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Abuse of Epidemiology:

Automobile Manufacturers Manufacture a Defense to Asbestos Liability

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Much of the "debate" about the relationship between asbestos exposure from automobile brake work and asbestos-induced cancer has been fueled by studies that have been funded by corporations with billions at stake in tort litigation. The authors explore how asbestos-lined brake manufacturers have corrupted medical literature to escape liability, analyzing studies funded by these companies to enable them to claim that work with asbestos brake linings never causes mesothelioma. They reveal how the companies have redefined scientific criteria for the determination of cause–effect relationships and manipulated scientific data to give the impression of an absence of effect. But the absence of evidence is not evidence of the absence of an effect. *Key words*: mesothelioma; asbestos; corruption; occupational health; brake mechanics.

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In recent years, thousands of automobile and "shade-tree" (amateur) mechanics have sought compensation for asbestos-related disease from manufacturers of asbestos-lined brakes. Despite the fact that these brakes are 40–70% asbestos, the brake manufacturers have vigorously denied that they contributed in any way to a single case of asbestos-caused disease.[1] The brake manufacturers have dismissed the fact that there is no known threshold of exposure associated with mesothelioma (a rare cancer of the pleura or peritoneum), and that in some cases the only documented worker exposures are those that have occurred as a result of exposures to asbestos from brakes.[2] Rather than accept the well-established scientific facts, the industry has funded scientists and lawyers to develop arguments and methods for defending against lawsuits brought by workers and their household members who have developed mesothelioma as a result of exposure to asbestos in brakes.[1,3–6] To support their arguments, the automobile manufacturers have hired consultants to reanalyze previously published hygiene and epidemiologic studies.[4–7]

Some manufacturers of asbestos-lined brakes—including GM, Ford, Daimler–Chrysler, and Bendix—have sponsored four notable examples of such research since the late 1990s. In 2001, Otto Wong, an epidemiologist working for a California-based health sciences company, fired the first salvo of their defense.[6] Although Wong's paper is couched as a critique of regulation of exposures to asbestos-lined brakes and EPA risk assessments, Bendix (an automobile brake manufacturer) first presented it as an expert report to defend against a lawsuit by a worker who had been exposed to asbestos brake linings and had contracted mesothelioma.[8] Three years later other manufacturers of asbestos-lined brakes (GM, Ford, and Chrysler) sponsored Goodman et al. to write a second brake-related lung cancer meta-analysis combined with a duplication of Wong's mesothelioma analysis.[5] The automobile companies then sponsored Hessel et al. to write a third paper which was an extension of a paper by Spirtas of the NIH that had already been included in Goodman et al. and Wong's meta-analysis.[4] Finally, the industry subsidized an incomplete analysis of historical exposures to asbestos in brake work.[3]

These companies have spent millions of dollars to generate these epidemiologic studies in order to refute claims of causation and thereby avoid compensation payments to victims and their families. Accordingly, all four papers demonstrate the use of two practices associated with the industry's involvement in scientific research: the redefinition of scientific criteria for the determination of cause–effect relationships and the manipulation of scientific data. In this paper we critique these methods, drawing examples from the first three of the four papers cited above. The first section delineates the process of redefinition of scientific criteria for determination of causation, followed by a more in-depth discussion of specific methods of scientific manipulation utilized in the studies by Goodman et al., Wong, and Hessel. As a whole, we analyze the value of this type of research in regard to its claims about the relationship between exposures to asbestos during brake work and induction of mesothelioma.

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REDEFINITION OF SCIENTIFIC CRITERIA FOR DETERMINATION OF CAUSE–EFFECT RELATIONSHIPS

This method, first developed by the tobacco industry, involves two parts.[9] First, industry lawyers and scientists redefine the type and amount of "proof" required to legally establish causation.[9] This is done by derogating unfavorable classes of evidence that are unfavorable to industries' litigation and regulatory positions and insisting that evidence that does not exist or is favorable to industry is most important or essential to establish a cause–effect relationship in court. For example, when a suspect carcinogen is found to cause cancer in human epidemiologic studies but not in animals, companies argue that animal studies are required to prove causation.[9] On the other hand when animal studies are positive and human epidemiology is incomplete or negative, companies argue that human evidence is required before the government can regulate the substance and before workers and others can be compensated.[9]

For example, tobacco companies argue that human epidemiologic studies cannot establish causation but instead only establish some "non-definitive" association between exposure to tobacco smoke and cancer.[10] They have argued that epidemiologic studies cannot distinguish a genetic link between the propensity to smoke and the propensity to contract cancer.[10] This critique of human epidemiologic studies is true, but irrelevant since there is no biologic basis for such speculation. On the other hand, when early researchers failed to induce cancer in animals that were exposed to tobacco smoke, tobacco companies insisted that only animal inhalation studies could "prove" causation.[10] After the now-famous beagle studies, these companies emphasized the importance of mechanistic understanding as a causal requirement.[10] They then argued that unless one could explain exactly how tobacco smoke caused cancer they had no "scientific proof" of causation.[10] Some chemical manufacturers have made comparable epistemological arguments when studies of their products have followed a similar fact pattern. In the early 1970s, for example, when researchers failed to induce cancer in animals following benzene exposure, industry expert witnesses stated that these missing animal data were required to establish that a substance was a human carcinogen.[11,12]

The second element of this method is industry's insistence on direct causal evidence related to specific forms of exposure in individual cohorts of workers. Human epidemiology is often lacking for most chemical-exposure cancer effects. Most chemical companies, therefore, argue that these missing "animal or other studies," or human studies in which the exposed workers are exposed to the substance in question only (a virtual impossibility), are required to establish proof of a cause–effect relationship. In the latter case, industry argues that animal and in vitro studies are rendered invalid as evidence of causation.[9] Since cancer effects have long latent periods and workers are generally subject to potential confounding exposures, these studies are rare and easily criticized.[9] When clear epidemiologic evidence of causation exists, as is the case of the relationship between asbestos and mesothelioma, companies and their experts have argued that before an injured worker can even file a claim for compensation two epidemiologic studies in similarly exposed individuals that find a statistically significant doubling of the risk must be published in peer-reviewed journals.[13] Some Texas courts have accepted this argument and even appear to require the publication of human epidemiologic studies for subgroups of particular industries with statistically significant rate ratios above two before a worker can even file a lawsuit.[14] Greenland calls the use of this criteria a "methodologic error that has become a social problem."[15]

These stringent legal requirements can be contrasted with the normal physician practice of assigning causation based on an analysis of all available evidence with no specific rate ratio or statistical requirements.[16] In general, practicing physicians attribute lung cancer causation to tobacco smoking if there is evidence of a history of smoking any cigarettes, regardless of brand, for often unspecified time frames prior to disease diagnosis.[9] Practicing physicians would not check to see whether a published, peer-reviewed paper showed that smoking ten cigarettes per day caused a statistically significant doubling of the risk of contracting lung cancer prior to making the determination that a patient's smoking had caused or contributed to his or her cancer. Physicians also take for granted that all brands smoked contributed to disease causation even in the absence of studies evaluating individual brands.

The asbestos-product manufacturers and their experts have constructed an epistemological straw man, asserting that epidemiologic evidence of causation is required in each and every worker cohort that has a documented excess exposure to a harmful substance before evidence of causation can be presented in court. Companies argue that, to prove causation, both the type of asbestos and the nature of exposure (same job, not just comparable exposure) must be clearly documented in an epidemiologic study as having a causal effect on the development of cancer.[13] Even the tobacco companies have not gone so far as to argue that an expert cannot assert that Virginia Slims cause a specific lung cancer subtype (e.g., bronchogenic cancer) in women absent an epidemiologic study of smokers of that particular cigarette showing a statistically significant twofold increased risk in that particular cohort of female smokers for that particular subtype of lung cancer. Yet the asbestos companies and their experts argue that separate cohort studies are needed to establish causation for the same disease for each fiber type and each product composed of that fiber despite the

fact that almost all workers are exposed to more than one fiber type from more that one product.[13]

As a result, companies and their experts attempt to show that exposures to asbestos from their product are somehow "different" or even irrelevant. Manufacturers argue that exposures to asbestos from their products are quantitatively or qualitatively unlike other asbestos exposures.[13] For example, asbestos in their products is "bound" or "degraded" or "decomposed" or "results in too low an exposure" to cause mesothelioma.[13] Unfortunately, some courts have adopted aspects of this reasoning.[17] In the case of chrysotile asbestos—the only fiber type that industry still claims does not cause mesothelioma—the argument that the particular type of asbestos in a company's product is different from other types is now generally recognized as the "amphibole hypothesis."[18–23] It is important to note that product manufacturers who used amosite fiber made similar arguments by claiming that there was insufficient epidemiologic evidence to establish that amosite caused mesothelioma.[24]

MANIPULATION OF SCIENTIFIC DATA—META-ANALYSIS AND EXPOSURE DATA MISREPRESENTATION

Manipulation of scientific data and misuse or reinterpretation of standard scientific reasoning is ubiquitous in the automobile industry–sponsored asbestos studies. The most common are: selection of inappropriate studies for re-analysis, selective presentation of study data, non-differential exposure-determination bias, inadequate sample size, comparison of an exposed cohort with an inappropriate control group, and misuse of confidence intervals. Here we present these strategies, illustrated with specific examples from the Bendix, Ford, General Motors, and Daimler–Chrysler studies.

Selective Presentation of Exposure Data

In his article, Wong outlines the "lack of exposure" argument as described in the previous section.[6] In doing so, however, he fails to report studies indicating that work with asbestos brake linings leads to exposures that have resulted in asbestos cancers in other occupational and non-occupational settings.[25] Wong not only ignores exposure studies whose results contradict his industry position; he also misrepresents the results of the studies he does report. He states that "studies have shown that brake lining dust contains little recognizable chrysotile fibers" and extrapolates from a few studies to claim that current exposures are "extremely low."[6] It is true that only some studies have examined decomposed (used) brakes; the heaviest exposure to asbestos occurs during the sanding and grinding of new brakes.[25] Of course, current exposures do not reflect past exposures or risk. Studies of workers' previous job activities reveal exposure levels hundreds of times higher than current permissible limits.[25] Wong cites some "data" from a 1987 Finnish study by Kauppinen and Korhonen by listing average fiber concentrations as <0.05 fibers/cc.[26] This study also found, however, that the grinding of brake linings produced asbestos concentrations as high as 125 fibers/cm^3. Kauppinen and Korhonen reported exposures up to 8.2 f/cm^3 during the cleaning of passenger-car drum brakes using a compressed air jet to remove brake dust.[26] (Unfortunately this is still a common practice in many nations, including the United States.) Average concentrations were between 0.1 and 0.2 f/cm^3 for truck and bus repair. The only data point Wong chose to report from this study represented average exposures during passenger-car repair. Contrary to Wong's misleading data selection and analysis, this study demonstrated that average asbestos concentrations in Finland may comply with TWA limits, but also showed that peak exposures often exceeded the OSHA excursion limit.[26]

Wong also selectively excerpts information from a paper by Agudo et al., whom he quotes stating, "Overall, 37% of cases of mesothelioma in our population are attributed to a sure (or almost sure) occupational exposure to asbestos and this proportion comes up to 62% when occupations with any probability of exposure are included." In turn, Wong concludes that "this observation underscores the high proportion of malignant mesothelioma cases not related to occupational exposure."[6] Wong makes this assertion but omits Agudo et al.'s subsequent qualifying sentence, which states, "Around 40% of cases of mesothelioma in our population could be due to causes other than occupational exposure to asbestos, although possibility of other occupational exposures in non-traditionally hazardous scenarios cannot be ruled out."

Manipulation of Meta-analysis: Inappropriate Study Selection and Selective Presentation of Data

Industry researchers can often influence results by careful selection of the epidemiologic studies they decide to evaluate. Studies favored by the industry perspective (those with negative results in regard to the relationship between exposure and cancers) are included, and others are ignored or derogated and then excluded. Goodman et al. and Wong reanalyzed a series of epidemiologic studies, claiming that they failed to find an association between brake work and an increased incidence of mesothelioma.[5,6] Both, however, disregard numerous methodologic problems in the individual studies they chose to incorporate in their analyses and ignore study limitations noted by the original authors. Furthermore, these authors selectively omit key information that undermines their conclusions and evidence.

Goodman et al. first attempt to evaluate the quality of 11 studies with potentially relevant information

about the relationship between brake work and mesothelioma. The authors use a self-created 11-point scale to evaluate the studies (the rating system allowed for negative scores). The highest ranked study—one of two purported "studies" based on "personal communications" by Goodman and Hessel themselves—garners a 5, out of 9. The scores for the rest of the studies included in the meta-analysis are unimpressive: 3, 4, 1, 4, 1, and 2, out of 9. Goodman et al. excluded studies that scored minus 1 (the rating system allowed for negative scores) but none of the included studies achieved a passing grade of 60% based on normal academic standards. Goodman et al. seem to believe that evaluating the studies in such a way somehow mitigates their underlying methodologic errors and inadequacies. Unfortunately, revealing errors is not the same as fixing them, and these studies, which were never designed to assess mesothelioma risk to brake-exposed workers, are beyond repair.

After this elaborate quality evaluation, Goodman et al. performed a meta-analysis using the same studies that Wong had reviewed three years before. They excluded two cohorts. The first of these was a study of 685 automobile mechanics that reported two mesotheliomas.[27] The second found a statistically significant excess of mesothelioma in mechanics with a reported rate ratio.[28]

Furthermore, Goodman and his colleagues present the data entirely out of context. The original authors of the underlying studies did not design them to examine the specific issue of exposure to asbestos during brake work and subsequent incidence of mesothelioma. The extraction, therefore, of occasional study participants who happen to be automobile mechanics not only lacks statistical power but cannot be independently used as concrete evidence proving the absence of a relationship between a complicated exposure and a potential outcome. Due to the inherent difficulty in determining asbestos exposure (especially in the case of brake work due to the large number of amateur brake jobs and part-time brake work that can easily go unnoticed when determining exposure) cohort studies must be specifically designed to address the issue of mesothelioma among those exposed to brake dust. Until such studies are conducted, it is wrong to conclude that epidemiologic studies fail to establish a relationship between brake work and asbestos-induced cancer. The converse, however, is not true. To paraphrase Karl Popper, finding a thousand white swans does not prove that all swans are white; the discovery of a single black swan disproves that hypothesis.[29] This is particularly true when a researcher is relying on studies of all bird species (all SIC codes) to determine the color of swans (risk in brake workers). As Lemen has shown, there are plenty of black swans in the context of asbestos-induced cancer; he has documented more than 220 published cases of mesothelioma in users of friction products.[25]

The automobile manufacturers have spent millions of dollars to reanalyze studies that were never designed to determine mesothelioma risk in brake mechanics. On the other hand, they have access to a cohort of their own and their dealers' workers, whose work involves the installation and repair of brakes. They are perfectly situated to use other demographically similar employees who work at these same facilities as a control population. In many cases they have access to medical and workers' compensation records that would allow them to efficiently conduct such a study. Why haven't they done so?*

Wong and Goodman et al. both exclude evidence from other epidemiologic studies that contradict their conclusions. Hansen, for example, examined the mortality of automobile mechanics and found an excess mortality from mesothelioma.[32] The study reported a single case of mesothelioma over a ten-year period among approximately 20,000 automobile mechanics, yet, because of the rarity of the disease, the authors concluded that, "asbestos exposure is known to occur during the replacement of brake linings, and the single case of pleural mesothelioma is an indication that this exposure has not been negligible."

Differential Exposure-determination Bias

In his meta-analysis Wong relied primarily on case–control studies that were fraught with problems of differential exposure-determination bias. Asbestos exposure is difficult to determine since many individuals are unaware of their exposures, especially in secondary cases in which an individual might inhale asbestos fibers from the clothing of a spouse or parent returning home from asbestos-related work. In the case of brake work, many individuals engage in part-time or amateur mechanic work, yet otherwise engage in other careers and may therefore be classified as unexposed if determination is based on a classical epidemiologic determination of "regular occupation." Of course the direction of any potential or actual bias is a key issue in analyzing its potential effect on the results of a study. Random exposure misclassification biases results towards the null. However, as we discuss below, in this case, because exposure is more often missed in the exposed cohort, the misclassification is likely to lead to an inverse relationship between exposure and disease.

In the case of mesothelioma, in which the time between diagnosis and death is usually a matter of months, retrospective study designs such as case–con-

*Or perhaps their lawyers have already conducted such a study and kept it secret. As has been noted, in tobacco litigation, company lawyers often contract with experts to conduct studies. If the studies are unfavorable the company does not have to produce these in litigation. The brake manufacturers' lawyers have funded and actually helped conduct some studies related to brake exposures.[30,31]

trol studies often require the interviewing of surrogates (spouse, children, etc) to determine exposure. Direct interviews of cases or controls are far more likely to uncover prior brake exposure than are interviews with surrogates. Individuals who did not work primarily as automobile mechanics are likely to be misclassified as unexposed if surrogate interviewees are unaware of any part-time or amateur brake work done earlier in life. Since mesothelioma cases are more likely to be deceased at the time of interview than controls, a differential exposure-determination bias may show that the "exposed" have less risk than the unexposed. Next-of-kin interviews are particularly subject to this result, since brake exposures often occur among "shade tree," occasional, or even high school mechanics in automobile repair courses. These exposures are more likely to be reported by patients themselves than by relatives, particularly children of patients. In many of the studies the researchers determined exposure from direct interview of controls, in comparison with greater reliance on interviews with survivors of mesothelioma patients. Next-of-kin interviews were therefore used more often to estimate exposure in mesothelioma patients than in controls. Since direct interviews are more likely to elicit a history of exposure to brakes than next-of-kin interviews, brake exposures are systematically more likely to be recorded for controls than cases. Goodman et al. acknowledge the problem of next-of-kin interview bias but omit any discussion of the fact that the consequence of this bias is a result showing that brake work protects against mesothelioma. This phenomenon is demonstrated by the fact that most of the studies Wong and Goodman et al. selected had rate ratios of less than one. Wong's overall point estimate was 0.90 (95% confidence interval 0.66–1.23), while Goodman et al. determined that exposure to brake dust produced a statistically significant and important reduction in the rate of mesothelioma of 0.67 (95% confidence interval 0.53–0.84) in all studies combined.† The finding that brake work reduces the risk of mesothelioma is a sign of systematic error in this meta-analysis, because exposure to asbestos brakes cannot reduce the risk of developing mesothelioma by 33%. That is, however, what these selected meta-analyzed data showed.

Other Bias Issues

The study conducted by Agudo and others, published in 2000, demonstrates how differential exposure determination can bias results when exposure histories of cases (who are dead or too sick to be interviewed directly) are more likely to be determined by surrogate interviews than are exposure histories for controls.[33] Forty-four percent of cases were deceased at the time of the study, and thus researchers determined their exposures through family-member interviews. Among the control group, however, the researchers directly interviewed all but one participant. Cases, therefore, may have been less likely to be classified as exposed, which would bias the resulting risk ratios to be less than one. In addition, the researchers considered only occupations that had been held for at least six consecutive months, meaning that workers with exposures from part-time or amateur brake jobs were omitted. This random misclassification biased the results of the study towards the null. The authors also assumed *without question* that brake work puts an individual at risk for asbestos exposure, by placing brake mechanics in the "risk of exposure" category in their analysis. The rate ratio for this entire category of asbestos-exposed workers was elevated, at 2.59, but the analysis of a small number of individuals within the category of at-risk occupations (i.e., the brake mechanics) cannot lead to any sound conclusions.

The study published in 1994 by Spirtas and others provides additional evidence that exposure-determination bias is a real threat to study validity.[34] In the study, younger cases had a higher attributable risk for mesothelioma from asbestos exposure than did older cases. This is likely to have resulted from more accurate exposure assessment among younger individuals, who were better able to remember more recent exposure events. Spirtas et al. did not include independent analyses of the members of the cohort who reported "brake lining work or repair" (105 of 741) because of the high rate of multiple asbestos exposures in this group.[34] Unlike the authors of the original study, Wong fails to note these non-brake exposures or the original authors' exclusion of these workers, and relies on these rejected data in his meta-analysis.[6]

The automobile manufacturers paid Hessel et al. to "update" the Spirtas cohort and reanalyze its brake-worker data in 2004.[4] The results of the analysis presented by Hessel and colleagues reveal the methodologic problems with the use of the NIH data set. First, the analysis of Hessel et al. indicated that non-occupational brake work prevented workers from developing mesothelioma (regression beta was -0.184). In addition, their analysis found that higher levels of exposure to asbestos among workers performing occupational brake work were more protective (regression beta was –0.307). In other words, these authors found a dose–response relationship between exposure to asbestos-lined brakes and reduced risk of mesothelioma. Of course, brake work cannot reduce workers' risk for contracting mesothelioma, and it certainly can't do this in a "dose"-dependent manner. The unbelievable dose–response relationship is further evidence that the study suffered from systematic error. Hessel and his colleagues also examined six other job categories of

† They found combined RRs of 0.92 (95% CI 0.55–1.56) in Tier I studies and 0.81 (95% CI 0.52–1.28) Tier II studies

asbestos-exposed workers, all of whom have been found to have developed asbestos-induced mesothelioma or other asbestos-related disease in other studies, including workers exposed to asbestos insulation in furnace or boiler installation or repair,[35,36] building demolition,[37,38] plumbing or heating repair,[39,40] elevator installation or repair,[41] production of asbestos textiles, and production of paper products.[42–45] In contrast to previous cohort studies, Hessel et al. found no increased risk of mesothelioma in workers performing these jobs. They found elevated odds ratios for shipbuilding and repair work (OR 6.04, CI 3.74–9.75) and insulation work (OR 3.38, CI 2.20–5.17). While elevated, these odds ratios are orders of magnitude lower than those found in cohort studies of these same two groups. For example, Selikoff found that about 10% of insulators died from mesothelioma, giving an approximate rate ratio of 1,000.[46] Thus, unless one is willing to believe that brake work protects against mesothelioma and that previous cohort studies of other job categories are wrong, Hessel et al. have provided results indicating that their method biases results to the null and/or reverses actual effects of exposure, turning harmful exposures into beneficial ones.

Teschke et al. used an occupation-classification scheme that may also have biased results towards the null.[47] The authors stated, "In addition, grouping of occupations was likely to result in non-differential misclassification, usually biasing risk estimates to the null value." Wong omitted this critical fact. The study is also another example of differential exposure-determination bias—the authors determined exposure histories for 13.6% of controls' histories of exposure were obtained through next-of-kin interviews, compared with 33% of cases. The study also had a higher non-participation rate among controls, which could lead to selection bias, and interviewers were not blinded to the case–control status of the interviewee, possibly leading to interviewer bias.

The Woitowitz and Rodelsperger study focused solely on the issue of a relationship between automobile mechanic work and mesothelioma.[48] Part of this study is of no value in determining the relationship between any asbestos exposure and mesothelioma because the authors used lung cancer patients as controls. Exposure status is likely to be similar among the control group and the cases, which would lead to little discernable difference in risk between the two groups, despite any real association that may exist between brake work and mesothelioma. Since asbestos exposure is a well-known risk factor for lung cancer, any mesothelioma case–control study with lung cancer patients as the control group will almost certainly produce results at or below the null. This study demonstrates this effect well, since the researchers used "population controls" as well as lung cancer patients as controls. The odds ratio (OR) for "hospital controls" was 0.75, almost half that for population controls, 1.32. Rather than report both results, Wong presented an average OR of 0.87. Goodman et al. published both ORs but included only the lower average in their meta-analysis.[5,6]

McDonald and McDonald conducted a case–control study, published in 1980, examining mesothelioma cases from Canada and the United States.[49] Like the Woitowitz and Rodelsperger study, this study relied on an inappropriate control group; control subjects were patients in cases diagnosed by pathologists in which "pulmonary metastases were present from a non-pulmonary malignant tumor."[18,19] For example, the control group may have included patients who had died from mesothelioma or other asbestos-induced malignancies such as laryngeal or colon cancer.[50,51] The choice of such controls biased results towards the null. In addition, the study reviewed occupational status only ten years prior to death. Since mesothelioma has a minimum latency period of about ten years, this study did not necessarily address any subject's most relevant exposures. McDonald et al. subsequently compared lung-fiber burdens between control and mesothelioma patients and found no statistically significant difference between the amounts of chrysotile, amosite or crocidolite.[52] This is further evidence that controls were not adequately chosen, since they were clearly exposed to as much asbestos as the 99 mesothelioma patients. This misclassification biases the results to the null.

Both Wong and Goodman et al. ignore other studies that reveal mesothelioma risk to brake-manufacturing workers. Since these authors base their argument for lack of risk on fiber length and the general issue of whether or not chrysotile can ever cause mesothelioma, they are clearly relevant. And while they are also compromised by numerous methodologic and other problems, they do show increased rates of mesothelioma in brake manufacturing workers.[53,54] Dodson has critiqued the "short fiber" argument elsewhere.[55] The risk to brake-manufacturing workers is relevant to the question of risk to brake-repair workers, since the fiber used in the manufacture of brakes is the same length as that in new brakes. If there is relevance to the short-fiber argument at all, it relates to exposures from used brakes. Brake-repair workers are exposed to fibers from both new and used brakes from tooling parts as well as blow-out of brake-wear dust.

In 1982, McDonald and Fry published results of a study of a Connecticut chrysotile asbestos brake-manufacturing factory and concluded that, "The failure to find a single mesothelioma among 1469 deaths in 4738 employees of the largest and oldest asbestos factory in the state suggests that chrysotile in the manufacture of friction products was not responsible for the problem."[54] In a study of three plants including the Connecticut plant, McDonald et al. reported "only" 0.1 cases of mesothelioma per 1,000 individuals in chrysotile asbestos factories over the course of approx-

imately 40 years [1/100,000 or 10 per million per year]. They then asserted that, "This finding supports much other evidence that amphibole are mainly responsible for mesothelioma whereas chrysotile has little or no mesothelioma-producing potential."[54] The authors present this evidence, however, without discussing the expected population rate for comparison. Teta et al. report an expected rate of 2.2 cases per million each year for the total population and 4 per million for Connecticut.[56] Comparisons with expected population rates are also problematic, since at least half of all mesothelioma cases are caused by occupational exposures to asbestos. The unexposed expected rate is no higher than 1 per million.[57] For a true comparison to be drawn, it would have to be with only those cases that were not occupational, since the risk of mesothelioma among automobile mechanics should not be compared with the risk of workers in other occupations known to cause the disease, but with those who were not occupationally exposed. The rate reported by McDonald et al. is therefore at least more than double the expected rate. McDonald's data thus support the claim that chrysotile asbestos causes mesothelioma.

The McDonalds' research suffered from other, more serious problems. In 1983, Teta et al. described findings from the state of Connecticut cancer registry and reported three mesothelioma deaths in the same Connecticut factory and during the same time frame used in the McDonald study.[56] One year after the publication of Teta's paper, in 1984, McDonald et al. published their "final" report on the plant. This "final" report, however, did not report the full data from the original cohort, which included both men and women, but reported data from the male portion of the cohort only.[58] Two "missed cases" occurred in women who were members of McDonald's cohort.[59] McDonald et al. reported that they had found not a single case of mesothelioma in this plant and failed to mention the cases Teta cited from the state of Connecticut registry.[53] In their 1982 paper, McDonald and Fry claimed their data were reliable, in large part due to the existence of the very same registry. They stated, "The opportunity for recognition of mesotheliomas was also very good at the chrysotile friction materials plant, as the state of Connecticut has maintained a renowned cancer register."[54] Clearly this would hold true only if the authors had checked the registry prior to the publication of their paper; unfortunately, it appears that they had not done so.[59,60] Teta et al. claim they informed them of the discrepancy and in 1986 McDonald tried to explain the omission away.[59] McDonald stated that she and her colleagues omitted the cases because mesothelioma had not been indicated on two of the deceaseds' death certificates, the primary measure of outcome in their study, and that they excluded the third case because he had terminated work prior to the beginning date of their study.[59] However, in 1986, by the time McDonald had commented on these discrepancies, at least two other cases of mesothelioma in the plant had been reported on death certificates (see Table 1, cases 1 and 2). Both fit the initial cohort definition and the first left employment before there was any alleged amphibole use. These cases occurred after the termination date of the McDonald study. We are now aware of at least six additional mesothelioma cases in workers from the plant, four of whom had no other possible exposures to asbestos (Table 1). At least four of these cases are known to the main sponsors of the McDonalds' research, since members of the Quebec Asbestos Mining Association (QAMA) were sued by three of them. Therefore, there were a total of at least nine mesotheliomas in this factory, which used chrysotile until 1957 only.‡ Perhaps by unfortunate coincidence, all of these cases occurred before or after the beginning and ending dates of the McDonalds' studies or the diagnoses were not reported on the death certificates.

Death certificates, in general, are often inadequate means of determining a mesothelioma diagnosis, due to the strong possibility of other related conditions' becoming the primary causes of death (e.g., cardiac arrest) and because mesothelioma is frequently misdiagnosed. Mesothelioma was not added as a specific ICD code until 1968.[61] The study was conducted in the 1970s, mostly examining data from prior decades, in which mesothelioma was a lesser-known disease that was frequently not accurately diagnosed. In addition, the Connecticut registry was an excellent source of data for a comparison of expected and plant rates. To make the data compatible, the registry should have been used to determine the mesothelioma rates for the plant workers. Had they done so, McDonald et al would not have missed the two mesothelioma cases that occurred during their selected observation period. Of course, the most important result of the exposure to chrysotile at this plant is the death of nine workers from mesothelioma in a population of about 4,500 workers. Although the McDonalds et al. stressed the importance of this cohort in asserting that chrysotile did not cause mesothelioma, these nine cases provide additional evidence that chrysotile causes mesothelioma.

Despite the fact that Teta is a co-author of one of the brake-manufacturer–funded papers and works for the company that generated three of these papers, the brake-manufacturer–funded researchers failed to use any of these studies or data to assess the hazard of exposure to chrysotile-lined brakes.[5,6] Other industry-funded researchers have also failed to use this information in assessing chrysotile risks. Recently, Crump and Berman completed a risk assessment for asbestos for the EPA.[62] To some extent this was an update of a previous assess-

‡Some anthophyllite was used beginning in 1957, and about 100 pound of crocidolite were used experimentally in the laboratory from 1964 to 1972.[53]

TABLE 1—Mesothelioma Case in a Chrysotile Brake Manufacturing Plant

	Date of Birth	Date of Diagnosis	Raymark Work Dates	Job Description	Other Exposures	Death Certificate/ Autopsy
Case 1	5/20/1908	5/21/1980	1926–1937	Office worker Shipping clerk	None: no known home repair, friction, or additional occupational exposures.	Left lobar pneumonia, mesothelioma
Case 2	7/7/1914	9/3/1985	1940–1985	Unknown	Unknown	Malignant mesothelioma
Case 3	4/21/1930	3/24/1994	1983–1984	Unknown	Was also exposed to asbestos in the Navy, and had other occupational exposures including EB, American Linen Supply, Upjohn and U.S. Rubber	Respiratory failure, mesothelioma
Case 4	9/15/1918	9/16/1996	1937–1962 1970–1968	Plant worker	None: worked in security and sales for other occupations; no known home repair or friction exposure	Respiratory failure, mesothelioma
Case 5	10/12/1991	5/24/1999	1940–1941	Carding/ spinning room laborer	None: truck driver and woodworker for other occupations	Mesothelioma
Case 6	9/23/1930	3/14/2000	1965–1985	Machine operator	None: no known home repair, friction or additional occupational exposures	Lung cancer Autopsy report: mesothelioma

Based on Lewinsohn's[62] Connecticut expected rate of 4 mesothelioma cases per million, the expected number of cases is 1.4, observed number is 9; therefore, the RR is 6.4 and $p < 0.05$.

ment they had done for the Asbestos Information Association, an asbestos industry lobby and public relations front, in 1984.[64] Berman and Crump ignored the published mesothelioma cases from the friction plant that McDonald had acknowledged in 1986, and based their dose–response analysis on the assumption that there were no cases in that plant,

> Perhaps the most interesting of the changes between the 1986 KL value estimates and the current KL value estimates involves the friction products plant in Connecticut (McDonald et al. 1984). Although a relatively small, positive exposure-response was estimated from this study in the 1986 Health Effects Update, the best current estimate is that this is essentially a negative study (no excess risk attributable to asbestos).[63]

Teta served as an official reviewer of Berman and Crump's paper, and although the omitted cases were noted in 1983, along with the need for further follow-up on this cohort, Teta recommended that the EPA adopt the Berman–Crump model before the cohort follow-up was performed.[65] The Berman–Crump model did not incorporate these 1983 data, and we have reported our partial follow-up of this population in this paper. Berman and Crump also relied on dose estimates from QAMA studies about which the authors themselves stated, "It remains doubtful, however, whether conversion [of particle dose estimates, the only measure of exposure in the QAMA studies] to a fibre equivalent can have much epidemiological validity."[66]

Inadequate Sample Size

Because of the broad nature of most of the studies, examining mesothelioma risks among many different occupational groups, the numbers used by Wong from each study (i.e., the number of garage mechanics in each study) is usually less than 25. Hessel et al. (the highest-rated study in Goodman et al.'s re-analysis) reports an OR for brake workers based on only two cases after "controlling" for insulation and shipbuilding exposure and on a single case after controlling for all other potential asbestos exposures. Any conclusions relative to safety based on these tiny sample sizes are reckless.

Use of Inappropriate Control Group

It is extremely difficult to find a comparable control group for hospitalized mesothelioma cases. Due to the rarity of the condition, mesothelioma cases are often referred to large medical centers. Some hospital controls who do not have "rare" diseases will not reflect the true demographics of the desired denominator population. Patients with mesothelioma are often referred from rural or suburban to urban hospitals for diagnosis or treatment. Patients from these urban environments are likely to be overrepresented in the control

group and are more likely to have been exposed to brakes than the rural or suburban neighbors of the cases (controls that more accurately reflect the demographics of the cases). This effect helps explain how all but one of the studies Wong and Goodman et al. analyzed found that brake work reduced the risk of the development of mesothelioma.

Misuse of Confidence Intervals

Almost all of the studies reviewed report confidence intervals that include a rate ratio greater than one.[5,6] When risk ratios are being calculated on small samples, point estimates cannot be considered particularly accurate, and examination of confidence intervals is more important in determining risk. Wong and Goodman et al., however, mention these confidence intervals only in passing and base their entire analysis on point estimates.

DISCUSSION

Despite the clear methodologic problems with the above-mentioned studies used in their meta-analyses, Goodman et al. and Wong present them as unquestionable evidence of the absence of an association between brake work and mesothelioma.[5,6] None of the studies used was designed specifically to examine this association, bringing in the possibility that unknown confounders could be at play. Despite this, Wong presents the studies under the heading of "Epidemiologic Studies of Mesothelioma among Auto Mechanics" and Goodman et al. title their paper, "Mesothelioma and Lung Cancer among Motor Vehicle Mechanics: A Meta-analysis." As we have shown, a study that is not designed specifically to determine brake-work exposure is likely to be fraught with bias due to the complexity of exposure determination.

The World Trade Organization issued a ruling on the matter in September 2000, after extensive expert testimony led to a conclusion that chrysotile asbestos does produce a real risk of mesothelioma to mechanics.[67] The ruling allowed European countries to ban the use of asbestos-containing brakes. Both papers omit this information as well.

After publication of Wong's paper but before the publication of that of Goodman et al., considerable evidence emerged from studies conducted in Australia by Leigh et al. supporting an association between automobile mechanic work and mesothelioma. Of the approximately 6,000 individuals in Australia's extensive mesothelioma death registry, 1.2% were automobile mechanics.[68–70] For many, the only source of asbestos exposure was brake-lining repair.[68,69] In a number of individuals examined, only chrysotile asbestos fibers were found, indicating that chrysotile exposure alone can cause malignancy.[69]

On the whole, Wong and Goodman et al. fail to adequately address the issue of the relationship between brake work and mesothelioma. The small numbers of individuals pulled from larger studies, from which Wong reports risk ratios to support his argument, lack statistical power as well as epidemiologic meaning due to the large amount of potential bias. The meta-analyses begin to the address the problem of a lack of statistical power. However, since the data used for the analysis are handpicked from the literature to the exclusion of contrary evidence, and those that are included are likely to suffer from various types of bias, the results reported are not reliable. Until prospective cohort studies specifically designed to determine asbestos exposure from brake-lining installation and repair are conducted, definite conclusions about the magnitude of this risk cannot be made. It is clear that a risk exists.[25]

Moreover, the entire argument addressed by these analyses, regarding the risks of chrysotile, is specious in light of the following undisputed facts:

1. Chrysotile causes lung cancer.[72]
2. Chrysotile causes asbestosis.[72–74]
3. Chrysotile used in the United States is contaminated with tremolite—an amphibole.[75]
4. Products made from chrysotile contain tremolite.[76]
5. Chrysotile is concentrated in the pleura.[77]
6. Populations with mixed exposures to amphiboles and chrysotile have double the rate of mesothelioma of those exposed to amphibole alone.[78–80]
7. Brake-repair workers get substantial airborne asbestos exposures from grinding brake and clutch parts and blowing out dust from brake assemblies.[25]

Almost all brake workers have had some exposure to amphibole with, or as well as, chrysotile. Thus, even if chrysotile alone is not a cause of mesothelioma it acts synergistically with amphiboles to increase the incidence of this cancer.

CONCLUSION

The methods utilized by the asbestos and related industries—the redefinition of scientific criteria for determining cause–effect relationships and the manipulation of scientific data and scientific inferences—have obscured the true picture regarding asbestos exposure and mesothelioma. In contrast to their experts' opinions, the relationship between exposure to asbestos and mesothelioma has long since been recognized by the brake-industry executives who retained Goodman et al. and Wong.[5,6] In his 1973 private presidential address to brake manufacturers, Ike Weaver, the Chairman of the Asbestos Study Committee of the Friction Materials Standards Institute, an industry trade organization, noted the importance of this phenomenon:

> I know of no way any of us can be absolutely sure that his friction products, regardless of whether they are sold as original equipment or on the replace-

ment market, will not be subjected to additional operations or alterations in the field that could result in excessive exposure of workers or bystanders to airborne asbestos fibre. I have been appalled to learn of a number of instances where this problem has occurred, and some of these cases involved people that certainly might have been expected to know better. . . .

If this kind of thing occurs in fabrication operations of major OE [original equipment] customers, it appears to me there can be no argument about the need for educational measures to reduce chances of unnecessary exposure during grinding, drilling, or cutting operations. To those who argue that labeling or other types of warning need not apply to replacement materials because fabricators or appliers handling replacement quantities are exposed relatively intermittently, I say emphatically this just ain't necessarily so! Large volume replacement users present major potential hazards, and even small job shops can needlessly expose people to high fibre concentrations if operations are performed without controls.[81]

Despite the secret industry acknowledgement of risk and high exposures, Goodman et al. and Wong manipulate epidemiologic science to conclude that exposure to asbestos from brakes does not induce asbestos-related malignancies. As we and others have noted, absence of evidence is not evidence of absence; in other words, failing to find an association does not provide any evidence that an association does not exist.[82] Once it is generally accepted that a substance can cause disease in humans, all that is required to establish causation is documentation of exposure to that substance. For example, the OSHA benzene standard did not require epidemiologic evidence of cancer risk in every sector covered by the standard.[83] In the case of vinyl chloride, chemical companies themselves removed the compound as a propellant in hair sprays based on animal studies alone because of the risk of unlimited liability.[84] The asbestos industry and the automobile industry, rather than hiding behind a "dust cloud" of misleading science, should do the same and stop using asbestos in brakes worldwide.

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14. For Appellees: Lynne Liberto, Houston, TX, Hector H. Cardenas, Austin, TX, R. O. Faulk, Houston, TX, and For Appellants: Richard H. Cardenas, Austin TX. Virginia Hernandez Frias Individually, and as next friend of Nicholas Brian Frias and Thomas Isaac Frias, George Anthony Frias, Jesse Valentin Frias Steven Simon Frias, Carlos Jesus Frias, Christina Mejia, and Jose Manuel Galvan, as representative of the estate of Jesus Valentin Frias, *Appellants v Atlantic Richfield Company, Lyondell Petrochemical Company, and Lyondell-Citgo Refining Company Ltd.* Appellees 2005. 104 S.W.3d 925; 2003 Tex. App. LEXIS 4115, Court of Appeals of Texas, Fourteenth District, Houston. May 15, 2003.
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