Are Low Dose Asbestos Exposure Studies Unreliable?

A Commentary by Mark G. Zellmer of Husch Blackwell LLP

In late 2010, Jonah Lehrer told a rather astonishing story of science, or more accurately, error in the scientific method. According to Lehrer, in 1991, Danish zoologist Anders Moller discovered that female barn swallows were more likely to mate with males with symmetrical feathers. In theory, females used symmetrical feathers as a proxy for better male genes. Over the next years, study of symmetrical features became the rage. Not only did further studies of barn swallows confirm the importance of symmetrical features, but the principle was also applied and studied in other species, including fruit flies and even humans. Researchers found that men with symmetrical features were consistently rated as better dancers. Women even reported more orgasms during sex with men who had symmetrical features.[1]

Then the wheels came off this hypothesis of symmetrical features and sexual selection. Studies of the hypothesis, once regarded as promising, no longer provided support, but rather refuted the hypothesis. In fact, an increasing number of studies failed to verify the hypothesis and suggested that it was, simply, not fact.

Such questioned results have not been limited to hypotheses on sexual selection. According to John P. A. Ioannidis, "[p]ublished research findings are sometimes refuted by subsequent evidence, with ensuing confusion and disappointment Refutation and controversy are seen across the range of research designs, from clinical trials and traditional epidemiological studies to the most modern molecular research."[2]

THE STUDIES OF LOW DOSE EXPOSURE

Since 1998, three articles on four epidemiological studies have attempted to prove the proposition that asbestos exposure at low, maybe even vanishingly low, levels of exposure have increased the risk of mesothelioma.[3]

These three articles, based upon case-control epidemiology, have formed the principal support for the theory that very low exposures to asbestos will in fact multiply the risk for, and thereby increase the incidence of mesothelioma. In each of these studies, one or more industrial hygiene experts, blinded to the purpose of their work, reviewed data about patients with a confirmed diagnosis of mesothelioma. Such data includes work histories, employment data, and answers to questionnaires. The hygienists then determined the likely exposure suffered by such patients. Matched controls were then selected and a similar process was completed for the matched controls, yielding the following results:

1. *The Iwatsubo Study*

Cumulative exposure of 0.5-0.99 f/cc-yrs produced an odds ratio of 4.2. Cumulative exposure greater than 10 f/cc-yrs showed an odds ratio of 8.7.[4]

2. *The Rodelsperger Study*

Exposure exceeding zero to 0.15 f/cc-yrs demonstrated an odds ratio of 7.9, while exposures 1.5-15 f/cc-yrs and greater than 15 f/cc-yrs led to odds ratios of 47.1 and 45.4, respectively.[5]

3. *The Lacourt Study*

The article by Lacourt, et al, reported two studies. Exposures of 0-0.1 f/cc-yrs were not statistically significant in Study A, but suggested an odd ratio of 1.9 in Study B. Exposures greater than 10 f/cc-yrs showed an odds ratio of 4.9 in Study A and 21.4 in Study B.[6]

These studies deserve further investigation and analysis. For instance, how do they affect the law governing causation of mesothelioma? How can these studies actually be replicated? And, most importantly, should the studies be regarded as reliable scientific evidence?

SUBSTANTIAL FACTOR

How have these studies impacted the current state of asbestos litigation? Obviously, the answer is related to the issue of causation.

Case law in some states has adhered to the standard common law concept of "but for" causation.[7] Although scientific research has provided the basis for the connection between asbestos exposure and mesothelioma, medical science has

not yet fully explained ***how*** asbestos causes mesothelioma.[8] Under such circumstances, experts for plaintiff have found it difficult to state that but for plaintiff or decedent's asbestos exposure, he would not have contracted mesothelioma.

Other case law has recognized the "substantial factor" test for causation, particularly in toxic tort cases.[9] Causation then has rested upon evidence that asbestos exposure has substantially contributed to cause plaintiff's disease. However, when a plaintiff expert has been allowed to opine that any asbestos exposure contributes to disease development, the substantial factor test has lost a good deal, if not all, of its meaning.[10] In asbestos cases, the substantial factor test has not been a test of actual causation; instead, it has been a test of measurably increased risk.

Various courts have expressed methods to determine whether an asbestos exposure is a substantial factor in the causation of a plaintiff's disease. The *Lohrmann* test, recognized by a number of courts, has asked whether an exposure allegedly caused by a particular defendant has occurred with regularity, frequency and proximity.[11] Other states have taken a more quantified approach. For example, Texas courts have asked whether exposure will double a plaintiff's risk of a disease before a jury may find causation.[12] To answer these tests of causation, plaintiff counsel has looked to any study or opinion that will bolster their position that only small — in fact, minimal — amounts of asbestos will cause or at least substantially increase the risk of disease. These studies, however, are lacking in a particularly important respect — the ability to replicate the results of the study from the work and data reported.

REPLICATION

In areas of science other than asbestos research, several initial studies on a subject have provided interesting, positive results, only to find that later studies do not replicate the results of the earlier studies. As a new paradigm is proposed, the "peer-review process is tilted toward positive results."[13] In later studies, the academic interests and incentives shift to efforts to disprove the paradigm.[14] Will this occur with these studies of low dose asbestos exposure as a cause of mesothelioma? There has been evidence that such will occur. However, before a shift can occur, a more basic question must be addressed — are these studies even subject to replication?

Certainly the three studies have certain similar designs and reach somewhat similar results. However, the apparent similarity of results can be overstated. For example, Iwatsubo only found statistical significance for exposures of 0.5-0.99f/cc-yrs with an odds ratio of 4.2. Rodelsperger found statistical significance at much lower levels being exposures of greater than zero to 0.15 f/cc-yrs with a higher odds ratio of 9.2. Interestingly, Iwatsubo had more subjects and controls than Rodelsperger.

Replicability of the results of a study has been the hallmark of the scientific method and the apparent, best guarantee of the reliability of scientific studies. Without replicability of results, subjectivity has replaced reliability. With replicability, scientists are less able to influence the results of a study to get the positive results that they may consciously or unconsciously desire.[15]

The problem with replication of the Iwatsubo, Rodelsperger and Lacourt studies is that, in substantial part, these studies have been a "black box." The basic method of these studies has been an estimation of exposure by one or more industrial hygienists. All of the studies explicitly state that the hygienists were blinded, but failed to reveal much about the details of the method. For instance, none of the studies address any of the following questions, all of which are crucial in the replicability process:

BY MARK G. ZELLMER

Mark G. Zellmer is a Partner in the St. Louis, Missouri, office of Husch Blackwell LLP. He is admitted to practice in Missouri (1982) and Illinois (1978) as well as in federal courts in those states. Zellmer earned his J.D. from Saint Louis University School of Law (1978). He earned his B.A. from the University of Notre Dame (1975).

Zellmer speaks and writes extensively on products liability law and asbestos litigation. Such writing and presentation on asbestos litigation include subjects such as premises liability, application of statutes of limitations, medical causation, the litigation in historical context, and exclusivity of remedies under workers' compensation.

Zellmer defends toxic tort cases, particularly relating to asbestos, as well as other substances and chemicals. Zellmer also defends various defendants in product liability regarding vehicular and industrial equipment. Zellmer's trial practice is active in state and federal courts from coast to coast, and he has acted as national counsel in asbestos litigation.

- ❖ What questions were asked of living subjects to establish exposure levels?
- ❖ What if anything was done to verify the credibility of the information obtained?
- ❖ Who were the interviewers?
- ❖ Who were the industrial hygienists?
- ❖ What were their qualifications?
- ❖ What were the exposures determined by the industrial hygienists?
- ❖ How did they determine those exposures?
- ❖ Did the industrial hygienists have a bias toward finding higher or lower exposures?

Without such data, later researchers are at a loss to evaluate the studies, or to recreate these studies, or to create new studies using exactly the same method. The details of the method are simply just not known. Without such information there is little or no guard against the creep of subjectivity into the studies. In fact, in a moment of candor, Lacourt et al admitted that "it was impossible to obtain retrospective quantitative asbestos exposure assessment in the context of case control studies."[16] They further wrote that their semi-quantitative approach was acceptable, but could not explain "the difference observed for [attributable risk] values."[17]

EVALUATION OF SCIENTIFIC STUDIES

Scientific studies have always been the domain of human beings and, hence, subject to human vagaries. The scientific method has been intended to substantially reduce the fallible, human element, although it can never entirely be eliminated. This element has often crept into the scientific method in a number of ways.

Size or power of the study

Due to the small numbers of subjects under study, epidemiological research has been subject to false results. Even the best, most statistically powerful epidemiological studies may have only a one-in-five chance of being true.[18] Studies involving mesothelioma among insulators and manufacturing employees presented bigger numbers and these studies were not case control research, but rather cohort studies. Selikoff insulator studies ultimately involved 17,800 insulators. The Iwatsubo, Rodelsperger and Lacourt studies involved as few as 125 subjects and never more than 460 subjects. The Rodelsperger study specifically warned about the low numbers.[19]

Various well known researchers on the hazards of asbestos exposures have already found evidence of a threshold below which the risk of mesothelioma is non-existent or is at least vanishingly small, i.e. low enough that it is neither measurable nor meaningful.[20] Studies of crocidolite exposure at Wittenoon, Australia did not find mesothelioma occurring below a cumulative exposure of 7 f/cc. Exposures of 1-7 f/cc had a relative risk of 1.[21] Similar results have been found in the recent study of the Libby, Montana residents.[22] Exposures ranged from 1.1 to 1.5 f/cc/year. The only person with mesothelioma with as few as two years of exposure (2.2-3.0 f/cc-yrs) also worked at an aluminum plant where she may have had further exposure.[23]

These are cohort studies, as opposed to case-control studies, and hence, more reliable and less subject to bias.[24] In addition, these studies have been based upon more empirical measurements than the "semi-quantitative estimates" of the Iwatsubo, Rodelsperger and Lacourt studies.

Admittedly there are three articles representing four epidemiological studies suggesting somewhat similar conclusions. However, if the design has been similar in each study and has introduced some sort of bias, the number of studies should not matter. According to David Sackett of Oxford University, bias is still bias, no matter how many times repeated.[25]

Bias

To the extent that they deviate from what is expected, the observed findings by chance have often been simply a measure of the prevailing bias.[26] A number of researchers on asbestos have often opined that there is no threshold, or at least no known threshold, for the causation of mesothelioma by asbestos exposure.[27] Efforts to prove the proposition that there is no threshold, or a very low threshold, for causing mesothelioma may inject bias into a study.

Bias has not just been an issue of what the researchers believe. Bias will creep into a study through the uncertain memories of the participants about exposure to a risk factor. This has been labeled "recall bias." In case-control studies people have had a tendency to recall an exposure that reputedly may have caused their disease. For example, studies have been done on whether fat or oral contraceptives cause breast cancer. Recall bias has crept into these studies as subjects with breast cancer have over-reported their intake of fat or their use of oral contraceptives, having heard that these factors are suspected of causing breast cancer.[28]

Mesothelioma has, by now, been long regarded as a signature disease for asbestos exposure. There should be no denying that the populace is acutely aware of this fact.[29] Subjects with mesothelioma should be expected to search their memories for almost any exposure (or the type of work that will reportedly lead to exposure), real or imagined, to explain their disease.[30] This tendency to report a small exposure that may or may not exist could have mislead-

ing effects on the odds ratios for exposure to small amounts of asbestos.

Traditionally, a large odds ratio or relative risk has been taken as a positive sign of the truth of the findings of a study. The problem, in part, is the focus on a p value of 0.05, i.e. confidence interval of 95 percent, as the proxy for true research findings. The p values only suggest a certain level of statistical significance.[31] John P. A. Ioannidis has argued that research should gauge the probability that its findings are true by determining a study's positive predictive value, i.e. PPV, or the degree to which a finding is more likely true than false.[32] The Iwatsubo, Rodelsperger and Lacourt studies have made no such calculation of PPV. That p values reflect only statistical significance and not the truth of the causal relationships alleged in the study has been a subject of agreement by others in the field of epidemiology.[33] Part of the problem has been that the 95 percent confidence interval has not included the "null result, which is the absence of an effect."[34]

And the problem has actually worsened. "[I]nvestigators have viewed large and highly significant effects with excitement, as signs of important discoveries. Too large and too highly significant effects may actually be more likely to be signs of large bias in most fields of modern research."[35] McDonald and McDonald have presented the relative risk for various occupations known to be exposed to asbestos.[36] *See Chart Below.*

A contrast between the McDonald research on persons occupationally exposed and the three subject studies on persons with reportedly very low exposures should at least suggest questions.[37] The odds ratios in the three subject studies were determined by the authors to be at levels exceeding the relative risks presented by McDonald and McDonald. As an example, an odds ratio in the Rodelsperger study of 47.1 for cumulative exposure of 1.5-15 f/cc is higher than the risk to insulators, a group generally regarded to be the highest exposed asbestos workers. In the Lacourt and Iwatsubo studies, the odds ratios for relatively low cumulative exposures approximate, or exceed, the risk of occupations such as asbestos production, heating trades, shipyard work and construction, all of which are known to be occupations with asbestos exposure. In the Iwatsubo study, the odds ratio for women was 18.8, higher than the risk of any occupation other than insulators as found by McDonald.

Case-control study of 344 male primary malignant mesothelial tumours of pleura and peritoneum, Canada 1960-1972, and USA 1972 [21]

Occupational Group With Definite or Probable Asbestos Exposure	Cases *(n=344)*	Controls *(n=344)*	RR
A – Insulation	27	1	46.1
B – Asbestos production and manufacture *(excl. A)*	25	7	6.1
Mining and milling	4	2	
Manufacture	21	5	
C – Heating trades *(excl. A, B)*	70	27	4.4
D – Shipyards *(exc. A, B, C)*	21	13	2.8
E – Construction *(excl. A, B, C, D)*	45	30	2.6
F – Other *(excl. A, B, C, D, E)*	55	90	1.0
G – None	101	176	1.0

J.C. McDonald et al, The Epidemiology of Mesothelioma in Historical Context, 9 European Respiratory Journal 1932, 1937 (1996).

Chasing significance

There have also been concerns of selective reporting of data. In particular, culling the data for positive results supporting the initial hypothesis can ultimately lead to different results than if the culling process was performed differently or not all.[38] One commentator of the scientific method has called this "significance chasing." That is simply playing with the numbers to find something worthy of publication.[39]

The rate of spontaneous mesothelioma has been determined as 1-2 cases per million population. The rate of total mesothelioma cases has been approximately 17 per million population, 14 for males and 3 for females.[40] Based upon these numbers, spontaneous mesotheliomas have been approximately 8 percent of all cases of mesothelioma.

In each of these studies, the rate of spontaneous mesothelioma was higher than the rate of 8 percent determined above. Most interestingly, the study with a rate closest to 8 percent was also the study with the highest odds ratios. In fact, as the rate of spontaneous mesotheliomas increased, the odds ratios tended to rise.

This would suggest that there should at least be questions about the interview or evaluation process that was used to determine the level of exposure. Any spontaneous mesothelioma that should have been included in one of the exposure ranges may have increased the odds ratios. This would also suggest that there has been some data culling to keep the odds ratios from reaching levels that would be suspicious, if not completely incredible. Computer programs have been developed to cull data selectively in order to reach the magic 0.05 p value of statistical significance. Whether the researchers in these studies used such computer programs is not known. However, Rodelsperger et al admitted that their odds ratios went up substantially from those reported if the exposure ranges were narrowed.[41]

Small measurements

Making small measurements can be a difficult issue. Ioannidis has recognized that as the effects to be measured get smaller, the results of the study become less likely to be true.[42] Similarly measurements of small differences in exposure should create the same problem. Others have echoed this concern. Michael Thun, Director of Epidemiology of the American Cancer Society, has agreed that epidemiology can "tell a little thing from a big thing," but has great difficulty telling "a little thing from nothing at all."[43] Ken Rothman, publisher of the Journal of Epidemiology, agreed already in 1995 that epidemiology was already "pushing the edge" of what can be done.[44]

The exposures subject to measurement in each of the three subject studies were very small. Small changes in those exposures should make significant differences in the results. In addition, when the measurements are small, the chance of a material mistake occurring increases.[45]

Flexibility in study design

"The greater the flexibility in designs, definitions, outcomes, and analytical modes in a scientific field, the less likely the research findings are to be true."[46] The flexibility of the design, definitions, outcomes and analytical modes in the three subject studies went largely without discussion in those studies. There was some indication of flexibility of definitions in the Rodelsperger study. Their odds ratios would have gone up substantially from those reported if the exposure ranges were narrowed.[47]

Hot scientific field

As an area of scientific study becomes a hotter topic, the research findings become less likely to be true.[48] As the competition to publish becomes fiercer, researchers press harder for positive results.[49] In addition, the results must be more unique to justify publication. Certainly no mineral has been more studied for health hazards than asbestos. The extent of the impact on these studies is a matter of speculation.

CHALLENGES TO EXPERT TESTIMONY

These studies may be subject to challenge depending upon the local, evidentiary standards for expert testimony.[50] Certainly these are not simple issues. The status of local law as well as the interest and ability of the judge to hear such a motion must clearly be factors relating to the chance of success. The defense should consider expert testimony to rebut these theories.

Although these studies have clearly been the subject of peer review and publication, such is only one factor in the analysis. Consider some of the other factors:

Error rate: The studies have been subject to bias, which likely has substantially affected the error rate or made it incalculable. The studies have failed to provide their positive predictive value.

Testing the theory or technique: To the extent that these studies use techniques, e.g. interviews and industrial hygiene assessments, for which the information has not been fully disclosed, the study results have not been subject to actual review and replication and have not undergone a true test of validity.

> ***"Presenting intensively scientific theories to a jury, particularly in the face of someone suffering from mesothelioma, can be difficult..."***

General acceptance: There are other studies, indeed other epidemiology, that have not had the same results identifying mesothelioma from low exposures.

Subjective interpretation: The use of the industrial hygiene assessments, even though blinded to the purpose of the study, cannot be considered as anything but subjective. The mere choice of hygienist will affect the estimated level of the exposure.

Non-judicial uses: Causation of mesothelioma has appeared to be an issue unrelated to the treatment of the disease and, rather, more related to payment of compensation for the disease.

CONCLUSION

Studies confirming likely flaws in the subject research by Iwatsubo, Rodelsperger, and Lacourt et al, although not absolutely needed, would bolster these arguments. The peer review process has had a publication bias toward positive results. The reasons should be easy to understand. Negative results have often simply been found to be much less satisfying and much less interesting. The researcher himself has had a tendency to prefer positive results supporting the hypothesis of the study. People have always preferred to be right rather than wrong. Of course, as faulty studies have become the target of further research and publication, the bias has in any number of instances been reversible.[51] The same could be true in this instance.

Presenting intensively scientific theories to a jury, particularly in the face of someone suffering from mesothelioma, can be difficult. Commonly people in this country have been conditioned to greatly fear exposure to asbestos. Part of the approach to the jury must be to convince jurors that such conditioning has been unjustified and overly exaggerated. For example, the EPA made much of the idea that a single fiber could cause cancer. EPA Director, W.K. Reilly, has since acknowledged that the EPA thereby created misperceptions that have led to unwarranted anxiety and unnecessary asbestos removals.[52]

When all is considered, the subject studies are likely beyond the reach of appropriate epidemiology and should not be treated as reliable evidence in court.

ENDNOTES

[1] J. Lehrer, *The Truth Wears Off*, The New Yorker Magazine 52, 54 (December 13, 2010).

[2] J. Ioannidis, *Why Most Published Research Findings Are False,* 2 PLos Medicine 8: e124 (2005). Dol: 10.1371/journal.pmed.0020124.

[3] Y. Iwatsubo et al, *Pleural Mesothelioma: Dose-Response Relation at Low Levels of Asbestos Exposure in a French Population-based Case-Control Study,* 148 American Journal of Epidemiology 2: 133 (1998). K. Rodelsperger et al, *Asbestos and Man Made Viteous Fibers as Risk Factors for Diffuse Malignant Mesothelioma: Results from a German Hospital-Based Case-Control Study*, 39 American Journal of Industrial Medicine 262 (2001). A. Lacourt et al, *Attributable Risk in Men in Two French Case-Control Studies on Mesothelioma and Asbestos*. European Journal of Epidemiology. (September 7, 2010).

[4] Iwatsubo, *supra* at 133.

[5] Rodelsperger, *supra* at 262.

[6] Lacourt, *supra.*

[7] *Callahan v. Cardinal Glennon Hosp.*, 863 S.W.2d 852, 860-61 (Mo. banc 1993) ("but for" causation applies except in cases when two independent torts are sufficient to cause the injury); *see also Harvey v. Washington*, 95 S.W.3d 93, 96 (Mo. banc 2003) ("but for" is the minimum causation requirement); *Vaughn v. N. Am. Sys., Inc.,* 869 S.W.2d 757, 759 (Mo. banc 1994) (same).

[8] V. Panduri et al, *P53 Mediates Amosite Asbestos-Induced Alveolar Epithelial Cell Mitochrondia-Regulated Apoptosis,* 34 American Journal of Respiratory Cell Molecular Biology 4: 443 (2006) (mechanisms for cause of asbestos diseases are not fully established).

[9] *Thacker v. UNR Industries*, 151 Ill.2d 343, 603 N.E.2d 449, 117 Ill.Dec. 379 (1992). *See Kraus v. Celotex Corp.,* 925 F. Supp. 646, 652 (E.D. Mo. 1996) (citing *Lohrmann*, 782 F.2d at 1162-63).

[10] *Bartel v. John Crane*, Inc., 316 F.Supp.2d 603 (N.D.Ohio 2004).

[11] *Lohrmann v. Pittsburgh Corning Corp.,* 782 F.2d 1156, 1163 (4th Cir. 1986).

[12] *E.I. du Pont de Nemours and Co. v. Robinson*, 923 S.W.2d 549 (Tex. 1995). *Merrell Dow Pharmaceuticals, Inc. v. Havner*, 953 S.W.2d 706 (1997). *BorgWarner Corp. v. Flores*, 232 S.W.3d 765 (Tex. 2007).

[13] Lehrer, *supra* at 55.

[14] *Id.*

[15] Lehrer, *supra* at 52.

[16] Lacourt, *supra*.

[17] *Id.*

[18] Ioannidis, *supra*.

[19] Rodlesperger, *supra* at 272.

[20] E. Ilgren et al, *Asbestos Related Mesothelioma: Evidence for a Threshold in Animals and Humans,* 13 Regulatory

A Note from HarrisMartin's Asbestos Editor

The preceding article is an abbreviated version of Mark Zellmer's commentary. For the full-length piece, please visit www.harrismartin.com and see Issue 124, March 2011, on the site's Asbestos Publication Archive Page.

Toxicology and Pharmacology 116, 119 (1991). K. Browne in Parkes Occupational Lung Disorders (Butterworth, Heineman) 481.

[21] J. Hansen et al, *Environmental Exposure to Crocidolite and Mesothelioma,* 157 American Journal of Respiratory Critical Care Medicine 69, 73 (1998).

[22] A. Whitehouse et al, *Environmental Exposure to Libby Asbestos and Mesotheliomas,* 51 American Journal of Industrial Medicine 880 (2008).

[23] *Id.* at 879.

[24] G. Taubes, *Epidemiology Faces Its Limits,* 269 Science 184, 185 (July 14, 1995).

[25] Quoted in Taubes, *supra* at 169.

[26] Ioannidis, *supra*.

[27] World Health Organization. Environmental Health Criteria 203. Chrysotile Asbestos. (Geneva: WHO, 1998).

[28] Taubes, *supra* at 167.

[29] A. Tsiouris et al, Malignant Pleural Mesothelioma: Current Concepts in Treatment, 4 Nature Clinical Practice Oncology 6:344, 345 (June, 2007) (mesothelioma is a "major social issue" due to "substantial media attention and large compensation claims . . . for . . . exposure to asbestos").

[30] A. Powers et al, *The Role of Environmental Carcinogens, Viruses and Genetic Predisposition in the Pathogenesis of Mesothelioma,* 1 Cancer Biology & Therapy 4: 348, 349 (July/August 2004)(discussing tendency of patients to err in remembering whether they have been exposed to asbestos).

[31] www.graphpad.com/articles/pvalue.htm. A p value of 0.05 does not show that there is only a 5 percent probability that the findings are due to chance, but, rather, that random sampling of identical populations would show a difference smaller than observed in 95 percent of experiments and larger in 5 percent of experiments.

[32] Ioannidis, *supra*.

"When all is considered, the subject studies are likely beyond the reach of appropriate epidemiology and should not be treated as reliable evidence in court..."

[33] S. Wacholder et al, *Assessing the Probability that a Positive Report is False: An Approach for Molecular Epidemiology Studies,* 96 Journal of the National Cancer Institute 6: 434 (March 17, 2004). Taubes, *supra* at 168.

[34] Quoted in G. Taubes, *supra* at 168

[35] Ioannidis, *supra*.

[36] J.C. McDonald et al, *The Epidemiology of Mesothelioma in Historical Context*, 9 European Respiratory Journal 1932, 1937 (1996).

[37] RR=p/q and OR=p(1-q)/q(1-p) where p is probability of the event in the subject group and q is the same in the control group. http://www.numberwatch.co.uk/rr&or.htm. Although the formula for odds ratios gives higher numbers than the formula for relative risk, that difference tends to narrow substantially as the percentage of the populations suffering the studied effect is smaller such as with asbestos associated diseases.

[38] Lehrer, *supra* at 55-56.

[39] Ioannidis, *supra.*

[40] J. Kukreja et al, *Malignant Pleural Mesothelioma: Overview of the North American and European Experience,* 14 Thoracic Surgery Clinics 4: 435 (November, 2004).

[41] Rodelsperger, *supra* at 272.

[42] Ioannidis, *supra*.

[43] Quoted in G. Taubes, *supra* at 164.

[44] *Id.*

[45] Lehrer, *supra* at 56.

[46] Ioannidis, *supra*.

[47] Rodelsperger, *supra*, at 272.

[48] Ioannidis, *supra*.

[49] *Id.*

[50] *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). *E.I. du Pont de Nemours and Co. v. Robinson*, 923 S.W.2d 549 (Tex. 1995). *State Board of Reg. v. McDonagh*, 123 S.W.3d 146 (Mo.banc 2003). *Donaldson v. CIPS*, 199 Ill2d 63, 767 N.E.2d 314, 262 Ill.Dec. 854 (2002).

[51] Lehrer, *supra* at 55.

[52] Quoted in D. Cugell et al, *Asbestos and the Pleura-A Review,* 125 Chest 3: 1103, 1107 (March, 2004).