, South Africa. Ann Occup Hyg 24(1):23–41.

Johnson S. 2008. Letter from Stephen L. Johnson, EPA Administrator to Dr. Agnes Kane, Chair of Science Advisory Board Asbestos Committee. 12/29/2008.

Kane A. 2008. Letter from Agnes Kane, Chair SAB Asbestos Committee to Stephen Johnson, Administrator U.S. EPA. 11/14/2008.

Landrigan P, Nicholson W, Suzuki Y, LaDou J. 1999. The hazards of chrysotile asbestos: A critical review. Ind Health 37:271–280.

Levin J, McLarty J, Hurst G, Smith A, Frank A. 1998. Tyler asbestos workers mortality experience in a cohort exposed to amosite. Occup Environ Med 55:155–160.

Liddell F, McDonald A, McDonald J. 1997. The 1891–1920 birth cohort of Quebec chrysotile miners and millers: Development from 1904 and Mortality to 1992. Ann Occup Hyg 41:13–36.

McDonald J, Liddell F, Dufresne A, McDonald A. 1993. The 1891–1920 birth cohort of Quebec chrysotile miners and millers: Mortality 1976-1988. Br J Ind Med 50:1073–1081.

Newhouse M, Sullivan K. 1989. A mortality study of workers manufacturing friction materials: 1941–1986. Br J Ind Med 46:176–179.

Nicholson W. 1983. Quantitative risk assessment for asbestos-related cancers. Occupational Safety and Health Administration Office of Carcinogen Standards. OSHA asbestos rulemaking docket H033C Exhibits 84-349 and 84-392. August 1983, revised October 1983.

National Institute for Occupational Safety and Health (NIOSH). 1972. Criteria for a Recommended Standard: Occupational Exposure to Asbestos. U.S. Department of Health, Education & Welfare, National Institute for Occupational Safety and Health, HSM 72-10267, p. V-16.

National Institute for Occupational Safety and Health (NIOSH). 2008. Revised Draft NIOSH Current Intelligence Bulletin: Asbestos and Other Elongated Mineral Particles: State of the Science and Roadmap for Research. Accessed 9/6/2008 at. http://www.cdc.gov/niosh/review/public/099-A/pdfs/revisedNIOSHAsbestosRoadmap_2008_draft.pdf.

Ohlson C, Hogstedt C. 1985. Lung cancer among asbestos cement workers: A Swedish cohort study and review. Br J Ind Med 42:397–402.

Occupational Safety and Health Administration (OSHA). 1986. Occupational Exposure to Asbestos, Tremolite, Anthophyllite, and Actinolite. 51 Federal Register 22612, 6/20/1986.

Pira E, Pelucchi C, Buffoni L, Palmas A, Turbiglio M, Negri E, Piolatto P, La Vecchia C. 2005. Cancer mortality in a cohort of asbestos textile workers. Br J Cancer 92:580–586.

Sebastian P. 1983. Analysis by Analytical Transmission Electron Microscopy of Fibrous Particles in Libby's Air Samples – Preliminary Results. Memorandum from P. Sebastian, McGill University to Henry A. Eschenback, W.R. Grace & Co. on June 10, 1983.

Selikoff I, Seidman H. 1991. Asbestos-associated deaths among insulation workers in the United States and Canada, 1967–1987. Ann NY Acad Sci 643:1–14.

Selikoff I, Hammond E, Seidman H. 1979. Mortality experience of insulation workers in the United States and Canada, 1943-1976. Ann NY Acad Sci 330:91–116.

Snare J. 2005. OSHA Standard Interpretation letter from Assistant Secretary Jonathan Snare to U.S. Senator Conrad Burns. 6/30/2005.

Stanton M, Layard M, Tegeris A, Miller E, May M, Morgan E, Smith A. 1981. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J Natl Cancer Inst 67:965–975.

Stayner L, Kuempel E, Gilbert S, Hein M, Dement J. 2008. An epidemiological study of the role of chrysotile asbestos fibre dimensions in determining respiratory disease risk in exposed workers. Occup Environ Med 65:613–619.

Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Guha N, Freeman C, Galichet L, Cogliano V. 2009. A review of human carcinogens—Part C: Metals, arsenic, dusts, and fibres. Lancet Oncol 10:453–454.

The Lancet. 2008. Asbestos-related disease—A preventable burden. Lancet 372(9654):1927.

U.S. Supreme Court. 1980. Industrial Union Department v. American Petroleum Institute. 448 U.S. 607 (1980).

U.S., Environmental Protection Agency (USEPA), Office of Health and Environmental Assessment. 1986. Airborne asbestos health assessment update. EPA 600/8-84/003F. June, 1986.

U.S., Environmental Protection Agency (USEPA). 1993. Integrated Risk Information System, Asbestos (CASRN 1332-21-4). Online. http://www.epa.gov/iriswebp/iris/subst/0371.htm, last updated 7/1/1993, accessed 9/6/2008.

World Health Organization. 2006. Elimination of asbestos related diseases. Geneva, Switzerland: World Health Organization.