

Journal of Law and Policy

Volume 15

Issue 3

SCIENCE FOR JUDGES VIII:

Regulating Pharmaceuticals and Scientific Issues

Regarding Asbestos

Article 22

2008

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Jonathan M. Samet, *Asbestos and Causation of Non-Respiratory Cancers: Evaluation by the Institute of Medicine*, 15 J. L. & Pol'y (2007).
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ASBESTOS AND CAUSATION OF NON-RESPIRATORY CANCERS: EVALUATION BY THE INSTITUTE OF MEDICINE

*Jonathan M. Samet, M.D., M.S.**

INTRODUCTION

Asbestos refers to several mineral species when they occur in a fibrous form.¹ The asbestos fibers have useful properties of weavability, flexibility, and chemical and physical durability.² Consequently, asbestos has been widely used in building materials, friction products, and fire-retarding fabrics.³ Asbestos consumption rose across the 20th century, peaking in the 1970s and then falling in response to a recognition of asbestos-related health risks, which ultimately led to bans of asbestos and substitution with other materials.⁴

Many of the millions of workers in the United States and other countries who have been exposed to asbestos have developed asbestos-caused diseases, and millions of current and

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¹ THE AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE 103 (4th ed. 2000).

² See James L. Stengel, *The Asbestos End-Game*, 62 N.Y.U. ANN. SURV. AM. L 223, 226 (2006).

³ See generally RACHEL MAINES, *ASBESTOS AND FIRE: TECHNOLOGICAL TRADE-OFFS AND THE BODY AT RISK*. (2005).

⁴ Margaret R. Becklake, *Asbestos-Related Diseases of the Lung and Other Organs: Their Epidemiology and Implications for Clinical Practice*, 114 AM. REV. RESPIR. DIS. 187-227 (1976).

former workers are still at risk, particularly of cancer.⁵ Thousands of lawsuits on behalf of affected workers have been filed against companies that processed asbestos and made asbestos-containing products.⁶ The costs of compensating the claims have led to bankruptcy for many companies, based on the numbers of claims already filed and anticipated future claims.⁷ The ever-increasing number of lawsuits and the costs to industry and insurers have led to calls for a legislative remedy at the federal level, but attempts to pass such legislation have been unsuccessful to date.⁸

Asbestos is known to cause both cancer and diseases of the lung and pleura, the membrane which surrounds the lungs in the thorax.⁹ Sentinel cases of asbestosis, the scarring disorder of the lungs caused by inhaling asbestos fibers, were reported in the early 20th century, but asbestos was not widely recognized as causing cancer until the 1950s and 1960s when epidemiological and clinical studies linked asbestos exposure to mesothelioma—cancer of the mesothelium (the surface lining the thoracic and abdominal cavities)—and lung cancer.¹⁰ The identification of asbestos as a carcinogen lagged its pattern of use because the increased risks for these cancers only become apparent decades after first exposure.¹¹ By then, however, asbestos had been widely used for more than a half century, millions of workers had been exposed, and asbestos-containing materials were in place in thousands of public and commercial buildings in the

⁵ Timothy Driscoll, et al., *The Global Burden of Disease Due to Occupational Carcinogens*, 48 AM. J. INDUS. MED. 419-31 (2005).

⁶ See Stengel, *supra* note 2, at 230-33.

⁷ ERIC STALLARD, KENNETH G. MANTON & JOEL E. COHEN, *FORECASTING PRODUCT LIABILITY CLAIMS: EPIDEMIOLOGY AND MODELING IN THE MANVILLE ASBESTOS CASE* (Springer 2004).

⁸ *Id.*

⁹ See Stengel, *supra* note 2, at 227-31.

¹⁰ See generally Becklake, *supra* note 4.

¹¹ Paolo Boffetta & Leslie T. Stayner, *Pleural and Peritoneal Neoplasms*, in *CANCER EPIDEMIOLOGY AND PREVENTION* 659, 659-73 (David Schottenfeld & Joseph F. Fraumeni, Jr. 3d ed., Oxford Univ. Press 2006).

CAUSATION OF NON-RESPIRATORY CANCERS 1119

United States.¹²

Asbestosis refers to the disease caused by diffuse fibrosis (scarring) of the lung's interstitium (fibrous skeleton); as the disease progresses, the lungs contract progressively and eventually cannot function sufficiently to support respiration.¹³ Epidemiological studies of workers show that asbestosis has been most frequent among those with particularly high exposures in the past.¹⁴ Asbestos exposure also causes fibrosis and plaque formation in the pleura, leading to physiological abnormalities that may impair lung function and pleural effusion, the accumulation of fluid in the pleural space.¹⁵

Inhalation of asbestos fibers also causes cancers of the respiratory tract, including cancer of the lung and mesothelioma. In the 1950s, Sir Richard Doll provided the first epidemiological evidence linking an excess occurrence of lung cancer to asbestos exposure.¹⁶ This finding has since been confirmed in many studies among workers and in the general population; however, uncertainty remains concerning the magnitude of the excess in non-smokers and the degree of synergism between smoking and asbestos exposure.¹⁷ In the early 1960s, the South African pathologist Chris Wagner described malignant mesothelioma and its association with asbestos exposure.¹⁸ While other risk factors have been postulated for mesothelioma, most cases are considered to be caused by asbestos fibers.¹⁹

¹² *Id.*

¹³ *See generally* Becklake, *supra* note 4.

¹⁴ *Id.*

¹⁵ LINDA ROSENSTOCK ET AL., *TEXTBOOK OF CLINICAL OCCUPATIONAL AND ENVIRONMENTAL MEDICINE* 825, 825-37 (1994).

¹⁶ Richard Doll, *Mortality from Lung Cancer in Asbestos Workers*, 12 *BRIT. J. INDUST. MED.* 81, 81-86 (1955).

¹⁷ *See generally* International Agency for Research on Cancer, *IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS: MAN-MADE VITREOUS FIBERS (2002)*, available at <http://monographs.iarc.fr/ENG/Monographs/vol81/volume81.pdf>.

¹⁸ J.C. Wagner et al., *Diffuse Pleural Mesothelioma and Asbestos Exposure in the North Western Cape Province*, 17 *BRIT. J. INDUST. MED.* 260, 260-71 (1960).

¹⁹ Rosenstock, *supra* note 15, at 825-37.

Most claims for compensation related to asbestos exposure have been filed for asbestosis, lung cancer, and malignant mesothelioma. Anatomic sites other than the lungs and mesothelial surfaces, however, are exposed to asbestos fibers as they transit through the upper airway in inhaled air and as fibers deposited in the lung are cleared via the mucociliary apparatus to eventually pass through the gastrointestinal tract. Epidemiological studies have shown associations of asbestos exposure with cancers of the oropharynx, larynx, esophagus, stomach, colon, rectum, and ovaries.²⁰ However, the evidence for asbestos as a cause of cancers of these sites is less abundant and less consistent than for lung cancer and mesothelioma.²¹

For a number of years, the United States Congress has given consideration to legislation for a national system to provide compensation for persons with asbestos-caused disease.²² In 2005, Senate Bill 852, the Fairness in Asbestos Injury Resolution (FAIR) Act, proposed an industry-underwritten trust fund to provide compensation for asbestos-exposed persons as well as affected people living in Libby, Montana.²³ The language of the bill called for the Institute of Medicine (IOM) to carry out a study of the evidence on the association of asbestos with colorectal, laryngeal, oropharyngeal, stomach, and esophageal cancers.²⁴ A multidisciplinary committee was appointed for this purpose, which included members with expertise in epidemiology, biostatistics, pathology, carcinogenesis, oncology, industrial hygiene, and mineralogy. The Committee's charge was to:

[c]omprehensively review, evaluate, and summarize the peer-reviewed scientific and medical literature regarding the association between asbestos and colorectal, laryngeal, esophageal, pharyngeal, and

²⁰ *see generally* INSTITUTE OF MEDICINE, ASBESTOS: SELECTED CANCERS (2006). [Hereinafter: ASBESTOS: SELECTED CANCERS]

²¹ *Id.* at Ch. 5.

²² STEPHEN J. CARROLL ET AL., ASBESTOS LITIGATION (2005).

²³ Fairness in Asbestos Injury Resolution (FAIR) Act, S. 852 109th Cong. § 1 (2005).

²⁴ *Id.*

CAUSATION OF NON-RESPIRATORY CANCERS 1121

stomach cancer. Based on its examination and evaluation of the extant literature and other information it may obtain in the course of the study, the committee will determine if there is a causal association between asbestos and colorectal, laryngeal, esophageal, pharyngeal, or stomach cancers.²⁵

This paper describes the committee's approach to addressing the charge and its findings with regard to whether asbestos is causally associated with the specified cancers. It then offers recommendations for future evidence reviews related to evaluating evidence for causality for the purpose of compensation.

I. COMMITTEE APPROACH

The committee construed its charge as calling for a classification of the evidence relevant to each anatomical site with regard to its strength in supporting a causal relationship.²⁶ The committee was not asked to address the carcinogenicity of asbestos fibers, which have long been classified as carcinogenic.²⁷ The committee did consider, however, that the substantial literature on mechanisms of carcinogenesis by asbestos fibers was relevant to its charge, as were data on the doses of fibers reaching target cells in the organs of interest.²⁸ The committee recognized that the epidemiological evidence would be of particular relevance.

In addressing its charge, the committee considered widely used approaches for systematically gathering and synthesizing

²⁵ ASBESTOS: SELECTED CANCERS, *supra* note 20, at 1.

²⁶ *Id.* at 20.

²⁷ International Agency for Research on Cancer, IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS: MAN-MADE VITREOUS FIBERS (2002) available at <http://monographs.iarc.fr/ENG/Monographs/vol81/volume81.pdf>; NATIONAL TOXICOLOGY PROGRAM (NTP), *ELEVENTH REPORT ON CARCINOGENS*, (Department of Health and Human Services, Public Health Service, 2005).

²⁸ ASBESTOS: SELECTED CANCERS, *supra* note 20, at 16.

evidence.²⁹ The committee judged that a full systematic review was needed that would involve gathering all of the relevant epidemiological evidence and combing the evidence qualitatively and quantitatively. Its approach used the evidence synthesis method generally referred to as “meta-analysis”—a replicable search strategy involving the abstracting of the findings of the individual investigations, and a quantitative summary of the results of the studies for the specified sites of cancer.³⁰

The committee debated whether to present the findings of the individual studies without estimating a summary measure of risk or combine the results, yielding a summary measure of the increased risk for cancer associated with asbestos exposure as well as a 95 percent confidence interval around the estimate, an indicator of the degree of statistical uncertainty. Such estimates are readily derived with standard statistical models and software, but their interpretation can be complicated by variation in the characteristics of the studies that are pooled. In a setting of substantial variability in study populations and methods, an overall estimate may have uncertain validity and generalizability. Nonetheless, the committee did calculate summary estimates while expressing caution in their interpretation and indicating that the level of statistical significance of the estimates was not a criterion for their interpretation or for causal inference.

Figures 1 and 2 provide examples of the committee’s meta-analysis.³¹ Figure 1 gives the results of risk for laryngeal cancer from cohort (follow-up) studies of workers. The risks from each study, comparing “exposed” to a non-exposed comparison group are given; the circle provides the point estimate of risk and the line is the length of the 95 percent confidence interval around the estimate. The line at the bottom gives the pooled result, which has a narrow confidence interval because information is

²⁹ The IOM itself does not have a formulaic approach to the task of evidence synthesis, but rather leaves the selection of review methods to individual committees. See *ASBESTOS: SELECTED CANCERS*, *supra* note 20.

³⁰ DIANA B. PETITTI, *META-ANALYSIS, DECISION ANALYSIS, AND COST-EFFECTIVENESS ANALYSIS: METHODS FOR QUANTITATIVE SYNTHESIS IN MEDICINE* (Oxford Univ. Press 2d ed. 2000).

³¹ *ASBESTOS: SELECTED CANCERS*, *supra* note 20.

CAUSATION OF NON-RESPIRATORY CANCERS 1123

pooled across studies. The committee also sought evidence for a dose-response relationship between asbestos exposure and cancer risk by analyzing the data for the most exposed group in each study compared to non-exposed (Figure 2).

To meet its charge, the committee needed to establish a transparent approach for causal inference. In doing so, it attempted to gather all of the epidemiological findings and to consider the broad range of other relevant evidence; it applied criteria for evidence evaluation, and it classified the strength of evidence for causality using a predetermined and uniform classification. Its criteria for evidence evaluation were based on those proposed in the 1964 report of the U.S. Surgeon General on smoking and health, a landmark report that found smoking to be a cause of lung cancer.³² Sir Austin Bradford Hill, a British medical statistician, had offered a similar set of criteria.³³ The criteria of the 1964 report included: (1) the *consistency* of the association; (2) the *strength* of the association; (3) the *specificity* of the association; (4) the *temporal relationship* of the association; and (5) the *coherence* of the association. Consistency, as a general matter, refers to the comparability of findings of studies; consistency of association with replication in multiple populations by different investigators using different research methods weighs against bias or other methodological problems as an explanation for the association. “Strength of association” refers to the extent to which risk is increased by exposure, a positive dose-response relationship, i.e., increasing strength of association with greater exposure to the agent of interest is one aspect of the strength of association relevant to causal inference. As the association becomes stronger, bias becomes a less plausible explanation for an observed association, particularly if there is a positive dose-response relationship. A proper temporal relationship between the putative cause and its

³² PUBLIC HEALTH SERVICE, U.S. DEP’T OF HEALTH, EDUC., AND WELFARE, *SMOKING AND HEALTH: REPORT OF THE ADVISORY COMM. TO THE SURGEON GEN. OF THE PUBLIC HEALTH SERV.* (U.S. Government Printing Office 1964).

³³ Austin Bradford Hill, *The Environment and Disease: Association or Causation?*, 58 *PROC. R. SOC. MED.* 295, 295-300 (1965).

effect is requisite, i.e., exposure must precede the occurrence of the outcome, rather than be a consequence of it. “Coherence” refers to the extent to which a causal association is plausible based in biological understanding of the basis of the association, and to the extent to which is complementary with other lines of evidence. “Specificity” refers to a unique exposure-disease relationship, as is characteristic of diseases caused by infectious organisms. For cancer, there are few examples of highly specific associations (the association between asbestos and mesothelioma being one such example), and this criterion is usually set aside in evaluating evidence.

To classify the strength of evidence for causation, the committee selected a four-level hierarchy based on that used by the 2004 report of the Surgeon General on the adverse consequences for health of smoking cigarettes (Table 1).³⁴ The categories reflect the adequacy of the evidence available and the degree of certainty with regard to the role of asbestos fibers in causing cancer of the particular site under evaluation. The first category, “evidence is sufficient to infer a causal relationship,” corresponds directly to the committee’s charge, requiring it to “determine if there is a causal association” between asbestos exposure and the listed cancers. The category “suggestive” refers to situations in which evidence is indicative of association but not sufficient to infer causality. This category would be considered if the biological plausibility of the association were uncertain or the epidemiological evidence limited in scope or inconsistent. With greater limitation of the available evidence, the category of “inadequate” would be applicable. The category “suggestive of no causal relationship,” refers to the infrequent circumstance of having strong evidence that the putative causal factor is not associated with disease. This category is used infrequently in causal inference as its application would call for convincing evidence of no association; i.e., a precise indication that the factor does not elevate the risk and for having no

³⁴ See generally CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. DEPT. OF HEALTH AND HUMAN SERV., *THE HEALTH CONSEQUENCES OF SMOKING: A REPORT OF THE SURGEON GENERAL* (U.S. Government Printing Office 2004).

CAUSATION OF NON-RESPIRATORY CANCERS 1125

biological basis for considering it as a risk factor.

The committee selected this four-level scheme in advance of reviewing the evidence. While its charge called only for determination of a causal association with asbestos exposure for each site, it considered that a standard and accepted classification scheme should be used and that a two-level classification should be avoided. The committee also determined *a priori* that its review of the evidence would be based in the long-applied causal guidelines.

The committee chose not to evaluate the evidence in relation to the major fiber types of asbestos. Although there is evidence that risk of mesothelioma differs by fiber type (chrysotile versus amphibole fibers),³⁵ the committee could not find a strong biological rationale for stratifying its approach by fiber type and it anticipated that the evidence would not be abundant by fiber type for the cancers considered. It also did not attempt to quantify cancer risk in relation to estimated exposures. Such quantification might be used for establishing a compensation scheme, but its development exceeded the committee's charge.

II. METHODOLOGICAL CONCERNS

The committee's review and judgments as to the level of evidence for causality were based largely in the epidemiological evidence available for the five cancer sites. The epidemiological findings came from studies of two designs: cohort studies of workers and case-control studies carried out in the general population. The cohort study design involves follow-up of exposed persons and a comparison group of non-exposed persons with assessment of cancer occurrence in the two groups. In the case-control study design, past exposures to asbestos are assessed for persons having the cancer of interest (cases) and for comparable persons not having the cancer (controls). The validity of findings from epidemiological studies of asbestos exposure depends on the accuracy with which asbestos exposure

³⁵ Bruce W.S. Robinson & Richard A. Lake, *Advances in Malignant Mesothelioma*, 353 N. ENGL. J. MED. 1591, 1592 (2005).

can be classified and on the availability of information on other factors, e.g., cigarette smoking, that may also cause the cancer and possibly modify the risk of asbestos exposure. In its assessment of the evidence, the committee carefully considered these methodological issues.

With regard to exposure classification, the cohort studies generally involved observation of asbestos worker groups and comparison of the incidence or mortality rates for the cancer of interest to rates in a comparison population—for many studies, the rates in the population in general. Employment in the asbestos industry is a surrogate for exposure, on the tenable assumption that workers in an industry involved with asbestos would have more exposure on average than the general population or a similar worker group in an industry not involved with asbestos. Some of the cohort studies also included semi-quantitative estimates of the exposures of the workers to asbestos fibers; generally, these estimates are based on a limited set of measurements of the concentrations of airborne fibers in workplaces, extrapolation of the measurements, and expert judgment of industrial hygienists. These estimates potentially have a high degree of error, but are useful for exploring dose-response relationship. Because the error is generally random, it tends to flatten dose-response relationships, making them more difficult to detect.

In the case-control studies, a variety of interview-based approaches have been used to classify exposure to asbestos. Generally, the study protocols include taking a full occupational history, covering each job and industry of employment. This work history information is then matched against a job-exposure matrix that gives the likelihood of being exposed for a particular job.³⁶ In the case-control studies considered by the committee,

³⁶ P.A. Stewart & W.F. Stewart, *Occupational Case-Control Studies: II. Recommendations for Exposure Assessment*, 23 AM. J. IND. MED. 313, 313-26 (1994). See also, P.A. Stewart et al., *A Novel Approach to Data Collection in a Case-control Study of Cancer and Occupational Exposures*, 25 INT'L. J. EPIDEMIOLOGY 744 (1996); P.A. Stewart et al., *Questionnaires for Collecting Detailed Occupational Information for Community-based Case-control Studies*, 59 AM. IND. HYG. ASSOC. J. 39 (1998).

CAUSATION OF NON-RESPIRATORY CANCERS 1127

there was a range of quality and sophistication in the exposure classification approaches. Studies in Montreal, for example, were based on a carefully constructed job-exposure matrix that was developed by industrial hygienists knowledgeable with regard to local industry; the interviews of each study participant were carefully reviewed.³⁷ Information from a job-exposure matrix can be used to qualitatively rank exposure profiles of study participants. At the other extreme, some studies only crudely inquired as to whether asbestos exposure had occurred.

The information obtained by interview in case-control studies may be affected by both random and systematic error, as participants may not remember the details of their work history or under-report or over-report past exposures. As for cohort studies, random error reduces the degree of association in case-control studies, while systematic error may increase or decrease associations, depending on the direction of the bias. One additional source of bias in case-control studies is the reliance on surrogate respondents in studies of cancers that are rapidly fatal, such as esophageal cancer. Surrogates, e.g., a surviving spouse or child, are likely to be less knowledgeable about the work history of the index study participant.

The committee recognized the potential for error in classification of asbestos exposure status to affect the results of the studies that it considered. It developed a pragmatic classification of the quality of the information available and stratified some of its analyses by the quality of the exposure assessment.

For each of the cancers considered, other causal risk factors have been identified (Table 2). Consequently, the committee considered whether other factors might have confounded the association of asbestos exposure with cancer risk, i.e., another factor spuriously produced the apparent association with asbestos, and whether other factors modified the association of asbestos exposure with cancer risk, i.e., whether asbestos and other factors interacted in a synergistic fashion. The term

³⁷ See e.g., J. SIEMIATYCKI, *RISK FACTORS FOR CANCER IN THE WORKPLACE* (CRC Press 1991).

“confounding” refers to the situation in a study when the effect of the exposure under study actually reflects that of another causal factor. For example, an association between asbestos and lung cancer would be found in a study if the asbestos-exposed workers were more likely to be smokers than the non-exposed workers, even if asbestos were not a cause of lung cancer. Smoking and alcohol consumption—strong causes of cancers of the oropharynx, larynx, and esophagus—were of particular concern as potential confounding factors. Most cohort studies do not have information available on potential confounding factors; one strength of the case-control method is that the studies almost invariably collect information on confounding factors. The committee evaluated the epidemiological findings and considered whether uncontrolled confounding could be excluded as a source of associations observed with asbestos exposure.

“Effect modification” refers to the interdependence of the effects of two or more factors.³⁸ For example, there is a synergistic interdependence (interaction) between smoking and alcohol consumption in causing cancers of the oropharynx, larynx, and esophagus;³⁹ either factor can cause these cancers, but if both are present the risks are particularly high and exceed the combined independent effects. For asbestos exposure, there is a potential for effect modification by other factors, particularly smoking and alcohol consumption. The existence of effect modification does not imply that asbestos does *not* act independently in causing cancer, but it would produce variation in asbestos-associated risks across populations as well as having potential implications for compensation schemes. The information available on effect modification was limited, coming primarily from the case-control studies. In its review, the committee remarked on findings relevant to effect modification.

³⁸ See e.g., K. ROTHMAN & S. GREENLAND, MODERN EPIDEMIOLOGY (Lippincott-Raven 1998).

³⁹ International Agency for Research on Cancer, TOBACCO SMOKE AND INVOLUNTARY SMOKING (2002) available at <http://monographs.iarc.fr/ENG/Monographs/vol83/volume83.pdf>.

CAUSATION OF NON-RESPIRATORY CANCERS 1129

III. COMMITTEE FINDINGS

Using its uniform approach, the committee worked in teams to assemble and evaluate the evidence for each of the cancers. Additionally, in introductory chapters, it reviewed relevant research findings on the carcinogenicity of asbestos fibers and on exposure and dose patterns for the target organs. It offered its summary findings for each cancer in a section labeled "Evidence Integration and Conclusion" that had the subheadings of "Evidence Considered," "Consistency," "Strength of Association," "Coherence," and "Conclusion."⁴⁰

The committee judged the evidence to be "sufficient" to infer causality only for cancer of the larynx. For cancers of the pharynx, stomach, and colon and rectum, the evidence was found to be "suggestive but not sufficient" while for esophageal cancer, the evidence was classified as "inadequate." These differing designations by the committee reflected variation in the quality and extent of the evidence available, the strength of association and indication of a dose-response relationship, and considerations of plausibility (Table 3).

Laryngeal cancer was the only one for which the committee judged the evidence to be sufficient to infer causality. That decision reflected biological plausibility, the consistency of the epidemiological evidence, the strength of the association and the presence of a dose-response relationship, and findings from the case-control studies that weighed against confounding as an explanation for the observed association. With regard to coherence, for laryngeal cancer the committee noted that the epithelium of the larynx is similar to that of the lung and that inhaled asbestos fibers pass through the larynx and may deposit there. For the three sites for which the evidence was suggestive, the epidemiological findings were not as strong, and biological plausibility was less certain. For esophageal cancer, the evidence was more limited in scope.

⁴⁰ ASBESTOS: SELECTED CANCERS, *supra* note 20, at 169, 175, 198, 211, 224.

CONCLUSION

This committee was asked to determine if exposure to asbestos causes five specific cancers. The charge was an element of a bill for a national compensation scheme; the committee recognized the potential implications of its findings and the need for an approach that could withstand criticism. Consequently, it adopted a transparent and comprehensive methodology and turned to established models for systematic reviews. It attempted to identify all relevant epidemiological and animal studies and to review the substantial body of evidence coming from laboratory studies of carcinogenesis by asbestos fibers. It utilized consultants to gain insights into potential mechanisms of carcinogenesis for the targeted cancers. A less comprehensive approach might have met with criticism because of potential bias in the selection of studies for review. To date, serious criticisms have not been voiced against the report and its conclusions.

The report's findings have not been part of the implementation of a compensation scheme because the FAIR Act was not passed in the 109th session of Congress. Notably, in presentations of the report to congressional staff, there was discussion as to the implications of the committee's category of "suggestive but not sufficient." For laryngeal cancer, the conclusion regarding the causality of association with asbestos exposure would readily be construed as a rationale for compensation. For the three cancers with evidence reaching the level of suggestive, however, a policy judgment would be needed on whether compensation should be offered in the face of still uncertain evidence.

CAUSATION OF NON-RESPIRATORY CANCERS 1131*Table 1: Four-level Hierarchy of Causation*

Evidence is sufficient to infer a causal relationship.
Evidence is suggestive but not sufficient to infer a causal relationship.
Evidence is inadequate to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting).
Evidence is suggestive of no causal relationship .

Source: CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. DEPT. OF HEALTH AND HUMAN SERV., THE HEALTH CONSEQUENCES OF SMOKING: A REPORT OF THE SURGEON GENERAL (U.S. Government Printing Office 2004).

Table 2: Some Causal Risk Factors For the Target Cancers

Cancer	Causal factors
Oropharynx	Smoked and oral tobacco, alcohol consumption, diet
Larynx	Smoked tobacco, alcohol consumption
Esophagus	Tobacco use, alcohol consumption
Stomach	Tobacco use, h. Pylori infection
Colon/rectum	Family history

CAUSATION OF NON-RESPIRATORY CANCERS 1133

Table 3: Summary of Epidemiologic Evidence Considered By the Committee

Type of Evidence	Type of Cancer Investigated				
	Pharyngeal	Laryngeal	Esophageal	Stomach	Colorectal
Cohort study populations					
Number of source citations⁴¹	14	29	20	34	31
Any Exposure vs. None					
n (subcohorts)	16	35	25	42	41
Aggregate RR	1.44	1.40	0.99	1.17	1.15
95% CI	(1.04-2.00)	(1.19-1.64)	(0.78-1.27)	(1.07-1.28)	(1.01-1.31)
Extreme Exposure vs. None					
n	3	11	7	13	13
Aggregate RRs	0.93	2.02-2.57	1.35-1.43	1.31-1.33	1.24-1.38
95% CIs	(0.21-4.15)	(1.47-4.49)	(0.79-2.58)	(0.97-1.79)	(0.91-1.69)
Case-control study populations					
Number of source citations⁴²	6	18	3	5	11
Any Exposure vs. None					
n	4	15	insufficient data for meta- analysis	5	13
Aggregate RR	1.47	1.43		1.11	1.16
95% CI	(1.10-1.96)	(1.15-1.78)		(0.76-1.64)	(0.90-1.49)
Extreme Exposure vs. None					
n	4	7	insufficient data for meta- analysis	5	7
Aggregate RR	1.25	1.38-1.53		1.42	1.02-1.14
95% CI	(0.68-2.30)	(1.02-1.93)		(0.92-2.20)	(0.57-1.89)

⁴¹ 45 unique citations on 40 main cohorts.

⁴² 36 unique citations

1134

JOURNAL OF LAW AND POLICY

CAUSATION OF NON-RESPIRATORY CANCERS 1135

Figure 1: Cohort Studies RR of Laryngeal Cancer With Any Exposure

Cohort studies: RR of laryngeal cancer in people with “any” exposure to asbestos compared with people who report none. INSTITUTE OF MEDICINE, ASBESTOS: SELECTED CANCERS 177 (2006).

LARYNGEAL CANCER AND ASBESTOS

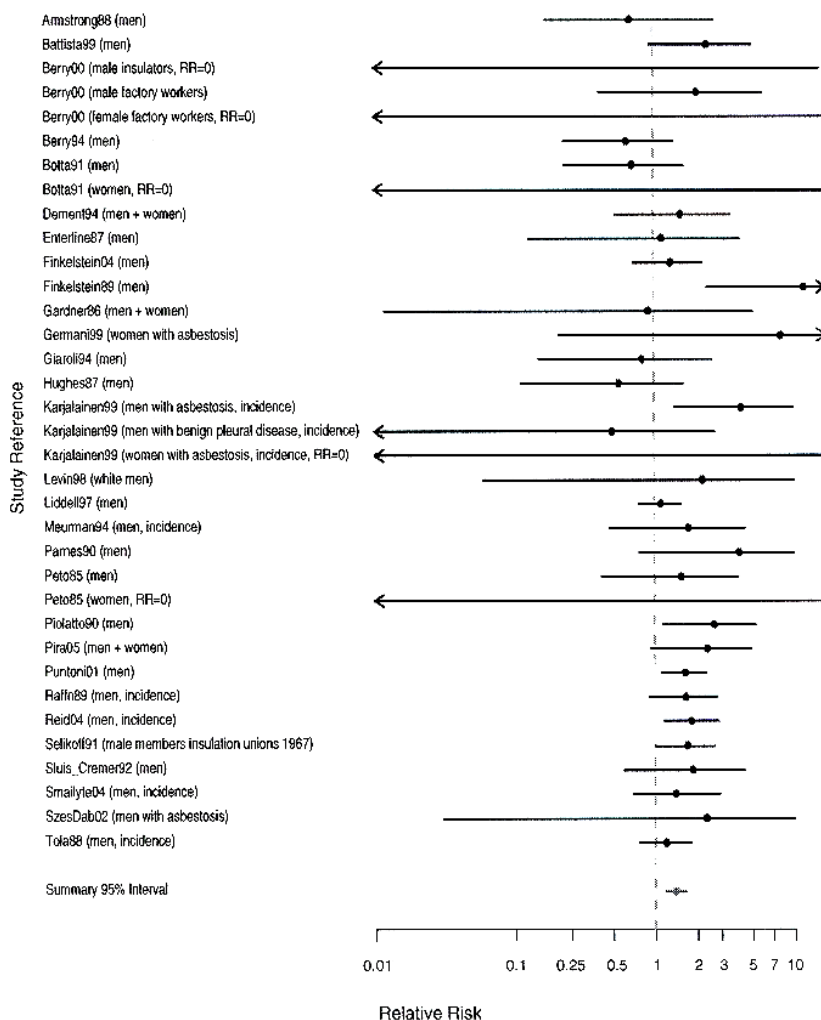


Figure 2: Cohort Studies RR of Laryngeal Cancer Among Extreme Exposure

Cohort studies: RRs of laryngeal cancer among people in most extreme exposure category compared with those with no exposure. (• = more than one exposure gradient reported in citation, so the plot contains both highest and lowest estimates of risk at most extreme category over all gradients)

