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# Mesothelioma from Asbestos Exposure in Brake Mechanics: Epidemiology in Context

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**Abstract**

Asbestos causes pleural and peritoneal malignant mesothelioma, in addition to lung cancer, other cancers and asbestosis and pleural plaques. Multiple scientific disciplines have made significant contributions to the strength of the cancer causality consensus conclusion which has led many countries to ban the use of asbestos. Epidemiology has been applied to the study of automobile repair workers who have been exposed to asbestos from the replacement and installation of brakes containing asbestos. It is important to clear up the misunderstandings of the limits of epidemiology methods and their interpretation in the investigation of brake repair workers in order to prevent mesothelioma and other asbestos diseases in developing countries which are continuing to use asbestos in brake pads and for other uses.

**Keywords:** Asbestos; Mesothelioma; Automobiles; Developing countries; Epidemiology

## Introduction

Chrysotile asbestos has been used in vehicle brakes since the 1940's in the United States, Canada, Europe and Australia. Brake repair and installation workers have been exposed to asbestos during many procedures utilized during the removal of the existing brakes and the installation of new brakes. Even though the epidemiology of asbestos exposure and resulting asbestosis, pleural plaques, mesothelioma, lung cancer and other cancers is well established, clarity using epidemiology alone has been elusive specifically for brake worker asbestos exposure and mesothelioma causation. The lack of understanding of the epidemiology of asbestos exposure in brake repair workers is especially important given the expansion in developing countries of asbestos use. It is imperative that the epidemiology of mesothelioma causation be clearly understood in order to have the knowledge to adequately protect workers in India, Pakistan, Thailand and other countries where there is large scale continued and even expanding use of asbestos, including use in automobile and truck brake pads [1-6].

Concerning mesothelioma causation and asbestos exposure generally, there have been many successful well-known epidemiology studies of mesothelioma causation which have characterized three significant exposure circumstances, occupational (direct and bystander), para-occupational (household or family), environmental and community (neighborhoods of industrial or mining activity). Unfortunately, the situation has appeared problematic to some when it comes to the application of epidemiology to mesothelioma from exposure to asbestos from brake repair and replacement with different analytic approaches providing apparently inconsistent results. Here we describe the history of application of epidemiology to automobile brake worker exposure to asbestos and mesothelioma causation and attempt to offer scientific clarity in this area of asbestos worker exposure where application of epidemiology has been frankly less than successful. The lack of adequate studies of the workforce of brake repair workers has led to misunderstanding and deliberate false policy concerning the possible safe use of chrysotile asbestos in such things as brake pads. Clearing up this issue is of crucial importance in so called "developing" countries where the use of chrysotile asbestos is continuing and even increasing. As epidemiologists, we offer a review of the important studies and commentary as they apply to the issue of the epidemiology of mesothelioma.

Lemen [7] and Egilman and Billings [8] reviewed the epidemiology of brake workers and mesothelioma. In the over 13 years since those reviews, given the size of the impacted past and current worker population, there are surprisingly few new brake worker epidemiology studies other than attempts to apply meta-analyses to existing data sets. This is despite the advancements made in mesothelioma surveillance with multiple comprehensive national mesothelioma registries now operational which have provided epidemiologists analytic data to better characterize dose-response relationships between asbestos exposure and mesothelioma, continuing to document the lack of an exposure threshold for mesothelioma, and to identify previously unrecognized asbestos exposure circumstances.

A core occupational medicine principle is that the exposure to a hazardous material and not the worker's job title causes injury. Since Bernardo Ramazzini's book [9] on occupational diseases in 1713, it has been clear to occupational health professionals that obtaining an individual lifetime occupational and environmental exposure history has been crucial to understanding individual work-related causes of disease. Obtaining such a history would appear to be a simple task, but is made difficult because such histories are rarely maintained prospectively for individuals in worksite or in health care records or in other administrative records. Commonly such histories are only obtained retrospectively when individual disease is under investigation. Unfortunately, workers often do not know the constituents in the materials they have handled and may not recall past work activity or personal activity such as doing automobile maintenance and repairs. Exposure characterization is crucial to successful application of epidemiological principles to understand occupational and environmental health hazards.

Once an exposure is known to cause a disease, it is important to be able to identify whether an individual with that disease has experienced the known causal exposure. This is especially problematic for diseases such as malignant mesothelioma which occurs late in life after a long latency (time between exposure and disease recognition) and has no exposure threshold for the disease. Asbestos exposures as short as one day [10] have caused mesothelioma, and as many as 3% of cases may only have had 3 months or less of exposure [11]. Identifying past asbestos exposures retrospectively when malignant mesothelioma is diagnosed remains challenging. Underscoring the challenge in identifying a source of asbestos exposures are the many observations of high lung burdens of asbestos fibers, indicating substantial asbestos exposure reported in individuals with uncertain sources of exposure [12,13]. Mesothelioma from exposure to asbestos from replacing worn brakes in automobiles is a public health issue potentially affecting more than 730,000 documented workers in the U.S. [14] with perhaps millions of others exposed in doing non-professional brake replacement, sometimes called shade tree mechanics [7]. Worldwide, asbestos use is expanding in countries such as India, Thailand and Pakistan where millions are potentially exposed without proper industrial hygiene protections [1-6].

The seminal publication associating mesothelioma of the pleura and peritoneum to exposure to asbestos was Wagner et al. [15] in 1960. Over 50 years later, there is overwhelming evidence that asbestos is responsible for this fatal cancer. Mesothelioma from asbestos is the most definitive example of an environmental cause-effect cancer, involving a quickly fatal disease that has a very long latent period. Due to the extensive occupational, community and para-occupational exposures to asbestos, a worldwide epidemic of mesothelioma has been reported [1,6,16-19].

Asbestos has two main types, the serpentines (of which chrysotile is the most common) and the amphiboles, which include crocidolite, amosite, tremolite, anthophyllite and actinolite. Chrysotile asbestos has comprised 95% of world asbestos production, largely in the past from Canada, but also from mines in several other countries around the world [20,21]. There is general agreement among scientists and health agencies that exposure to any type of asbestos (chrysotile or amphibole) can increase the likelihood of lung cancer, mesothelioma, and nonmalignant lung and pleural disorders [1,6,19,21-26].

There are numerous epidemiological studies that have clearly linked all types of asbestos, including crocidolite, amosite and chrysotile, to pleural and peritoneal mesothelioma [20,24]. This conclusion is supported by international groups of experts in their consensus reports [21,27-29]. The global magnitude of mesothelioma is estimated to be 38,900 in a group of 33 countries that report the disease. The actual number of cases is probably much greater as one mesothelioma is missed in every four or five reported cases because of the difficulty in establishing a pathologic diagnosis [17].

It is the consensus of the medical and scientific community that there is no known threshold of exposure below which mesothelioma will not occur [30-32]. Multiple studies have shown that all levels of exposure to asbestos increase the risk of mesothelioma [21,33,34]. Since there is no known threshold, current regulatory levels for asbestos are capable of causing mesothelioma and this is recognized in the support documentation for enforcement standards [35]. Brief or low exposures to asbestos are capable of causing mesothelioma [36,37]. Lacourt et al. [38] found a four-fold increased risk of mesothelioma at cumulative exposure levels less than 0.1 f/cc/yrs. Mesothelioma incidence is proportional to cumulative asbestos exposure [28,29,39]. Intensity and duration of asbestos exposure are determinant of mesothelioma risk [29].

The mainstream scientific community has concluded that there is no safe level of exposure to asbestos of any type and that an occupational history of brief or low-level exposure should be considered sufficient for mesothelioma to be designated occupationally related to asbestos exposure [27].

## Exposure

Chrysotile asbestos has been the predominant type used in vehicle brakes since the 1940's in the United States, Canada, Europe and Australia [7,40]. Typically, drum and disc brakes contained between 35 to 60% asbestos [1]. Workers repairing brakes are exposed to asbestos during a number of procedures utilized during the removal of the existing brakes and the installation of new brakes which contain asbestos.

During the removal of the existing brakes, a common practice has been the use of compressed air to blowout the dust that had accumulated in the wheel well overtime during the braking process. The major component of this brake dust is a particulate substance known as forsterite, a non-fibrous magnesium silicate that is created by the transformation of chrysotile asbestos during the heat and pressure of braking [41]. Not all of the chrysotile asbestos, however, is transformed. Researchers from General Motors Corporation, reported finding 90,000 unaltered chrysotile asbestos fibers in a nanogram of brake dust, the small fibers (less than 5 microns in length) outnumbering the longer fibers (5 microns and greater) at a rate of 300 to 1.7 For every gram of brake dust, this translates to the equivalent of 90 trillion short asbestos fibers and 300 billion long asbestos fibers [7].

During the installation of the new asbestos containing brakes, workers often manipulate the surface through beveling, sanding and/or grinding to insure a proper fit. The manipulation of the new brakes using these techniques does not result in the transformation of the chrysotile asbestos into forsterite but rather liberates free floating chrysotile fibers into the worker's environment [7].

The first published studies documenting the amount of asbestos generated from the repair and replacement of brakes did not occur until 1970 [40]. Since that time, repeated measurements of the dust generated from removing old brake linings and manipulating the new brake linings prior to installation have confirmed the presence of significant levels of asbestos fibers in the workplace. For example, Rohl et al. [41] measured fibers in dust samples from car brake drums and found chrysotile in all samples. In addition, measurable concentrations of asbestos were found up to 75 feet from where the compressed air was being used during the blowout of this brake dust. Concentrations in the brake dust averaged 16 fibers/ml of air. Lorimer et al. [42] measured mean fiber concentrations of 3.8 fibers/ml among New York City brake repair workers. In Finland, researchers found that the use of an air hose to clean out the brake dust before the brakes were removed could create a cloud of visible dust leading to airborne concentrations of 8.2 f/cm$^3$ in the immediate vicinity of where the work was being performed. They further found that the grinding of brake linings prior to installation led to asbestos fiber counts as high as 125 fibers/cm$^3$ [43].

Gustavsson et al. [44] conducted personal monitoring for asbestos during brake repair and reconstruction modeling of previous exposures from working in bus garages as part of a study of Swedish bus garage workers. The cumulative mean exposure was approximately 2.2 fibers per milliliter and the maximum was 6.0 fibers per milliliter. These exposures are in the millions of fibers per day in the bus garage workplace air. Atkinson et al. [45] conducted an experiment to evaluate the potential of asbestos to be released from the manipulation of brake components. Samples were collected from each brake component by gently rinsing the exposed surface with water from a squeeze bottle. The wash was then analyzed by analytical transmission electron microscopy (TEM) for chrysotile asbestos fibrils, bundles, clusters and matrices. X-ray energy dispersive analysis and selected area diffraction was used to confirm the presence of chrysotile asbestos. The samples contained from 44.7% to 76.1% chrysotile asbestos particulates with the mean length of fibrils being less than 4 microns, a size that can be taken deep into the respiratory system and thus pose a respiratory hazard. Since the manipulation in this study was simple rinsing, and not the usual more aggressive procedures used to prepare the brakes for installation, like beveling, grinding, and sanding, the authors concluded that brake installation and repair would lead to release of large numbers of chrysotile asbestos that posed a respiratory hazard to workers.

Cely-Garcia et al. [46] conducted personal monitoring for asbestos in three brake repair shops in Bogota Columbia. Standardized NIOSH methods were used to measure full shift (8 hour TWA) and short term (30 min) exposures. Personal asbestos concentrations based on transmission electron microscopy counts were “extremely high, ranging from 0.006 to 3.493 $fcm^{-3}$ for 8-h TWA and from 0.015 to 8.835 $fcm^{-3}$ for 30 minute samples.” All asbestos fibers detected were chrysotile. Cleaning and grinding facilities showed the highest counts [46].

Although a significant portion of the chrysotile asbestos fibers generated during brake replacement are shorter than 5 microns, a review by Dodson et al. [47] describing the work of many scientists makes it clear that these small chrysotile small fibers are capable of carcinogenicity. Moreover, it has been shown that these small chrysotile fibers migrate to the pleura from the lung and that they can contribute to the development of mesothelioma [48-50]. A comprehensive review of the literature on asbestos fiber size and toxicity concluded that the toxicity of short asbestos fibers cannot be dismissed [51].

It is universally accepted that it takes a greater exposure to asbestos to cause asbestosis and pleural plaques than the amount needed to cause mesothelioma [30]. Brake repair and clutch lining workers have been diagnosed with both pleural plaques [52,53] and asbestosis [42,54,55] indications that their exposures to asbestos were significant. Where there has been excess respiratory impairment, workers have definitely been exposed to asbestos levels high enough to cause mesothelioma [56]. As a result of the documented exposures to asbestos from friction materials in auto repair, Huncharek [57] reported a forecast of 20,000 deaths from asbestos-related cancers among auto mechanics during the next 40 years in the United States.

## Epidemiology Research Methods

As is often the case in epidemiological research, not all studies have reported statistically significant excess mesotheliomas in classes of workers such as auto mechanics. This is especially true when an unknown proportion of the worker class being assessed may not be exposed to the agent being studied. Brake repair work is included within the class of auto mechanics, but not all auto mechanics would be considered brake repair workers. The differences in results can often be explained by the fact that epidemiologic research methods have not been adequately applied to the question of whether auto mechanics are at an increased risk of mesothelioma. Many of the studies cited for the proposition that exposure to asbestos from brakes cannot cause mesothelioma, are plagued by issues of inadequate study design, methodological flaws, small study size, lack of accurate and complete work histories, using occupation as surrogate for exposure, difficulty of mesothelioma diagnosis and other weaknesses [8,32,58]. There have been review articles, re-analyses of previous studies and meta-analyses that conclude there is no hazard of mesothelioma among workers whose work includes brake repair, which are compilations of studies that were not designed to answer that question [59-64].

### Case reports and case series

Medical case reports of rare diseases or causes of death historically have often alerted the occupational research community to investigate possible causal factors. According to Checkoway et al. [65] case series reports are particularly informative in situations where there are identified occurrences of very rare conditions for which there are few, if any, established causal factors. In those instances, even a small number of cases" can sometimes be invoked as prima facie evidence of exposure to the putative causal agent". Mesothelioma is one of the two diseases Checkoway et al. [65] uses as an example of this principle. In fact, the Wagner et al. [15] case series from South Africa, has been widely regarded as sufficient to causally tie asbestos to mesothelioma, since mesothelioma had previously been such a rarely reported disease and exposure to asbestos was present in every case. Ever since Wagner et al. [15] mesothelioma has been considered a sentinel for asbestos exposure.

There have been many published case reports and case series concerning mesothelioma in workers whose activities included brake installation and repair, their family members and even their pets. Newhouse and Thompson [66] studied a series of 83 patients from the London Hospital with a diagnosis of confirmed mesothelioma. One male case worked in the manufacturing of brake linings. Godwin and Jagatic [67] describe a peritoneal mesothelioma in a 43 year old woman who had spent three years weaving brake linings made of chrysotile asbestos. Greenberg and Davies [10] report mesothelioma in a motor mechanic. In a study of 52 mesothelioma cases of females from New York State, Vianna and Polan [68] found two women whose husbands had exposure to brake linings, and another who was a textile worker and whose husband was a brake lining worker. In a nested case-control study which included these three women, the authors found that this pattern of exposure yielded an estimated relative risk of 10 with a 95% CI of 1.42 to 37.40. Langer and McCaughey [69] described the case of a diffuse pleural mesothelioma in a 55 year old male who had worked in the car, tire and car repair business since the age of 19. He routinely had done replacement of brake linings, and he had no other known source of asbestos exposure history. The authors report their analysis of lung tissue showed the presence of chrysotile fibers and no amphibole fibers by electron diffraction. Cutler [70] describes the case of a mesothelioma in a 12-year-old child who was exposed to brake drum dust from work his father (a heavy goods vehicle mechanic) brought home. In eighteen dogs with mesothelioma identified from veterinary hospital records, Glickman et al. [71] identified two German shepherds whose owners were automobile mechanics, another German shepherd who accompanied his owner to his auto body and used parts supply business, and a mixed breed whose owner was involved in auto body repair.

Huncharek et al. [72] found a pleural mesothelioma in a 47 yr old male who's only known exposure to asbestos was as auto mechanic from age 30-41. That would be a latent period of 17 years. Muscat and Wynder [73] described a case of mesothelioma in a woman married to an automobile mechanic. Rees et al. [74] identified a motor vehicle mechanic among 123 mesothelioma cases in South Africa. Maltoni et al. [75] describe "a case of pleural mesothelioma arising in the wife of a garage mechanic professionally exposed to asbestos present in brakes and clutch discs". Burdorf et al. [76] describe the occupational background of mesothelioma cases collected by two law firms. 5 of the cases are listed as car mechanic. Okura et al. [77] report on a 61-year-old man with mesothelioma who had worked at a car repair shop dealing with brakes and clutches from 1963 to 1970. Ruiz-Tirado et al. [78] describe an 88 year old woman with peritoneal mesothelioma whose husband worked in the automotive industry as a brake specialist. Roggli et al. [12] report on exposure histories of 1445 cases of mesothelioma obtained from litigation files. 51 of these cases were listed in the category automotive industry which included auto mechanic, brake repair worker, brake line worker. 24 of the 51 cases had this as their sole occupation [12].

## Registries

Many countries have established registries to gather information about the incidence of cancers including mesothelioma. Like a case series, these registries collect cases of mesothelioma as well as some limited information regarding the occupation. Also, like a case series, no comparison is made to a control group. These registries typically contain a portion of mesothelioma cases where the individual was engaged in automotive repair work.

Malker et al. [79] conducted a systematic assessment of pleural mesothelioma occurrence in Sweden from national population-based registries linking cancer incidence from 1961 to 1979 with 1960 census data. Based on finding of 16 cases of mesothelioma in the category of mechanics and repairmen, the authors calculated a standard incidence ratio (SIR) of 2.4, more than double the expected incidence. The authors, however, did not specify how many of those cases occurred in automotive mechanics. Neumann et al. [80] found 48 mesotheliomas in the German mesothelioma register 1987-1999 (1605 total mesotheliomas) that worked in the automobile sector. The mean age of these 48 cases was 57.8, with a mean latent period of 35.7 years. Leigh et al. [11] studied the 6329 mesothelioma cases on the Australian National Mesothelioma Registry 1945-2000. 77 of the cases had documented exposures to brake linings in their work, with 58 having brake lining work as their only occupational exposure to asbestos. Using this data from the Australian mesothelioma registry, Dr. Douglas Henderson, an appointed expert for the World Trade Organization, calculated that vehicle mechanics doing brake work have approximately a 10-fold increased risk of contracting mesothelioma as compared to the general population [81].

Goldberg et al. [82] studied the industry and occupation in the French National Mesothelioma Surveillance Program (PNSM). 6.66% were in the transportation and communication economic sector. In 2009, the PNSM listed 29 motor vehicle mechanics in the registry [83]. Pan et al. [84] studied mesothelioma cases from the California Cancer Registry. 46 of the cases were classified occupationally as mechanics. There is no indication of how many, if any, of these mechanics were involved in automotive repair. Pukkala et al. [85] studied 45 (1961-2005) years of cancer incidence in the Nordic countries of Denmark, Finland, Iceland, Norway and Sweden. There were 6017 pleura/peritoneal mesotheliomas recorded in total. By occupational category, 85 were listed as transport workers, and 851 as mechanics. Again, the authors did not indicate how many of the transport workers or mechanics were involved with repairing automobiles or trucks.

## Case-control studies

Epidemiologists often rely on estimating relative risk by comparing reconstructed past exposure histories of persons with the disease or cause of death of interest (cases) to persons free of that disease or cause of death (controls). These retrospective case-control studies are not designed with the intent of determining the risk of disease for any specific occupation. Instead, the researchers work backwards from a collection of cases with the disease with the intent of uncovering occupations or exposures that appear more frequently in the case group than the control group. Since all the data is gathered retrospectively, relative risk cannot be directly calculated in case-control studies, but is estimated by a biostatistical measure called the odds ratio.

These types of epidemiologic studies can be useful but often are prone to the possibility of exposure misclassification, i.e., the exposure data is inaccurate for the cases, controls or both. In the case of mesothelioma, exposure misclassification is likely because the exposure data is reconstructed from the distant past. Given the short life expectancy of an individual diagnosed with mesothelioma, the cases are often deceased at the time of the study and researchers have to rely upon the memory of relatives or friends to reconstruct the deceased worker's exposure. Relying upon relatives and friends of mesothelioma victims for an occupational exposure history as compared to interview with often live controls can lead to a differential bias in exposure information (differential exposure misclassification) [86]. Non-differential exposure misclassification can occur if both cases and controls lack precise ways of collecting information about past exposures [87].

Exposure misclassification plagues most of the case-control studies cited for the proposition that brake mechanics are not at risk for mesothelioma. McDonald and McDonald [88] conducted a matched case-control study in North America and found 11 mesothelioma cases in the category of garage workers as compared to 12 in the control group. Since the category of garage workers is not limited to only those workers who replaced brakes, there is a strong probability of non-differential exposure misclassification which tends to underestimate any risk of producing a false negative finding [87]. A prior McDonald et al. [89] study utilizing the more specific occupational category of installation of brake linings, on the other hand, found an increased risk of mesothelioma.

Teta et al. [90] studied 201 cases of mesothelioma from the Connecticut Tumor Registry. For the category of automobile repair and related service, the authors calculated a relative risk of 0.65 (95% CI 0.08 to 5.53). The extremely wide confidence interval is a consequence of the limited amount of cases in the study related to automobile repair-6, a figure that included both cases and controls. The authors acknowledged that a major difficulty in their non-interview retrospective study relate to the inadequacy of occupational histories and the potential for misclassification of exposure status. They further conceded that the true magnitude of the RR [relative risk] is likely to be higher than [their] findings indicate [90].

Spirtas et al. [91,92] conducted a case-control study of malignant mesothelioma cases from the Los Angeles County Cancer Surveillance Program, the New York State Cancer Registry, and 39 large Veterans Administration hospitals that was based upon information from telephone interviews of next-of-kin. These interviews yielded 33 mesothelioma cases that had a reported history of "Brake lining work or repair". The authors did not calculate an odds ratio specific for this exposure. Ten years later, Hessel et al. [62] after eliminating 5 cases, ascertained that all but one of the remaining 28 mesothelioma cases with brake lining exposure had a history of asbestos exposure as insulators or in shipbuilding.

Woitowitz and Rodelsperger [93] reported on 16 mesothelioma cases that were classified as either motor vehicle mechanics or motor vehicle repair workers. Without revealing any odds ratios, the authors concluded that there was no evidence that car mechanics are exposed to an increased risk of mesothelioma even if they do brake repairs. The difficulty of classifying exposure in these types of studies is highlighted by the fact that only 6 of the 16 mesothelioma cases were definitively engaged in brake service [93].

Teschke et al. [94] studied 51 mesothelioma cases as compared to 154 population-based controls for occupational histories and possible asbestos exposures. Vehicle mechanics had a relative risk of 0.8 (95% CI 0.2 to 2.3) based upon 6 cases and 20 controls. Individuals engaged in brake lining installation or repair had an OR of 0.3 (95% CI 0 to 1.4) based upon 2 cases and 17 controls. The authors, however, recognized that this was an extremely small study and that the grouping of occupations was likely to result in non-differential misclassification. In addition, since one-third of the case group was based on next-of-kin interviews and only one-seventh of the control, relative risk estimates for such exposures would be expected to be biased downward whenever there were a smaller proportion of next-of-kin interviews among controls. Teschke [58] describes the difficulties in conducting epidemiology case-control studies to elucidate a possible exposure-response relationship between asbestos from brakes as an auto mechanic by classifying cases and controls by occupation.

"Of course, it is impossible to study every occupation-disease relationship. In addition, even where a job has been studied, the potential for variable exposures within a job to dilute the relationship is probable for many jobs and would preclude a person with high exposures from having their occupational disease recognized, simply because others in the same job were not similarly exposed. The question is whether the exposure caused the disease. A job cannot cause disease, its exposure may.… In other words, the effects of chrysotile are not properly assessed via the surrogate measures of exposure vehicle mechanic or brake repair" [58].

Agudo et al. [95] conducted a case-control study in Spain of mesothelioma. In a footnote, the authors reveal that there were 3 cases of mesothelioma in the category of mechanics, motor vehicle as compared to 14 controls. The authors reported, however, that while all but one of the controls were interviewed, 44% of the cases were deceased and information regarding exposure came from the spouse, a son or daughter, another relative or a neighbor. The authors conceded the possibility of some degree of misclassification. Welch et al. [96] conducted a case-control study of 40 cases of primary peritoneal mesothelioma cases compared to controls. 8 of the cases had engaged in brake lining work compared to 6 controls, resulting in an excess risk.

Rolland et al. [97] conducted a case-control study in France of 462 pleural mesothelioma cases as compared to 897 controls. 17 mesotheliomas occurred among motor vehicle mechanics as compared to 22 in the controls for an Odds Ratio of 1.50 (95% CI 0.76-2.95). In the category of repair of motor vehicles and motorcycles, 19 mesotheliomas were found as compared to 29 in the controls for an Odds Ratio of 1.20 (95% CI 0.65-2.24). While neither finding is statistically significant, they are still suggestive of an association given the limitations of probable under-diagnosis of mesothelioma and the high probability of exposure misclassification in both cases and the controls, especially in relation to the lack of inclusion of multiple occupations. Rake et al. [98] conducted a case-control study in England of 622 mesothelioma patients and 1420 population controls. The authors reported an OR of 0.4 (95% CI 0.1 to 1.7) for vehicle maintenance involving work with brakes or gaskets without disclosing the number of cases or controls involved in the work activity. There was apparently no blinding of the researchers who elicited exposure classification of the cases and controls in the Rake study [98]. Peto et al. [99] using the same data as Rake et al. [98] disclosed 18 motor mechanics with mesothelioma as compared to 54 controls resulting in an OR of 3.8 (95% CI 1.9 to 7.8). After removing any mesothelioma case that also had potential exposure elsewhere, the motor mechanic mesothelioma cases were reduced to 2 with 24 controls resulting in an OR of 0.7 (95% CI 0.2 to 3.5).

Aguilar-Madrid et al. [100] conducted a case-control study of 119 malignant pleural mesothelioma cases listed on the Mexican Institute of Social Security compared to 353 controls from the same system. There were 8 mesothelioma cases in the economic activity of Sale, maintenance and repair of motor vehicles and motorcycles; retail sale of automotive fuel as compared to only 5 controls. In the occupational category of Mechanic, automobile, however, there was only 1 mesothelioma case versus 4 controls. The authors recognized that the results of their study depended on a hygienist to estimate exposure and that the hygienist could have introduced non-differential misclassification bias which always dilutes the strength of the association.

## Proportionate mortality studies

Studies have been done which perform epidemiologic analyses based on job title information such as that provided on death certificates in vital statistics and general cancer registries. A recent editorial in the Annals of Occupational Hygiene [101] provided a perspective on the utility of job title studies for known carcinogens. Such studies can be valuable when investigating possible new or unknown carcinogens, but for known carcinogens such as asbestos when the results of such studies are negative they cannot be used to exclude that there is no effect of a known carcinogen within an occupation or industry [101].

Data on deaths collected by various government entities on mortality in vital statistics registries can be used to detect possible elevations in a specific cause of death as compared to all causes of death in that group. A Proportionate Mortality Ratio (PMR) is often calculated to compare the proportion of the deaths from one cause to all other causes of death. A PMR measures only the relative frequency of a particular cause among all causes of death and does not measure the risk of death from that specific cause. PMR studies are usually an early attempt to explore an association epidemiologically because they can be completed much more rapidly and with considerably less expenditure of resources than other analytic epidemiologic studies.

Since a PMR is typically calculated using information on death certificates, there are two significant limitations in interpreting its impact. First, the occupational information is limited to that listed on the death certificate which is intended to be the longest held occupation and industry, but those definitions are inconsistently applied and can simply be the last occupation of the deceased. The important occupational exposure to asbestos, on the other hand, may have occurred in an earlier occupation in the person's lifetime. Second, since the cause of death is based solely on that listed on the death certificate; there are concerns about the completeness of the ascertainment of death and the accuracy of the coding of the cause of death. For these reasons, Goodman [60] declined to include the data from any of these types of studies in their meta-analysis, as they were deemed unreliable.

Milham and Ossiander [102] conducted a proportionate mortality analysis of deaths in Washington State. Among automobile mechanic and repair workers, they found 7 pleural mesotheliomas (PMR 75) and 2 peritoneal cases (PMR 53). Roelofs et al. [103] coded occupations mesothelioma cases on the Massachusetts Cancer Registry from 1988-2003. For comparison, 80,184 cancer cases were also coded for occupation and industry and standard morbidity odds ratios (SMORs) were computed. Based on 10 mesothelioma cases, automobile mechanics had an SMOR of 2.1 (95% CI 1.1-4.0). In addition, based on 11 mesothelioma cases, automotive repair and related services industry was assigned a SMOR of 2.2 (95% CI 1.2-3.9).

The British Health Safety Executive did a PMR analysis of British death certificates cautioning that a PMR of 100 does not represent the background risk for mesothelioma (the level that would be expected in the absence of all asbestos exposure) [104]. Rather, according to the HSE, a hypothetical group of men with no asbestos exposure would likely record a PMR of approximately 6. Since the HSE calculated a PMR of 48.4 for automobile mechanics based upon 60 mesothelioma deaths, multiple times higher than the hypothetically non-exposed group, the HSE's data should not be interpreted as providing evidence that automobile mechanics are not at risk of developing mesothelioma. Coggon et al. [55] conducted a proportionate mortality analysis of occupation of deaths age 20-74 in England and Wales during 1979-1980 and 1982-1990. 12 deaths were recorded for pleural cancer (PMR 46) and 3 for peritoneal deaths (PMR 88) in motor mechanics. Interestingly, 2 deaths in motor mechanics from asbestosis were also recorded (PMR 80). Hodgson et al. [105] utilizing data from the HSE's mesothelioma register, reports that motor mechanics have a PMR less than 100 without specifying the exact calculated PMR or the number of cases included in that calculation.

Based upon their inherent limitations, it would not be reasonable to rely solely upon PMR studies like Coggon et al. [55], Hodgson et al. [105], Milham and Ossiander [102] and HSE [104] to conclude that automobile mechanics are not at risk for developing mesothelioma or to rely on the Massachusetts PMR study Roelofs et al. [103] to prove there is a risk.

## Cohort studies

Cohort studies are generally the most rigorous of the epidemiologic study designs in occupational epidemiology. A population of workers with documented exposure is enumerated and followed for disease and mortality as compared to another occupational group, without the exposure of interest, or the general population. These studies can either be done prospectively in real-time or historically. Both prospective and historical cohort studies select workers based on exposure and follow them through time for disease occurrence or death. A relative risk is calculated by comparing the rate of disease in the exposed cohort to a non-exposed group or, in the case of historical cohort studies, the general population.

Prospective cohort studies usually require considerable time and money and are rare in an occupational setting. Such studies of asbestos exposed cohorts present a particular problem because of the long latency of asbestos diseases. To capture the true occurrence of asbestos diseases, a cohort with occupational exposure to asbestos would have to be followed for decades. The studies of insulators by Selikoff and coworkers at Mount Sinai are among the most well-known examples of prospective cohort studies in occupational epidemiology [106,107]. Unlike the unionized insulation workers studied by the Selikoff group, however, workers who have performed brake repair and replacement are not a workforce amenable to systematic study because of the lack of a sufficient number of such workers in a central location or union, and because of the intermittent and transient nature of the occupation. As aptly described by Welch [32].

"There have not been definitive epidemiology studies of brake mechanics because of the nature of the workforce. It is generally non-unionized and spread out in car repair shops all over the world. Well-defined asbestos worker studies of insulators and asbestos textile manufacture have been in factories or highly unionized workforces where exposure is clearly documentable by the nature of their job or job title or industry. Exposure to asbestos from brakes can occur to automobile or truck mechanics anywhere in a vehicle repair shop and the workers are highly transient and not documented. In fact thousands if not millions of non-occupational amateur car repair-persons have been exposed while changing their brakes outside in alleys or on the street or in their own home garages" [32].

In fact, there has not been any prospective cohort studies conducted on a group of automobile mechanics. There have been, however, several historical cohort studies of workers in plants manufacturing friction materials such as brakes and clutches. Robinson et al. [108] reported the mortality patterns in a friction materials manufacturing plant of 3276 workers followed for mortality 1968-1975. 99% of the asbestos in the plant, which had been operating since the early 1900's was chrysotile with some small amounts of amosite and crocidolite being used during the years of WWII. Mesotheliomas accounted for 4.3% of the deaths. 17 cases of mesothelioma were found, 5 pleural, 6 peritoneal, and 6 with site unstated. Newhouse et al. [109] reported a mortality study of workers in a factory producing friction materials. 10 deaths were due to pleural mesothelioma. Even though the factory only used chrysotile except during two well-defined periods (1929-33 and 1939-44) in well-defined areas of the factory when crocidolite was used, the authors attributed none of the mesotheliomas to chrysotile exposure. Newhouse and Sullivan [110] extended this study by seven more years and found 3 additional mesotheliomas for a total of 13. Of the three new cases, one was a grinder who was only exposed to chrysotile asbestos. Another of the three worked at the factory when only chrysotile was being used and died of a malignant right pleural effusion but a diagnosis of mesothelioma could not be confirmed. Finkelstein [111] conducted a mortality study of 1657 employees at two Ontario automotive parts factories that manufactured friction materials containing chrysotile asbestos. Elevations were found for laryngeal and lung cancer. Two of the lung cancer cases were suspected to actually be cases of pleural mesothelioma.

There have also been a handful of historical cohort studies of workers engaged in automotive repair work. Rushton et al. [112] studied 8490 London bus transport maintenance workers, 2313 of which were mechanics. Under the category of Cancer of the lung and pleura, there were 102 deaths but no breakdown as to the number, if any, of pleural cancers. The authors emphasize that their study was inadequate to determine mortality patterns because both the number of men included and the years of follow-up, a mean of 5.9 years, were inadequate. Jarvholm and Brisman [113] reported one pleural mesothelioma in a cohort of 21,905 Swedish men who had and occupational title of mechanic or an industry code of car repair as listed in the 1960 Swedish census. Without explanation, the authors state that the data indicates no increased risk of mesothelioma in car mechanics even though they were unable to calculate a risk ratio because of the lack of information regarding the expected incidence of mesothelioma in the general population. Hansen [114] conducted a study of 21,800 auto mechanics in Denmark and observed a case of mesothelioma. Because no cases of mesothelioma were expected based upon the death rates of the comparison population, the standardized mortality ratio (SMR) was essentially infinite leading the author to conclude the population was at an increased risk of contracting the disease. The author states 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. Significantly, the population of auto mechanics studied was quite young with nearly 93% of the man age 54 or younger at the end of the study's ten-year follow-up. Given the long latency period associated with mesothelioma, it is likely that this study underestimated the risk in this population. Gustavsson et al. [44] found two mesotheliomas among 696 workers in bus garages in Stockholm Sweden. The authors speculated, however, that both might have been exposed to asbestos during previous employments. The authors cautioned that no conclusions could be drawn regarding risk estimates for any of the disease due to the limited size of the study group. Merlo et al. [115] conducted an historical mortality study among bus drivers and bus maintenance workers in Genoa, Italy. The authors observed 26 cases of pleural mesothelioma. When compared to the entire Italian male population death statistics with an expected rate of mesothelioma death of 7.08, the standardized mortality ratio (SMR) was 3.67 (95% CI of 2.50-5.39). When, however, compared to the local Ligurian male expected mesothelioma death rate of 25.6, no statistically significant increased risk was detected.

## Limits of epidemiology

Interpreting the existing epidemiologic studies to determine whether there is a link between exposure from brake work and the subsequent development of mesothelioma is difficult for a variety of reasons. For any study that relied upon disease information recorded on death certificates prior to 1999, there is a general under-ascertainment of mesothelioma as the underlying cause of death because of the lack of a specific International Classification of Disease (ICD) code for mesothelioma [116].

Proportionate mortality studies are not designed to answer the question of causation from a specific occupation. Instead, these types of studies are, at best, a general surveillance tool.

Few cohort studies of brake workers exist and those that have been conducted do not have sufficient latency or population size to accurately assess the risk from a rare disease like mesothelioma. No cohort studies of workers predominately repairing and installing brakes have been conducted in the United States because these workers are not a cohesive, or unionized group that can be followed either in real time or historically, as has been done for asbestos insulators or textile manufacturing workers.

Case-control studies that include automobile mechanics have been plagued with exposure misclassification in both the case and control groups which can lead to a bias toward a null result or even a seeming protective effect of working with asbestos dust from brakes. In studies involving mesothelioma, the cases are often deceased, and exposure histories depend on information from living relatives or friends, whereas the exposure histories are taken from living controls. The live controls are more likely to accurately report brake work history, especially home garage or shade tree mechanic history as compared to information gathered from the relatives of deceased cases. The issue of misclassification is further highlighted by the lack of uniformity in how the existing case-control studies categorize the occupation: brake lining installation [89], garage worker [88], automobile repair and related services [90], motor vehicle mechanics/motor vehicle repair workers [93], vehicle mechanics/brake lining installation and repair [94], mechanics - motor vehicles [95], tire or brake-lining work [96], vehicle maintenance involving work with brakes or gaskets [98], motor mechanics [99], and automobile mechanics/sale, maintenance & repair of motor vehicles & motorcycles - retail sale of automotive fuel [100]. Using occupation as a surrogate for brake dust exposure tends to bias all these case-control studies toward the null [58]. Because of the rarity of mesothelioma, there is an overarching issue applicable to all of the case-control studies regarding the inadequate statistical power of these studies to detect an increased risk if it exists. The existing studies are all small and thus not likely to detect a risk that would be detected in a larger study [117].

Since, cohort (prospective) studies have not been adequately applied to workers with asbestos exposure from brakes and mesothelioma, we have to try to get information from studies that were not designed specifically for that exposure. In the medical literature, we have been able to count over 400 cases of mesothelioma in workers who have been possibly exposed to asbestos from brake repair. Epidemiology is just one facet of the totality of the evidence concerning asbestos and mesothelioma causation. As spelled out by IARC [21] and many other sources, the biological and toxicological literature is clear that exposure to asbestos of all types and of all fiber sizes increases the human risk of mesothelioma.

A review of the brake worker associated scientific literature leads to a conclusion that a weight-of-the-collective-evidence approach is best suited to resolving the causality question. A widely accepted method for determining cause and effect for causation in epidemiology are the guidelines that were originally suggested by Hill [118] for evaluating the studies on cigarette smoking and lung cancer and other diseases. These guidelines are not limited to just formal epidemiological studies but rather incorporate and evaluate the totality of the science on a given issue including cell biology, animal studies, and mechanistic studies. As Hill stated, none of his nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine quo non [118]. Lemen [119] applied the Hill model to discuss chrysotile asbestos and mesothelioma causation, concluding that there is no doubt that the scientific evidence supports the carcinogenicity of chrysotile alone in the induction of mesothelioma.

The most utilized modern list of viewpoints derived from Hill's work are contained in the textbook, Epidemiology, by Leon Gordis [120]. They are:

- Temporal relationship
- Strength of the association
- Dose-response relationship

- Replication of the findings
- Biologic plausibility
- Consideration of alternate explanations
- Cessation of exposure
- Consistency with other knowledge
- Specificity of the association

The application of the Hill Criteria to the issue of car mechanics who repair and replace brakes:

**Temporal relationship:** This requires that the cause come before the effect. This criterion is easily satisfied in the current context as the mechanic's exposure to asbestos in brake dust occurs many years, usually decades, before the diagnosis of the disease, mesothelioma.

**Strength of the association:** In epidemiology, strength of association is most often measured by comparing the incidence of disease in the exposed divided by the non-exposed in a cohort study. In the case of brake workers and mesothelioma, no adequate cohort studies have been done, so there has not been any reliable calculation of the relative risk. Likewise, most case-control studies are plagued with exposure misclassification that leads to unreliable calculations of the odds ratio estimate of relative risk.

**Dose-response relationship:** There is clear evidence of asbestos dose-response in mesothelioma causation. Iwatsubo [35] did a rigorous assessment of occupational exposure to asbestos in 405 mesothelioma cases and 387 controls. The authors found a clear dose-response relation between cumulative asbestos exposure and pleural mesothelioma. Examining data from the French mesothelioma registry, Lacourt [38] also found a clear dose-response relationship between asbestos exposure and pleural mesothelioma. In fact, there are many studies cited by IARC [21] that show that every additional exposure to asbestos leads to a greater risk of mesothelioma. Thus if a brake worker, was also exposed to asbestos from another source, the asbestos in brake work would put the brake worker at heightened risk of mesothelioma.

**Replication of findings:** The peer-reviewed published literature contains more than four hundred mesothelioma cases that have occurred in workers, their families and their pets from exposure to asbestos from the replacement of brakes in locations all over the globe.

**Biologic plausibility:** While the exact biologic mechanism explaining how mesothelioma develops has not been definitively identified, there is abundant literature that conclusively establishes the exposure to any form of asbestos can result in the formation of mesothelioma [21]. There is also abundant literature that confirms that the process of removing and replacing brakes can liberate substantial amounts of asbestos in the worker's environment. Accordingly, it is biologically plausible that such exposure can cause mesothelioma.

**Consideration of alternate explanations:** There are very few documented causes of mesothelioma other than exposure to asbestos. The scientific literature contains a handful of mesothelioma cases that were purportedly caused by the administration of therapeutic radiation. In addition, exposure to erionite, an asbestos-like mineral found in Turkey, has been linked with the development of mesothelioma. Neither of these would apply as an alternate explanation for mesothelioma in brake mechanics. While there have been reports of idiopathic or spontaneous mesotheliomas, this term has been reserved for those instances where there is no discernable history of exposure to asbestos. Given the strong relationship between mesothelioma and asbestos, it is likely that a significant portion of those cases that have been labeled idiopathic are not cases where the asbestos exposure has not occurred but rather simply could not be adequately documented. It is highly unlikely that the multitude of reported mesothelioma cases that have occurred in workers and their family members from exposure to asbestos from brakes is due to chance alone.

**Cessation of exposure:** While many new and recent model cars were built with brakes and clutches that did not contain asbestos, it still may be present in both old and replacement brakes. Given the potential for continued exposure to asbestos and because of the long latent period associated with mesothelioma, whether or not the incidence of mesothelioma in automobile mechanics will decrease will not be known for several decades.

**Consistency with other knowledge:** The published literature is replete with data demonstrating that workers exposed to chrysotile asbestos from products that are not friction products are at risk for developing mesothelioma. Moreover, there are studies of brake mechanics that document asbestosis and/or pleural plaques that are also consistent with significant exposures to asbestos.

**Specificity of the association:** This is the one criteria derived from Hill that is not useful in environmental/occupational epidemiology. For instance, cigarette smoke causes multiple diseases including lung cancer, emphysema, bladder cancer, heart disease and many other diseases. Likewise, asbestos causes malignant mesothelioma, lung cancer, other cancers, asbestosis and pleural plaques.

## Conclusion

The use of asbestos is unfortunately expanding around the world even though in many western countries its' use has been banned. In countries like India and others it is being used without proper industrial hygiene controls. There are a tremendous number of automobile mechanics potentially exposed in removing old brakes and installing new ones. Epidemiology has been flawed and not adequately applied and then often results misinterpreted. Despite these shortcomings, the weight of evidence conclusion is that workers performing brake repair and installation with asbestos containing products are at significant risk of developing mesothelioma. A review utilizing the Bradford Hill criteria supports the causal link between asbestos exposure during brake repair and installation work and malignant mesothelioma.

While we have focused on the strengths and weaknesses in the application of individual epidemiology methods, we must not lose sight of the fact that the industrial hygiene exposure assessment literature as well as toxicological animal studies independently confirm the conclusion that brake repair and installation results in hazardous levels of exposure to asbestos and that the chrysotile asbestos in those products causes malignant mesothelioma. Our review and commentary does not use meta-analysis or systematic review techniques, it offers in-depth analysis of the studies and issues relating to the epidemiology of mesothelioma which is hoped to be a useful update on these issues. As in all scientific discussion, there is room for disagreement on salient facts and interpretations and we did our best to offer the best interpretation from a perspective of public health and epidemiology practitioners.

Even though much of the chrysotile asbestos in brake products is converted into forsterite during the braking process, unaltered chrysotile fibers remain in very high numbers in the brake dust removed during blowout with compressed air. Moreover, significant exposure to unaltered chrysotile results from the beveling, grinding, sanding and other procedures to fit new brakes.

Asbestos and asbestiform fibers are essentially the sole occupational cause of mesothelioma. The role of epidemiology is best focused on estimating the magnitude of the mesothelioma health impact from asbestos exposure rather than causality because causality is already well established. It is unnecessary to study every type of asbestos occupational exposure through the application of epidemiologic methods to establish a causality link between asbestos exposure and mesothelioma.

As summarized here, over four hundred cases of mesothelioma in automobile mechanics and brake repair workers have been reported in the medical and scientific literature around the world. These individuals are part of the worldwide mesothelioma epidemic. The reports in the literature are the tip of the iceberg as there is no registry in the US for mesothelioma that includes detailed occupational exposure histories and thus no data on the number of mesothelioma cases exposed to brake repair asbestos dust. The Bureau of Labor Statistics estimated in 2014 that there were over 739,000 workers in the automotive service technicians and mechanics category [14], and many more brake workers are so called shade tree mechanics. Automobile mechanics have been exposed to asbestos in brake dust in a car shop unknowingly. Epidemiology has never been adequately directly applied to studying exposure from removing old brakes and installing new ones. The studies that have been used to look at the issue were not designed to answer the brake worker mesothelioma issue. They generally all suffer from lack of exposure specificity, exposure misclassification, lack of statistical power and other methodological flaws and shortcomings. An historical cohort study of a large group of brake workers would have been ideal but has never been carried out. Even without such a study, there is an abundance of evidence that performing brake installation or repair releases substantial amounts of asbestos into workers' breathing zones. The documentation of such exposures supports the weight of evidence epidemiologic conclusion that asbestos from brakes can and does cause mesothelioma in workers handling asbestos containing brake materials. If mesothelioma is to be prevented it is imperative that brake repair and installation only use non-asbestos containing products and workers be protected when removing old asbestos containing brake materials. This is of crucial importance in countries around the world where asbestos use is continuing.

## Author's Contributions

Marty Kanarek conceived of the work and drafted the original manuscript. Henry Anderson added sections and edited the manuscript. Both Kanarek and Anderson revised and reviewed the manuscript for submission.

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Both Kanarek and Anderson have served as consultants to government and international agencies on asbestos health effects, and have been consultants and witnesses on plaintiff's litigation concerning asbestos and disease.

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