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PLAINTIFF'S EXHIBIT
USX-1062

May 11, 2001

Re: All Allegheny County, Pennsylvania USX Remnant Cases

Evolution of medical knowledge ("State of the Art")
in
Asbestos related diseases

Dear Mr. Taylor,

In response to your request for a general statement about my opinions regarding the "State of the Art" in asbestos medicine, please accept this document and the attached table of medical journal articles dating back to 1898.

Physicians and attorneys use the term "State of the Art" (SOA) differently. When physicians speak of SOA they mean what is currently known about a topic of scientific importance. SOA articles published in the medical literature typically include an introductory review of previous beliefs and old understanding about a topic based on previously published work, but emphasize what is currently known and propose topics for further research. Medical journals typically identify such articles as "State of the Art". For example, in May 1998 the American Journal of Respiratory and Critical Care Medicine, the official organ of the American Thoracic Society, published under the heading "State of the Art" a review of what is currently known about the pathogenesis of asbestosis and silicosis.[1] When attorneys speak of "State of the Art" in medicine they refer to historical reviews or a historical description of the evolution of knowledge regarding a certain topic. Such historical articles are also published in the medical literature. In July 2000 the American Journal of Respiratory and Critical Care Medicine published under the heading "How it really happened" an article about the evolution of knowledge regarding smoking and lung cancer written by

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Sir Richard Doll[2] who, in 1950, published one of the first epidemiological articles on the subject.[3] Thus, when attorneys use the term State of the Art they are referring to something that doctors call evolution of knowledge or medical history. Both State of the Art (the medical item) and history of medicine articles are routinely published in the medical literature as witnessed by the regular appearance of such articles in the peer reviewed literature as in the example of the "State of the Art" and "How it really happened" sections of the American Journal of Respiratory and Critical Care Medicine which is a journal addressed to both pulmonary research scientists and pulmonary clinicians. Reading and studying such articles is the duty of pulmonary clinicians and is a normal part of clinical practice. Few if any pulmonary research scientists or pulmonary clinicians characterize themselves as "medical historians", although some clinicians such as myself devote large amounts of time and study to such topics. I have studied the evolution of knowledge regarding asbestos related diseases for the past 20 years.

Based on my careful study of the old medical literature, I have selected certain dates of knowledge, i.e. that certain medical facts or ideas were clearly stated and were widely believed by experts in the field. These dates are summarized as follows:

1. **The existence of the disease asbestosis in heavily exposed asbestos textile workers**: suggested by case reports published early in the 20th century[4], but first reported in an epidemiological report by Merewether in **1930**.[5]

2. **The concept that the risk of asbestosis is dose related and that only heavily exposed workers would develop asbestosis** was first stated in **1938** by Dreesen[6] who also proposed a "threshold limit value":

> From a practical standpoint, one of the most important results of a medical and engineering study such as this is the definition of safe working conditions in the industry under study. Ideally, a threshold concentration of dust should be the highest dust concentration that would not produce pneumoconiosis in originally healthy workman during their entire working life.
>
> Because clean-cut cases of asbestosis were found only in dust concentrations exceeding 5 million particles per cubic foot and because they were not found at lower dust concentrations, 5 million particles per cubic foot may be regarded tentatively as the threshold value for asbestos-dust exposure until better data are available.

3. **Confirmation that the TLV proposed in 1938 by Dreesen was protective** was tested in the frequently cited **1946** study of World War II naval shipyard workers published by Fleischer[7] and usually referred to as the Fleischer-Drinker report. The authors concluded that the Dreesen TLV was highly protective. It was not until the mid 1960's that their conclusions were found to be incorrect (because long latency was not properly considered).

4. **Indication that the Dreesen TLV was not sufficiently protective and that asbestosis could occur in workers such as hands-on asbestos insulators** was made by Selikoff in **1964** and **1965**[8]. Prior to Selikoff's work, asbestos insulators were believed to have relatively light, intermittent asbestos exposure compared to asbestos textile workers. Selikoff did not suggest that heavy industry workers such as steel plant workers were at risk for the development of asbestosis.

5. **The concept that lung cancer risk is increased in patients who have asbestosis**, not in all asbestos exposed individuals, i.e. that it is asbestosis and not asbestos exposure that increases lung cancer risk: first suggested in **1947** in another epidemiological work by Merewether[9] and clearly expressed in a 1949 editorial in the Journal of the American Medical Association.[10] Despite early support for this concept by Sir Richard Doll[11] this idea was re-discovered after the 1987 publication by Kipen et al (including Selikoff).[12]

6. **The existence of the disease mesothelioma**, that is, not a form of bronchogenic carcinoma: in a clinical-pathological conference (CPC) published in **1947** in the New England Journal of Medicine.[13] The authors specifically stated (incorrectly): "I believe that asbestosis was not a factor in the illness and that, if present, it was of secondary importance."

7. The fact that **crocidolite (South African) asbestos exposure caused diffuse malignant mesothelioma**: Wagner **1960**.[14]

8. Demonstration that **amosite, another kind of South African amphibole asbestos can cause mesothelioma**: Selikoff **1972**.[15]

9. **Chrysotile asbestos does not cause mesothelioma**: McDonald **1982**[16] and **1984**,[17] eventually proven in 1997 by Liddell, McDonald and McDonald[18] with further confirmation also published in 1997 by McDonald and McDonald[19] and McDonald and Case et al.[20]

10. **Suggestion that steel plant workers may have risk of asbestos-related conditions**: In **1991** Kronenberg et al[21] suggested that in 1989 "workers who did not directly use asbestos had been found to be at risk" for the development of asbestos-related diseases in a special publication of the New York Academy of Sciences that predicted a "third wave" of asbestos disease. Such a "third wave" of asbestos disease has not materialized. The 1991 Kronenberg report described a study of 898 steel plant workers in Tyler, Texas. The authors stated that the purpose of their study was to present "preliminary observations on the prevalence of asbestos-related disease in workers at two industrial sites not generally associated with asbestos exposure - a glass bottle-manufacturing plant and a steel mill." In fact, Kronenberg failed to demonstrate a risk of asbestos disease in the steel workers. A much more extensive series of papers published by Lloyd of the National Institute of Environmental Health Sciences, and others from 1969[22] to 1978 did not identify asbestos-related disease in 59,072 steel workers.

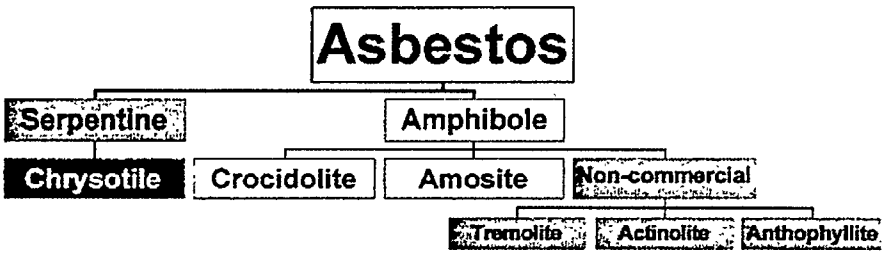
A detailed review of the history of mesothelioma and the relationship between asbestosis and lung cancer follows. Also, attached to this statement please find a bibliography of important articles published in the medical literature. The bibliography appears in tabular form. I have selected important quotations which reflect the concepts proposed and/or proven by the authors.

Allan Feingold, M.D.

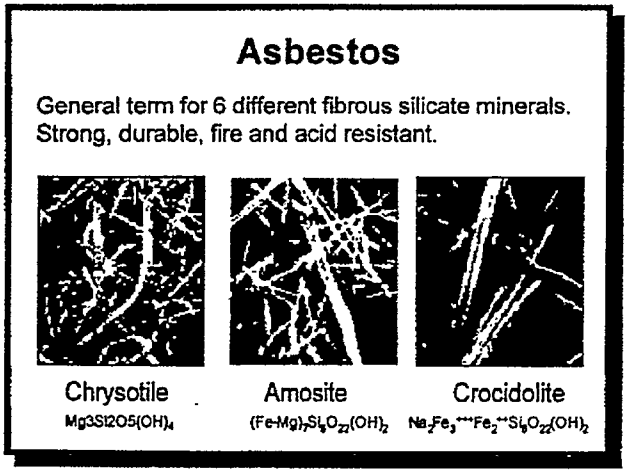
Signed electronically by:
I.A. Feingold, M.D., F.R.C.P.(C), FCCP

Definition of asbestos fibers

Asbestos is a general term for a family of fibrous magnesium and calcium silicate minerals. There are two main kinds of asbestos: serpentine, consisting of only one type, that is, chrysotile asbestos, and the amphibole group which includes the commercially mined crocidolite and amosite and several non-commercial fibrous minerals, notably tremolite. The different kinds of asbestos are summarized below:



Chrysotile asbestos has a distinctly different microscopic appearance and chemical composition than the amphibole forms of asbestos, as demonstrated below:



More than 90% of the asbestos that was used in insulation products manufactured in the United States was chrysotile asbestos mined in the Eastern Townships region, northeast of Montreal, Quebec; however, the amphibole forms of asbestos, i.e. amosite and crocidolite, were imported (mostly from South Africa) into the United States for use in special applications. Amosite was specified by the United States Navy as the type of asbestos to be used in the construction of World War II era warships. Amosite was heavily used in the Brooklyn Navy Shipyard and many other yards that produced naval vessels. Amosite was also used in the manufacture of asbestos cement products and in certain kinds of pipe covering insulation such as Kaylo (Owens-Corning). Although most of the asbestos used in construction was chrysotile, amosite had certain applications in construction insulation; specifically, in the construction of large commercial buildings during the 1950's to the 1970's amosite asbestos was, in some cases, the kind of asbestos used to spray the underside of steel decks that create the floors of "skyscrapers". An amosite product that was used in such spray-on applications was Limpet (T&N). Some construction products such as transite boards contained amosite.

Relatively little crocidolite was used in the United States and Canada. Crocidolite was used in the manufacture of World War II era military gas masks. Some construction products manufactured by Johns Manville contained crocidolite.

In contrast to the specialized use of amphiboles, chrysotile was used in the manufacture of a large variety of products, including many kinds of construction materials and insulation. Some kinds of products always, or almost always, contained chrysotile only, with no use of amphiboles. Almost all friction products (brakes and clutch linings) contained chrysotile only (there was very limited manufacture of crocidolite-containing brakes). Asbestos-insulated wire and cable could not contain amphiboles as the latter contained iron; therefore, only chrysotile was used. The type of asbestos used in the past in the manufacture of specific products can usually be determined by reference to engineering or marketing specifications.

Since 1965 asbestos fibers have been defined as structures at least 5 • m in length with aspect ratios (length to width) of 3:1 or greater. OSHA and other regulatory agencies state permissible asbestos exposures in terms of fibers equal to or greater than 5 • m in length. In a 1991 review and consensus report[23], the Health Effects Institute-Asbestos Research (HEI-AR) stated:

> . . . for calculations of risk from exposure to airborne asbestos, the Panel has focused on fibers longer than 5 • m. The Panel's decision was based on two major factors. The exposure-response relationships observed in epidemiologic studies are the basis for risk estimation of asbestos; the exposure data in such studies have been expressed in terms of fibers longer than 5 • . In addition, toxicity data suggest that shorter fibers are less toxic than longer fibers.

Short asbestos fibers (<5 • m) are generally considered non-fibrogenic; indeed, Browne[24] described "almost unassailable evidence that the specific pathogenicity of asbestos fibers only exists at lengths greater than 5 • m (probably greater than 8 • m)."

Recognition of mesothelioma

Malignant pleural and peritoneal mesothelioma was first described without an asbestos association in the 1940's. Considerable controversy was seen in the medical literature as many pathologists did not accept that mesothelioma was a distinct entity. The report of the weekly clinical-pathological exercise at the Massachusetts General Hospital published in the New England Journal of Medicine in 1947[25] described the case of a malignant pleural tumor in a 37 year old Swedish asbestos worker. In that report, Dr. Benjamin Castleman stated:

> A number of papers have been written to the effect that there is no such tumor as mesothelioma of the pleura, that the cells lining the pleura do not form tumors and that these tumors really arise from a small focus in the lung. We have held a similar opinion for a long time. *This is perhaps the first case in which we believed that there was actually such a tumor.*" [Emphasis added]

Commenting on the differential diagnosis in the CPC, Dr. Donald S. King stated:

> One should comment first on the occupation. This man worked with asbestos, cutting insulating board. Exposure to asbestos causes lung changes but never, in my experience, to the extent that was present in this case. *I believe that asbestosis was not a factor in the illness and that, if present, it was of secondary importance.*" [Emphasis added]

It should be noted that the above described CPC, often referred to as the Mallory report (in fact, Mallory was a NEJM editor) is often misrepresented as an early identification of the relationship between asbestos exposure and mesothelioma. As can be determined from the actual text of the CPC (above) the report was an early acceptance of the pathological entity of mesothelioma in a prestigious English language journal, but that report actually refuted a possible relationship between asbestos exposure and mesothelioma.

More than 10 years after the NEJM CPC, McCaughey[26] published an early pathological characterization of malignant mesothelioma but did not suggest any relationship to asbestos exposure. It was not until 1960 that Wagner, Sleggs and Marchant[27] reported the surprising finding of 33 cases of diffuse pleural mesothelioma, all but one of which had a history of exposure to crocidolite asbestos.

Asbestos fiber type and mesothelioma

Wagner's paper was the first report of a significant relationship between asbestos exposure and mesothelioma and in fact, Wagner suggested that it was only "Cape Western Blue" or crocidolite asbestos that was the cause of mesothelioma. In 1986 in the journal Cancer, Wagner[28] recalled how it was that in the late 1950's (prior to his 1960 publication) he came to the conclusion that crocidolite asbestos caused mesothelioma:

> We were puzzled as to why we were seeing so many of these tumors. I then recalled that we had seen asbestos bodies in the first case and that 90 miles west of Kimberley were the large mines which had been developed along the so-called blue asbestos mountains, a range of hills stretching for more than 400 miles from the Orange River in the south to the Botswana border in the north. We then meticulously examined every scrap of lung tissue that had accompanied the biopsy specimens, and in three more cases we found occasional asbestos bodies. I therefore suggested that we should consider an association between the blue (crocidolite) asbestos mines and development of the mesotheliomas...
>
> From further cases referred by Dr. Sleggs, [Dr. Wagner's co-author on the 1960 paper] we obtained histories showing that few of the patients had been employed by industry working as insulators with blue asbestos on steam

> locomotives. The majority, however, had only lived in the vicinity of the asbestos mills, some for very short periods, and, on average, their tumors developed 44 years after exposure.
>
> The next question was, were the tumors confined to exposure to blue asbestos or were other types of fiber involved?... Through the South African Pneumoconiosis Bureau, we were able to examine the lungs of the majority of asbestos miners who died, revealing that mesotheliomas of pleura, and occasionally of peritoneum, were only observed in the workers from the Cape asbestos mines and those living in the vicinity. In recent years, a few cases have been reported from the amosite mining areas, but detailed analysis is required to see if these men had worked on the associated crocidolite deposit. No cases have been recorded among chrysotile miners or from the mines of the neighboring counties of Swaziland and Zimbabwe...
>
> A further question arose as to whether a similar situation existed with the manufacturers of asbestos products. In 1962, we began to investigate the problem in the United Kingdom.... By going through hospital records and material in the pathology departments, we discovered more than 100 cases during the next 2 years, and in association with various colleagues (Dr. Muriel Newhouse deserves special mention), we were able to establish the association with exposure to asbestos dust. In Britain, however, as we found later in other industrial countries, the actual fiber implicated was much more difficult to assess, as the majority of workers had been exposed to most varieties of asbestos dust.

In 1965 Selikoff[29] was the first to identify mesothelioma cases in the United States and observed:

> This remarkable concentration of cases in one area of South Africa was explained by the hypothesis that mesothelioma was the result of exposure to one special type of asbestos (crocidolite) .... [but] ... mesothelioma may not necessarily be a problem of only one kind of asbestos (crocidolite)...."

Also in 1965 Sluis-Cremer[30] reported on a methodical search for mesothelioma cases outside of the South African North West Cape Province crocidolite mining area and

concluded that there were no cases from the amosite mines of the Transvaal Province. It was not until 1972, in a study of New Jersey amosite asbestos cement workers, that Selikoff, Hammond and Churg[31] demonstrated that amosite was a cause of mesothelioma. In 1980 Selikoff, Seidman and Hammond[32] reported on a further study of amosite factory workers. Selikoff et al noted that:

> In 1941, with the encouragement of the U.S. Navy, a factory was established in Paterson, New Jersey, to manufacture asbestos products for the armed forces for industrial uses. We have ascertained that amosite asbestos was used almost exclusively (with very small amounts of chrysotile asbestos also being used).

Amosite was specified by the U.S. and other navies for the construction of World War II era war ships. Steampipes, boilers and bulkheads were insulated with amosite asbestos. Sheers and Coles (HM Naval Base, Devonport, England)[33] noted "Two major developments since 1944:

> (1) the very extensive use of crocidolite for environmental insulation and fire protection from 1944 to 1963, and (2) the large increase in the amount of amosite used for machinery insulation between 1950 and 1963.

An earlier report by Harries[34] described the same kind of amosite use in British shipyards.

Another World War II application of asbestos was in the production of gas masks, both for military personnel and civilian populations. In 1982 Acheson et al[35] provided details about the production of gas masks in Great Britain:

> It was known that the standard respirators issued to the armed Forces of the British Commonwealth before and during the second world war contained filters consisting of activated charcoal, merino wool, and West Australian crocidolite...
>
> In Britain respirators were also manufactured to protect the civilian population. A contract was placed with a factory in Blackburn, Lancashire, in1936 to manufacture more than 70 million civilian gas masks and work continued in this factory until the end of the war. From contempory data (Ministry of Supply,

> Home Office, and War Office papers 1927-45) and analysis of the contents of surviving masks, civilian gas masks are known to have contained chrysotile, charcoal, and merino wool but not crocidolite. At Leyland, Lancashire, the same firm operated a factory that from 1927 held a monopoly for the manufacture of gas masks for the armed Forces. At an unknown date in the 1930s these respirators were modified to contain crocidolite, and gas masks of the improved type continued to be manufactured there throughout the war and thereafter. Industrial gas masks containing crocidolite were made there until 1969. From the testimony of workers it is known that some civilian gas masks containing chrysotile were also made during the war at the Leyland factory...

Acheson et al studied the mortality pattern during the period 1951-80 of the two groups of female gas mask assemblers, including the 578 women who worked with chrysotile in the Blackburn factory (the Blackburn group) and 757 women who worked with crocidolite (and some chrysotile) in factories in Leyland and Preston (the Leyland group). Significant differences in the mortality pattern between the two groups of women were identified. Mesothelioma was the cause of death or contributed to the death of 5 of the Leyland group. Mesothelioma was identified in only 1 of the Blackburn (chrysotile-exposed) women but that woman was believed to have worked at a smaller Blackburn plant that did use crocidolite in the manufacture of service gas masks. Furthermore, the Leyland group women experienced a statistically significant increase in mortality from ovarian cancer. In retrospect, some of the ovarian cancer cases may have been cases of peritoneal mesothelioma.

Acheson et al concluded:

> The probable explanation for the differences between Leyland and Blackburn lies in the different nature of the exposures in the two factories. The most obvious difference was that at Leyland crocidolite was the principal type of fibre to which the women were exposed while at Blackburn chrysotile was the only type of asbestos used.

In 1983 and 1984 McDonald et al reported on a series of studies[36] [37] [38] that demonstrated a marked difference in mesothelioma risk associated with different asbestos fibers. This series of papers is summarized in the table below:

McDonald AD, Fry J, Woolley, McDonald JC: Dust exposure and mortality in an American chrysotile textile plant. Brit J of Industr Med 1983;40:361-367.	"2543 men employed for at least a month from 1938 to 1958 in a textile plant in South Carolina in which chrysotile was the only type of asbestos used. Of these, 863 men (34%) had died before 31 December 1977, one from malignant mesothelioma." "These findings agree closely with those from another study in this plant and confirm that mesothelioma is rarely associated with chrysotile exposure."
McDonald AD, Fry J, Woolley, McDonald JC: Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture. Brit J of Industr Med 1983;40:368-374.	Pennsylvania plant: "...mainly chrysotile, with some amosite and a small amount of crocidolite, were used primarily in textile manufacture." "4137 men comprising all those employed 1938-59 for at least a month... By the end of 1974, 1400 (35%) had died, 74 from asbestosis and 70 from lung cancer." Mesothelioma identified in death certificate in 14 cases. "The much greater risk of mesothelioma from exposure to processes in which even quite small quantities of amphiboles were used was also confirmed."
McDonald AD, Fry JS, Woolley AJ, McDonald JC: Dust exposure and mortality in an American chrysotile asbestos friction products plant. Brit J of Industr Med 1984;41:151-157.	Connecticut factory manufactured friction products and packings from chrysotile only with no use of amphibole. "3641 men employed for one month or more, 1938-58, 3513 (96.5%) were traced, 1267 (36%) had died, and death certificates were obtained for 1228 (96.9%)." No mesothelioma deaths.

In 1989 Newhouse and Sullivan[39] described a long term follow up of men who had worked in a factory that produced friction materials (principally brakes). The factory used chrysotile asbestos except for certain specific contracts. All of the mesothelioma cases were attributed to crocidolite exposure.

In 1989 Warnock[40] reported on the lung tissue fiber burdens of workers in a shipyard in the

Solano County area of California who developed mesothelioma. The median fiber burden for all types of amphiboles was 2.7 million f/g dry lung. Warnock noted that amosite was the most prevalent fiber type.

In 1992 Begin[41] identified a total of 49 cases of mesothelioma in former Quebec chrysotile asbestos mine and mill workers and challenged the concept that amphibole asbestos (in the form of tremolite, a minor contaminant of Quebec chrysotile) was the cause of the few cases of mesothelioma seen in Quebec. Begin noted:

> The present study documents an increasing incidence of cases of malignant mesothelioma in chrysotile miners and millers of the Eastern Townships of Quebec, with 49 cases in the last 23 years, and a rate of 2.5 cases per year in the last 10 years in the primary industry. . . .
>
> In the past, these cancer cases among Quebec chrysotile miners and millers were considered to be likely attributable to amphibole contamination of the worksite and/or of the mineral ore. . . Nonetheless, cases of mesothelioma in Quebec miners have been documented where chrysotile fibers were the only fibers in lung tissue.

Begin noted evidence for a significant difference in the tremolite contamination of chrysotile ore mined in the two main Quebec asbestos centers, the towns of Asbestos and Thetford Mines, but the incidence of mesothelioma was proportional to the work force and not related to residence in one of the two areas.

> Our data suggest that some of the cases of malignant mesothelioma in Quebec chrysotile miners and millers may not be necessarily attributable to amphibole and could be chrysotile-induced.

The response to Begin's challenge would be given some years later by McDonald et al in a series of reports (see below).

In 1993 Churg et al[42] reported on the fiber burdens in the lungs of 94 long term chrysotile

asbestos miners from Thetford Mines, Quebec. In the patients who had mesothelioma, the chrysotile fiber burdens were very large, with a mean of 34 million f/g dry lung. The tremolite burdens in the mesothelioma cases were even greater, 180 million f/g dry lung. Churg et al concluded:

> . . . in this population of heavily exposed chrysotile miners and millers, the presence of airways fibrosis and asbestosis and, probably, mesothelioma reflects high tremolite burden. Whether chrysotile fibers themselves play a role in disease induction remains uncertain.

In a subsequent report, Churg and Vedal[43] reported on a study of 144 shipyard workers and insulators from Oregon, Washington State and British Columbia. Churg and Vedal stated:

> Our results show clearly that, despite known historic exposure to amosite and chrysotile, amosite is by far the predominant residual fiber, and there are correlations between amosite measures and disease. Chrysotile was present inconstantly and in relatively small amounts, and no correlations were found between chrysotile measures and disease.

Churg and Vedal also commented on the issue of tremolite contamination of chrysotile:

> We have proposed elsewhere that tremolite, which is a natural minor constituent of chrysotile ore, might serve as a substitute marked for chrysotile, and that tremolite rather than chrysotile may actually be the agent responsible for "chrysotile-induced" mesothelioma . . . .

Becklake[44] provided an in-depth editorial comment of Churg and Vedal's study. Professor Becklake noted that:

> . . . the major contribution of the two studies of Churg and associates reviewed here is in adding further weight to the already substantial body of evidence concerning differential disease-generating potential for different asbestos fiber types. Although the facts of differential clearance of chrysotile are acknowledged in both papers, we believe the authors are right to conclude that "there are major differences in the relationship of fiber

> concentration and disease for chrysotile and tremolite compared with amosite or crocidolite."

A most definitive series of papers was published during 1997 in the Annals of Occupational Hygiene, the official journal of the British Occupational Hygiene Society. Liddell, McDonald and McDonald[45] reported on the long term follow up of approximately 10,000 Quebec asbestos miners and millers born between 1891 and 1920 and followed until 1993, at which point 75% had died and the youngest survivor of the cohort was 72 years old. These Quebec asbestos workers had very high life time asbestos exposures, but almost only to chrysotile. The exposure levels of the miners was estimated to be about 80 fibers/cc in the 1940s and lifetime exposure was typically 1000 f/cc-years. The incidence of mesothelioma was very low - 0.4%.

McDonald and McDonald[46] provided further information about the cause of mesothelioma in the chrysotile-exposed Quebec asbestos miners. The authors studied malignancies including mesothelioma reported in miners who worked in Thetford Mines Quebec. Chrysotile asbestos from Thetford was previously identified as having a higher tremolite contamination than asbestos mined in Asbestos, Quebec. McDonald and McDonald correlated the incidence of mesothelioma with work in the 5 central Thetford mines which had a high tremolite burden vs work in the 10 peripheral mines which had a 4 fold lower tremolite contamination. The authors concluded that:

> In the peripheral mines, there was little or no evidence of increased risk for any of the five cancers [including mesothelioma]. The hypothesis that, because of the difference in distribution of fibrous tremolite, cancer risks in the central area would be greater than in the periphery was thus substantiated.

The last in the series of definitive studies on the Quebec asbestos worker cohort was reported in 1997 by McDonald, Case, Churg, Dufresne, Gibbs, Sebastien, and McDonald[47] who provided a detailed case-by-case analysis, including lung asbestos fiber burden analysis, of the 38 deaths from mesothelioma that were identified in the cohort of 10,000 men. Of the 38 cases, 5 occurred in asbestos factory workers; of these 5, fiber burden analysis was available on 2. One of these 2 factory workers had 10.1 million fibers of crocidolite per gram dry lung plus 1 million fibers of amosite per gram dry lung and the other case had 4 million fibers of crocidolite per gram dry lung. Neither crocidolite nor amosite was ever mined in Quebec. These findings were consistent with the known use of

crocidolite in some factory applications in Quebec (including the manufacture of World War II gas masks) and justified exclusion of the 5 factory workers from further analysis. Eight of the remaining 33 mesothelioma cases came from Asbestos, Quebec while the other 25 cases lived and worked in Thetford Mines. All of the 8 cases from Asbestos were in millers, while the 25 cases from Thetford were in miners. Of the 8 cases from Asbestos, 4 had substantial quantities of crocidolite ranging from 700,000 to 14.7 million fibers per gram dry lung.

The mesothelioma cases from Thetford Mines were subjected to additional analysis. Most of these cases had enormous lung burdens of tremolite, ranging from 12.6 to 2,400 million fibers per gram dry lung. Detailed analysis of the work records of the miners in Thetford was carried out. It was discovered that many of the miners had worked only in the central mines (Area A) or the peripheral mines (Area B). It was known that the asbestos ore from the Area A mines had a greater tremolite contamination than the ore from Area B mines. This difference in the ore, and the fact that many of the miners worked only in Area A or only in Area B mines was used to test the hypothesis that the few case of mesothelioma seen in Quebec asbestos miners who had not been exposed to crocidolite were actually caused by the amphibole tremolite. The authors discovered "... that service in the central area led to definite risks of mesothelioma." Table 4 of the study which gave the odds ratio for service in the central vs. the peripheral mines is partially reproduced below:

Table 4. Odds ratio (with 90% confidence limits) at the main complex in Thetford Mines	
Some or all years in central area	All years in peripheral area
2.50 (1.49-4.20)	0.80 (0.27-2.38)

McDonald, Case, Churg, Dufresne, Gibbs, Sebastien, and McDonald concluded:

> Within Thetford Mines, there is clear evidence from case-referent analysis that the risk arising from employment in the localized area of central mines in the main complex (Area A) was much higher than in the peripherally located mines (Area B), where it was minuscule. As we have no reason to suspect that

> geographical variation in the character of chrysotile per se could account for these differences, the presence of other minerals in or near the ore body would appear to offer the best explanation. The only candidate capable of filling the role is fibrous tremolite, and there is considerable supporting evidence.

The cytogenetic mechanism of asbestos induced mesothelioma

Recent studies of the molecular biology of mesothelioma have begun to shed light on the pathogenetic mechanism of this disease. Berube et al, including Mossman[48], have demonstrated that crocidolite asbestos causes "protracted, dose-dependent increases in steady-state mRNA levels of the proto-oncogenes c-fos and c-jun, and AP-1 DNA-binding activity in normal rat pleural mesothelial (RPM) cells." This and related findings have raised important additional questions: What are the consequences of asbestos-induced induction of proto-oncogenes and are there differences between the potency of serpentine and amphibole asbestos which may explain the epidemiological observations in mesothelioma.

Asbestos and many other agents capable of DNA damage can induce delays in cell reproductive cycles. Delays at various points in cell reproduction have been described, including the G1 and G2 phases.[49] Leverese et al [50] and other authors have suggested that such delays are protective in that they "permit DNA repair before the continuing of DNA synthesis or mitosis.... Failure in repair processes could result in fixation and propagation of genomic changes necessary for neoplastic transformation." Leveresse et al describe apoptosis as another kind of protective cellular mechanism:

> "Under certain circumstances, DNA damage may trigger a rapid programmed death of the cells, apoptosis, a process that has already been described in asbestos-exposed mesothelial cells. This cell death is a useful process for eliminating highly damaged cells and avoiding propagation of abnormalities. Conversely, disregulation of the cell response to apoptotic signals may be an important even in neoplastic transformation."

In 1995 Dopp et al[51] noted:

> "It is known that asbestos and other mineral fibers induce lung cancer and mesothelioma. However, the primary mechanisms of fiber-induced carcinogenesis still remain to be elucidated. Previous studies, including our own, have shown that asbestos causes specific mitotic disturbances, micronucleus formation and typical changes in chromatin structure resembling those of apoptosis."

Dopp et al investigated:

> "...the induction of apoptosis by asbestos (amosite, crocidolite, chrysotile) and ceramic fibers. The typical ladder pattern of DNA fragments was identified by means of gel electrophoresis, the intracellular calcium concentration was measured and flow cytometry analyses were carried out to determine the percentage of apoptotic cells. The different fibers showed different potencies for the induction of apoptosis in Syrian hamster embryo (SHE) cells. Depending on the type of fiber applied 3-33% of cells underwent apoptosis. Chrysotile proved to be the most potent inducer of apoptosis compared to the other fibers. In addition, an increase intracellular calcium level was observed in apoptotic SHE cells.... In view of these findings we hypothesize that chrysotile induces apoptosis resulting from long-term changes in intracellular regulation pathways."

In 1996 Hamilton et al[52] studied the effects of "chrysotile (CHR) and crocidolite (CRO), along with a control fiber, wollastonite (WOL), to characterize their relative cytotoxicity and ability to stimulate apoptosis in vitro" on human alveolar macrophages. The authors discovered that:

> "With respect to the apoptotic potency of the two forms of asbestos, CHR induced more apoptosis at much lower concentrations than CRO in the Cell Death ELISA, and CHR produced a more pronounced DNA latter (and less remaining genomic DNA) than CRO.... The differences maybe explained in part by the fact that CHR may induce greater DNA fragmentation than CRO in cells undergoing apoptosis. Therefore, our results would suggest that both forms of asbestos are cytotoxic and apoptotic, but CHR is more effective and

may be active at submicrogram quantities in inducing DNA fragmentation.

In 1997 Leveresse et al (citation 29, noted above) demonstrated that chrysotile was more effective than crocidolite in inducing blockage of cell replication at the G0/G1 checkpoint. Leveresse also demonstrated that apoptosis occurred at a higher rate in cells exposed to chrysotile compared to cells exposed to crocidolite. Commenting on the work of Leveresse and others, Broaddus[53] noted, in an editorial published in the American Journal of Respiratory Cell and Molecular Biology:

> "In response to DNA damage, the cell can either arrest (allowing time for repair) or initiate an active form of cell death termed apoptosis... either path, to cell cycle arrest or to apoptosis, serves to maintain the stability and fidelity of the genome.... For chrysotile asbestos, and to a lesser extent for crocidolite asbestos, Leveresse and colleagues showed evidence of a cell cycle arrest in G1/S and G2/M as well as an increase in p53 protein, all strongly suggestive of a cellular response to DNA damage. Interestingly, these authors find little evidence of apoptosis (0.05% of cells exposed to crocidolite...."

In summary, studies of the molecular biology of the effect of chrysotile and crocidolite asbestos fibers on DNA indicate that while both kinds of fiber are capable to DNA damage, chrysotile is more effective in inducing cell cycle arrest and apoptosis. The latter two mechanisms are protective in that they prevent the evolution of malignant cells. Differences in the effect of serpentine and amphibole asbestos on cell replication may provide a biological explanation for the differences in mesothelioma induction identified in epidemiological studies.

Conclusions from the medical literature regarding asbestos fiber type and mesothelioma:

At this time there is strong scientific support for the following conclusions about mesothelioma:

1. Without an amphibole contaminant, chrysotile is very unlikely to be a cause of malignant mesothelioma. Furthermore, commercial chrysotile products contain very little or no tremolite. For example, multiple industrial hygiene studies of fiber release characteristics of asbestos gaskets[54] and asbestos insulated wire and cable[55] did not identify a single tremolite fiber and a recently published lung fiber burden analysis study by Roggli and Sanders[56] of heavily exposed asbestos workers demonstrated a combined non-commercial amphibole content of <220,000 fibers per gram dry lung compared to the average tremolite burden reported by Churg in the Quebec asbestos workers of 180 million f/g dry lung (and the latter was associated with 0.4% overall incidence of mesothelioma).

2. Mesothelioma cases in Quebec chrysotile asbestos miners were caused by tremolite contamination of chrysotile ore in the central mines of Thetford Mines.

3. In terms of mesothelioma inducing potency, the different forms of asbestos should be rated as: crocidolite • amosite • tremolite • ?chrysotile

3. In terms of frequency, amosite represents the cause of most mesothelioma cases in the United States. Amosite exposure was typical of World War II era shipyard work.

Lung cancer: The risk of primary lung cancer (all cell types) is significantly increased in asbestos-exposed individuals who have the non-malignant lung disease asbestosis, or an amount of asbestos fibers in lung tissue typically associated with asbestosis.and almost all cases of lung cancer occur in former or present cigarette smokers. Asbestos-exposed individuals who do not have asbestosis, or an equivalent pulmonary asbestos fiber burden, do not have an increased risk of lung cancer.

In the absence of radiological or pathological evidence of asbestosis, the claim can be supported by an asbestos fiber lung tissue burden in the range typically associated with

asbestosis (i.e. 2.5 million fibers per gram dry lung be scanning electron microscopy) or by a reliable occupational history of hands-on work in a trade historically associated with moderate to heavy asbestos exposure such as construction insulator, insulator-sprayer, pipefitter, steamfitter, boiler-maker.

The history of knowledge regarding asbestos exposure, asbestosis and increased risk of lung cancer and the evidence supporting the association of lung cancer with asbestosis (but not with simple asbestos exposure), is reviewed below:

Asbestosis, not just asbestos exposure, increases the risk of lung cancer

In 1947 the British Annual Report of the Chief Inspector of Factories noted that "Thirty one cases of carcinoma of lungs and pleura were found at autopsy of 235 cases of Asbestosis.[57] Commenting on this report, a 1949 editorial in the Journal of the American Medical Association[58] observed that ". . . the available evidence shows that the occurrence of cancer of the lung is related to pulmonary asbestosis and is not merely a possible sequella of exposure to asbestos dust . . . ."

In 1955 Doll[59] reported that of 113 men who worked for at least 20 years with asbestos, 11 developed lung cancer compared to an expected incidence of 0.8. Doll observed:

> "All the cases of lung cancer were confirmed histologically and all were associated with the presence of asbestosis."

The landmark 1979 study by Hammond, Selikoff and Seidman[60] attempted to define the relative risks of lung cancer in a group of 17,800 asbestos insulators. Hammond et al quoted a lung cancer incidence of 11.3/100,000/year for non-smokers and 122.6/100,000/year for smokers who had not worked with asbestos. Of the 17,800 insulators studied, 891 claimed to have been nonsmokers and 4 died of lung cancer, resulting in a corrected incidence of 58.4/100,000/year. The rest of the group studied by Hammond et al were considered cigarette smokers and they were found to have an incidence of lung cancer of 601.6/100,000/year.

Unfortunately, the 1979 Hammond report did not identify the sub-cohort that had asbestosis. Subsequent analysis of lung cancer cases derived from the original 17,800 cases published

by Kipen et al (including Selikoff)[61] revealed that all of the patients who died of lung cancer also had pathological evidence of asbestosis.

In 1980 Liddell and McDonald[62] reported a study of Quebec chrysotile asbestos miners. Liddell and McDonald identified 118 lung cancer deaths which represented an excess of 52 deaths over predicted. Of 49 men whose last chest x-ray was rated as normal by the ILO system, the SMR for lung cancer was not elevated at 1.08; however, of the remaining miners whose x-rays were abnormal (and who presumably had asbestosis) the SMR for lung cancer was 3.5. Liddell and McDonald commented:

> ". . . most, but not necessarily all, cases of lung cancer attributable to chrysotile exposure in mining and milling probably have small parenchymal opacities before death."

In 1981 Berry[63] reported on a study of asbestos workers who were certified by British Pneumoconiosis Medical Panels as having asbestosis. Berry observed that the standardized mortality ratio (SMR) for lung cancer increased from 9.1 for men classified as 10% disabled to 25 for men with a 50% disability. These findings suggest an increasing risk of lung cancer with increasing degrees of asbestosis.

In 1989 Sluis-Cremer and Bezuidenhout[64] reported an autopsy study of 399 former amphibole asbestos miners in South Africa. Thirty-five cases of lung cancer were identified on autopsy. Of the 399 patients, 302 were found to have no pathological evidence of asbestosis, 69 had "slight" asbestosis and 28 had moderate to severe asbestosis. In the group of 302 without asbestosis, the authors calculated that 12.4 lung cancers were expected (based on smoking habits) but only 11 were observed for an SMR of .887. Of the 69 patients with slight asbestosis, 3.6 lung cancers were expected but 15 were observed resulting in an SMR of 4.16. Among the 28 patients who were demonstrated to have moderate or severe asbestosis on autopsy, 1.6 lung cancers were expected but 9 were observed for an SMR of 5.63. The authors concluded:

> "The SPMR for both the 35 cases proved by necropsy and the 25 cases certified as bronchial cancer on the death certificate show no excess bronchial cancer in the group without asbestosis whereas there is an excess in those with asbestosis. The excess increases with the severity of the asbestosis found at necropsy.

> In conclusion this study suggests that asbestos caused bronchial cancer is almost always associated with some degree of histologically demonstrable asbestosis."

Sluis-Cremer and Bezuidenhout also observed that:

> "In the absence of asbestosis at necropsy a bronchial cancer in a man exposed to asbestos is unlikely to be due to asbestos."

In 1991 Hughes and Weill[65] described a study of all 839 workers employed in two New Orleans asbestos cement factories in 1969. By 1983 154 of the 839 men had died and death certificates of 153 of these men were available. X-rays on all of the men were interpreted by three prominent radiologists using the ILO system. The authors observed:

> "Among workers with no x-ray film abnormalities in 1969, the lung cancer risk was not raised (five mesotheliomas, however, were found). For the long term workers in this group, there were six lung cancers compared with 5.8 expected. By contrast, among those with small opacities, profusion • 1/0, there were around seven excess malignancies, all of them due to lung cancer; the lung cancer risk was significantly raised (9 v 2.1; $p<0.001$) and significantly different from the risk in long term workers without abnormalities ($p<0.01$, likelihood ratio test)."

Hughes and Weill commented that:

> "The current study is the latest in an emerging body of evidence supporting the view that asbestos is a lung carcinogen because of its ability to cause lung fibrosis. . . .
>
> Because detectable asbestosis is not likely to result from current occupational and general environmental exposures, the prevention of the effect of exposure on lung fibrosis is likely also to prevent the excess risk of lung cancer. . . . Finally, these data may provide further evidence to support the common practice of attributing lung cancer to exposure to asbestos only if asbestosis is also present; otherwise, these tumors are, in most part, due to cigarette smoking."

In a 1995 paper that was subsequently criticized for methodological error (see below), Wilkinson et al[66] published in Lancet a paper titled "Is lung cancer associated with asbestos exposure when there are no small opacities on the chest radiograph?" The authors summarized their investigation and results as follows:

> "This study was designed to test the hypothesis that the risk of lung cancer from asbestos exposure is confined to persons with radiographic evidence of pulmonary fibrosis. Occupational and smoking histories were obtained from 271 patients with a confirmed diagnosis of primary lung cancer and 678 referents (279 with other respiratory disease and 399 with cardiac disease). Histories were reviewed blind to assess the timing, duration, and probability of exposure to asbestos. To allow for a lag between asbestos exposure and the development of lung cancer, subjects were classified by the time they had spent in an occupation entailing definite or probable exposure more than15 years before diagnosis. The presence and extent of fibrosis was assessed blindly from chest radiographs by three readers and scored for small opacities with the ILO 1989 International Classification of Radiographs of the Pneumoconioses. 93 (34.3%) cases had worked in an occupation with definite or probable asbestos exposure compared with 176 (25.8%) referents (crude odds ratio for lung cancer 1.49, 95% CI 1.09-2.04). After adjustment for age, sex, smoking history, and area of referral, the odds ratio (95% CI) was 2.03 (1.00-4.13) in the subgroup of 211 with a median ILO score for small parenchymal opacities of 1/0 or more, and 1.56 (1.02-2.39) in the 738 with a score of 0/1 or less (ie, those without radiological evidence of pulmonary fibrosis). These results suggest that asbestos is associated with lung cancer even in the absence of radiologically apparent pulmonary fibrosis."

The 1995 Wilkinson paper in Lancet prompted a detailed response published in 1996 in the British journal Thorax by Robert Jones (Department of Medicine, Tulane University), Janet Hughes and Hans Weill (Department of Biostatistics and Epidemiology, Tulane University).[67] Jones, Hughes and Weill presented detailed criticism of Wilkinson's methodology:

> "The authors actually ignored their subjects' assertions concerning whether or not each was exposed to asbestos. Why it was preferable to use a mesothelioma study job classification is not explained. The dose-response relationship of asbestosis and asbestos-attributable lung cancer are similar to each other but differ greatly from those of mesothelioma. Only the jobs in the authors' 'definite' category - asbestos production, heating trades, and insulation work - inspire much confidence that each individual so classified would probably have had moderate or heavy exposure. The controls proved to have greater prevalence of 'definite' exposure than the cases! Jobs listed in the 'probable' and 'possible' categories included many for which there is inadequate evidence of asbestos-related lung cancer. In the analyses the authors combined 'definite' and 'probable' as both a categorical variable and a criterion for computing length of exposure."

In addition to the above problems, in the Wilkinson study a non-standard method of chest x-ray interpretation was performed, involving "masking" as much as two quadrants of the film. Jones et al commented that "Masking the radiographs would be expected to reduce the chance of a correct judgement, leading to both false positive and false negative assessments" and further observed that "In fact, Wilkinson et al failed to find a relation between exposure to asbestos and the presence of small opacities." About the Wilkinson paper, Jones et al concluded:

> "When the adjusted odds ratios (ORs) were further broken down for small opacities of category 0/1 or less and category 0/0 alone, the authors [Wilkinson et al] found 'evidence that ORs increased' with duration of exposure in both categories. However, in both categories the ORs for less than 10 years' exposure were much higher than the ORs for10 or more years' exposure, and the ORs of the latter were not significantly >1.0 in all subjects or in men aged 40 years or older. This is surely evidence against, not for, a dose-response relationship in groups with 'negative' radiographs. In the end, the cited observations rest only on dichotomised exposures, estimated according to a scheme that may be valid for mesothelioma but cannot be presumed so for lung cancer. Under the weight of additional concerns about the study of hospital patients with masked radiographs, this work does not provide convincing support for an asbestos-attributable risk in the absence of small opacities."

Jones, Hughes and Weill also provided a review of the epidemiological literature, beginning with the 1947 publication of the British Annual Report of the Chief Inspector of Factories, cited above. Additionally, the authors gave a detailed review of other published data, including studies of the relationship between forms of lung fibrosis other than pneumoconiosis and an increased risk of lung cancer, lung cancer registry studies, asbestos fiber burden studies, animal studies and pleural plaque epidemiological studies. Summarizing all of the available evidence, the authors provided the following "Learning Points" table:

1. *Lung fibrosis of many causes - known and unknown - is associated with increased risk of lung cancer.*
2. *The much discussed synergism between asbestos "exposure" and studies of insulation workers turns out to be a synergism involving asbestosis, not just asbestos exposure.*
3. *The site of origin and cell type of a lung cancer are not regarded as reliable indicators of causation (or non-causation) by asbestos.*
4. *In asbestos inhalation experiments animals develop excess lung tumours only when lung fibrosis is also produced.*
5. *Pleural plaques have not proved to be a reliable marker for increased risk of lung cancer.*
6. *Excess lung cancer deaths In populations exposed to asbestos are generally first detected at about the same cumulative exposure levels as those at which asbestosis begins to appear.*

In addition to the above table, the authors concluded by stating:

> "While the issue of whether asbestosis is a necessary precursor to asbestos-attributable lung cancer cannot at this time be considered settled, the weight of the available evidence strongly supports this proposition."

In February 1999, the journal Chest published a major review and meta-analysis by William Weiss[68], titled "Asbestosis: a marker for the increased risk of lung cancer among workers exposed to asbestos." The author focused on the published cohort studies that provided evidence regarding the hypothesis "that excess lung cancer risk occurs only among those workers who develop asbestosis" (thus avoiding the methodological problems of the Williamson study cited above). Weiss presented the data from multiple cohort studies dating back to 1960 (many of the studies cited by Weiss are also described above) that included information about the presence or absence of asbestosis and the occurrence of lung cancer. Additionally, Weiss presented data from 7 studies dating back to 1980 of asbestos-exposed cohorts in whom no deaths from asbestosis were recorded and for which the summary SMR for lung cancer was exactly 1.0, obviously leading to the conclusion that "if the asbestos exposure was not sufficient to cause any deaths from asbestosis, there is no increased risk of lung cancer."

In addition to the above, Weiss provided data from 38 cohorts reported in 30 reports in which "it is possible to estimate the rates for each disease, [asbestosis and lung cancer] using the number of individuals at the start of observation as the denominator and calculating the cumulative rates..." Twenty-nine of the 38 cohorts included more than 1000 subjects and 4 of the studies included more than 10,000 workers. Figure 1 of Weiss' report, a scattergraph of the data from all of the 38 cohort reports, is reproduced below:

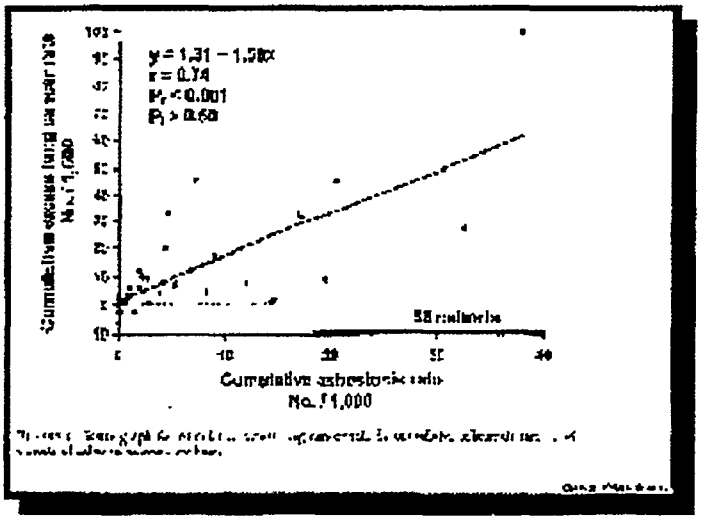
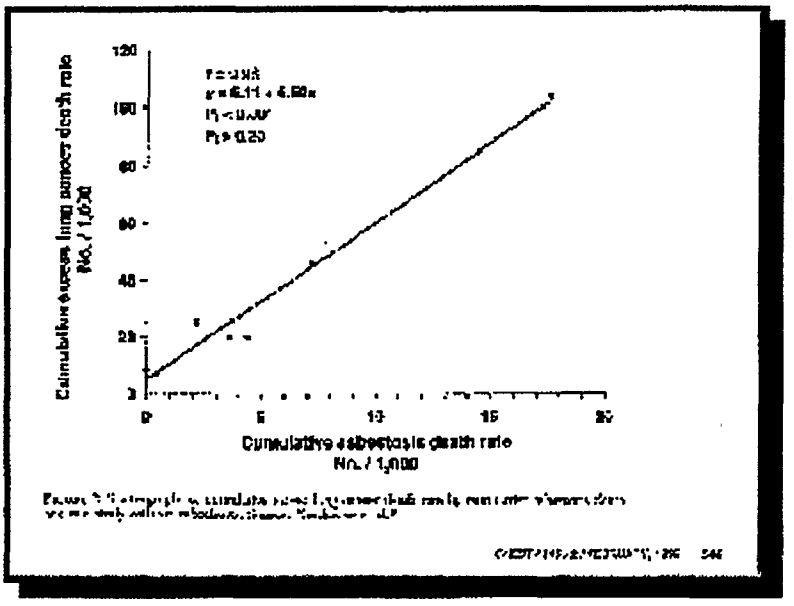


Figure 1 from the Weiss report (above) demonstrates a linear correlation coefficient of 0.74 which was statistically highly significant, indicating a significant relationship between excess lung cancer rates and asbestosis death rates.

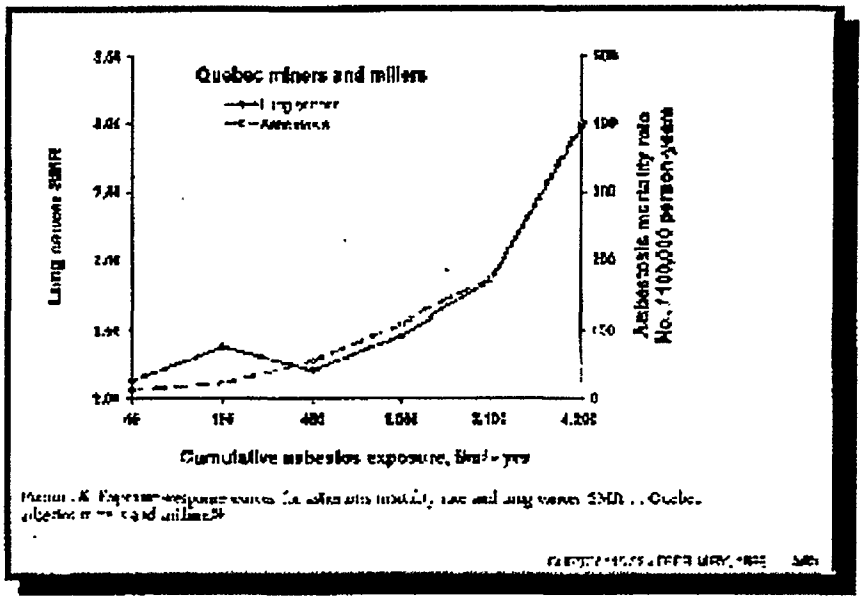
Weiss further considered data from an important paper by Newhouse[69] which reported on 6 subcohorts of 512 to 1,369 workers. Figure 2 from the Weiss report is reproduced below. Similar to Figure 1 (above), Figure 2 is a scattergraph of cumulative excess lung cancer death rates plotted against cumulative asbestosis death rates for the 6 subcohorts.



Weiss explained that in the above figure,

> "The four male factory subcohorts are represented, from left to right, by the first three points and the last one. For these four points, the linear correlation coefficient is 0.99. The points for the laggers and female factory workers (fourth and fifth points) were close to the regression line for all six sets of data; the correlation coefficient was 0.98, statistically highly significant, and the intercept was not significantly different from a zero excess lung cancer rate."

Thus, Weiss concluded, "the cumulative asbestosis mortality rate is an excellent predictor of the cumulative excess lung cancer mortality rate." Weiss also provided detailed analysis of an important paper published in 1997 by Lidell, McDonald and McDonald[70] in the Annals of Occupational Hygiene pertaining to the 1891-1920 birth cohort of Quebec chrysotile asbestos miners and millers, the largest cohort published in the medical literature. Figure 5 from the Weiss report, which plots the relationship between lung cancer SMR and asbestosis mortality rates against cumulative asbestos exposure in fiber/ml-years, is reproduced below:

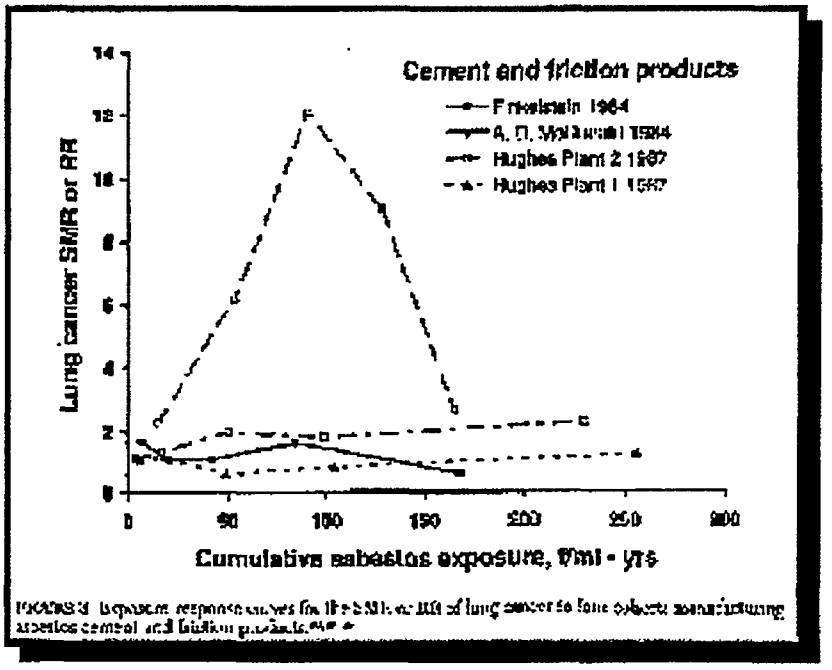


Regarding the data shown in Figure 5 from the Weiss report reproduced above, Weiss commented:

> "The exposure-response curve for the asbestosis mortality rate was plotted in Figure 5 in terms of the number per 100,000 person-years. The curve rises very smoothly from the very lowest to the highest exposure category, suggesting that there is a much lower threshold, if any, for asbestosis deaths than for lung cancer deaths. The rates rise from 12 to 399 per 100,000 person-years. Above a median exposure of 450 f/mL-years, the curves for

lung cancer and asbestosis are almost identical. The two curves are based on disease measures that are not the same for lung cancer as for asbestosis. Nevertheless, the correlation is remarkable."

The medical literature contains other reports which plotted the relationship between lung cancer SMR and estimates of cumulative asbestos exposure, although few studies benefit from asbestos dust counts such as those reported by the Liddell report, in which case many of the counts were obtained in the mines by a single investigator over many years. Of the studies that challenged the relationship between asbestosis and lung cancer, the Finkelstein paper, published in 1984 in the American Review of Respiratory Diseases, was singled out by Weiss for particular criticism. Weiss observed that plotting the relationship between lung cancer SMR and cumulative asbestos exposure as reported by Finkelstein resulted in "a curve with a very strange shape." That plot, shown in Weiss report as Figure 3, is reproduced below:



In my experience, the Finkelstein report is sometimes cited in medical-legal cases involving asbestos exposure and lung cancer. In contrast to reliable data such as that from Newhouse and Liddell, presented in detail and cited above, Weiss gave the following commentary about the 1984 Finkelstein report:

> "The Finkelstein curve is based on a 1984 report in which the lung cancer risks presented were not SMRs. They were rate ratios based on mortality rates per 1,000 man-years among 535 exposed male employees in an Ontario asbestos-cement factory run by the same company as those plants covered in the article by Hughes et al [1987]. The comparison was to rates for Ontario men and the various rates were standardized to the age and latency distribution of the entire cohort. Flaws in the design of the study are as follows: tracing was only 84% complete, the Ontario male rate was based on statistics for 1970 to 1974 whereas the period during which person-years of exposed men were accumulated is not given, the numbers of lung cancer deaths in each stratum of exposure were small, and exposure estimates in the early years of exposure were uncertain. Interpretation of this strange exposure-response curve is impossible."

Progression of asbestosis and the risk of lung cancer

Additional evidence in support of the hypothesis that asbestos exposure increases the risk of lung cancer in those patients who develop asbestosis was provided by the June 1998 report in Chest by Oksa[71] and colleagues from the Finnish Institute of Occupational Health, University of Helsinki, who reported on a study of 85 asbestosis patients (78 men and 7 women) who had serial chest x-rays between 1979 and 1987. Among the asbestosis patients who demonstrated progressive interstitial fibrosis by serial chest radiographs there was a remarkably high incidence of lung cancer. All of the asbestosis patients who developed lung cancer were current or ex-cigarette smokers. The authors concluded that:

> "Asbestosis patients with radiographic progression of small opacity profusion over a few years are at a higher risk of lung cancer than those with a less aggressive course of the disease. The progression of pulmonary fibrosis may be an independent risk factor that, in addition to smoking history and the intensity of asbestos exposure, could be used to estimate lung cancer risk."

Whether or not progressive asbestosis is an independent risk factor for lung cancer, this study provides further evidence of the importance of asbestosis in the development of lung cancer.

Non-occupational asbestos exposure

Another way to study the effects of asbestos exposure on the risk of lung cancer is to examine family contacts of asbestos workers. In the medical literature such exposure has been typically described as low dose, although some non-occupational secondary exposure was of moderate, and not really low, intensity.

The largest and most recent study of non-occupational asbestos exposure was performed by Michel Camus and his associates[72] of the Epidemiology and Biostatistics Unit of the Institut Armand-Frappier and the Department of Epidemiology and Biostatistics, McGill University. Camus et al:

> "... determined the number of deaths that occurred between 1970 and 1989 among women at least 30 years of age who lived in 2 chrysotile-asbestos-mining areas or 60 reference areas in the province of Quebec. . . . Over the entire observation period, among women 30 years of age or older, there were 221,375 person-years in the asbestos-mining areas and 8,629,630 person-years in the reference areas."

Three mining areas were defined: Asbestos, Quebec, Thetford Mines, Quebec and Black Lake, Quebec. (Previous studies by McDonald and McDonald[73] demonstrated that chrysotile asbestos from Thetford had a higher tremolite contamination than asbestos mined in Asbestos, Quebec. McDonald and McDonald correlated the incidence of mesothelioma with work in the 5 central Thetford mines which had a high tremolite burden vs work in the 10 peripheral mines which had a 4 fold lower tremolite contamination. Thus it was not surprising that Camus et al identified several possible mesothelioma cases in the housewives.)

Camus et al undertook a complex estimate of:

> "... the population's average cumulative exposure to asbestos, which is the product of the intensity and the duration of exposure. These two components were estimated separately for each of three possible types of exposure: neighborhood exposure, resulting from emissions from asbestos mining or milling in the towns' outdoor air; household exposure, resulting from dust brought home by asbestos workers; and occupational exposure. . . . Average annual ambient levels were estimated to have peaked at 1 fiber per milliliter or more (this value reflects the number of fibers longer than 5 micron and visible on optical microscopy per milliliter of air) between 1940 and 1954 and to have been above 0.2 fiber per milliliter from about 1905 to about 1965."

Additional exposures were calculated for the estimated 70% of the women who had lived in the same household as an asbestos worker and the 5% of women who actually worked in the asbestos industry. The estimated average cumulative asbestos exposure was 25 fiber-years, which is interesting because it is equivalent to the previously identified threshold exposure for asbestosis.[74 75 76]

Camus et al found that of 2242 deaths among the housewives studied, there were 2 deaths from asbestosis. Whether or not those two women were among the 5% of women who worked in the asbestos industry was not stated. For lung cancer, Camus identified 71 deaths among the asbestos exposed housewives compared to 71 deaths that were expected based on Quebec population statistics, resulting in a standardized mortality ratio of exactly 1.0. Using a somewhat different statistic, the standardized proportionate mortality ratio, resulted in a value of 1.1 ($P>0.05$), suggesting between 0 and 6.5 excess deaths from lung cancer among the women with non-occupational exposure to asbestos. Seven deaths from pleural cancer were observed (relative risk, 7.63; $P<0.05$). Camus et al concluded: "We found no measurable excess risk of death due to lung cancer among women in two chrysotile-asbestos-mining regions. The EPA's model overestimated the risk of asbestos-induced lung cancer by at least a factor of 10."

Pulmonary parenchymal asbestos fiber burden and risk of lung cancer

Greenberg and Roggli[77] have agreed that there is a relationship between asbestosis and lung cancer but suggested that the presence of an elevated tissue asbestos burden (without associated asbestosis) might also be enough to increase the risk of lung cancer:

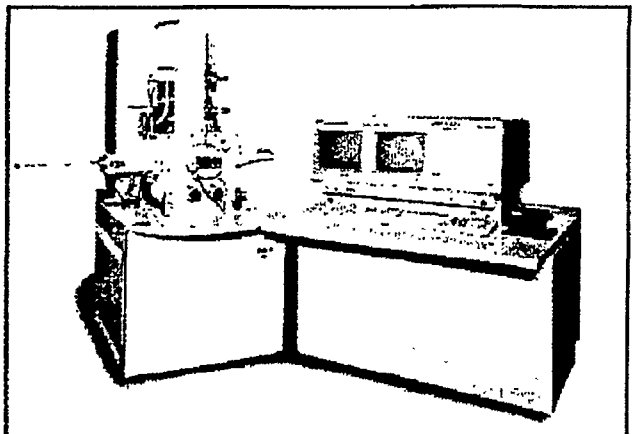
> ". . . the weight of the evidence at this time seems to indicate that, in an asbestos worker with carcinoma of the lung who also smokes cigarettes, asbestosis must be present clinically or histologically (*or there should at least be a tissue asbestos content within the range of values observed in patients with asbestosis*) [emphasis added] in order to assign a substantial contributing role to asbestos in the causation of the lung cancer."

Roggli, Pratt and Brody[78] reviewed 5 reports of tissue asbestos content in asbestosis. In all 5 reports the median uncoated fiber count exceeded (usually by a considerable amount) 1×10^6 fibers per gram of dry lung tissue. Roggli et al suggested that 1×10^6 fibers is a threshold tissue burden for the development of asbestosis. Roggli further reported that the mean uncoated fiber count in 76 patients who had pathological evidence of asbestosis was 3.3×10^6 fibers per gram of dry lung tissue. Roggli et al also reported on a study of 143 patients who had been exposed to asbestos and who developed lung cancer. All but 6 were cigarette smokers or ex-smokers. Among the 48 patients who had pulmonary parenchymal asbestosis the mean asbestos fiber count was 3.07×10^6 fibers per gram of dry lung tissue.

Roggli[79] reported that of 76 patients who had asbestosis, the mean asbestos body count was 378,000 per gram dry lung. Roggli, Greenberg and Pratt[80] reported that of 48 patients who had asbestosis and lung cancer, the mean asbestos body count was 334,000 bodies per gram dry lung.

In the March 2000 edition of the Annals of Occupational Hygiene, Roggli and Sanders[81] presented additional detailed analysis of asbestos fiber burden in the lung tissue of asbestos exposed patients who had lung cancer. Roggli and Sanders studied lung tissue from 234 cases, most of which had been referred for medical-legal evaluation. Lung tissue was examined pathologically for the presence or absence of asbestosis, defined as "peribronchiolar fibrosis with or without alveolar septal fibrosis in association with asbestos bodies." The presence or absence of pathologically demonstrated pleural plaques was also noted. Asbestos body counts were made in all cases, according to the light microscopy method described by Roggli and reported in AB/g wet lung compared to a background level in normal lung of 0-20 AB/g with a LOD (limit of detection) of 3 AB/g.

In addition to asbestos body determination, Roggli and Sanders performed asbestos fiber burden analysis using a JEOL JSM-6400 SEM (scanning) electron microscope. Asbestos fiber type was determined by an EDXA (energy dispersive x-ray analysis) unit fitted to the SEM. For purpose of analysis, the patients were divided into 3 groups: Group I had light microscopy evidence of asbestosis, Group II had pleural plaques without asbestosis and Group III were pathologically normal. The results are summarized as follows:



JEOL 6401 SEM

	Asbestos bodies/g wet lung	Total fibers >5• m/g wet lung
Group I (asbestosis)	27,300	253,000
Group II (plaque)	710	14,000
Group III (normal, but asbestos exposed)	80	4,990
Normal, not asbestos exposed	2.9	<600

Results from such studies are often reported in the medical literature per gram dry lung. Multiplication of the above values by approximately 10 gives results per gram dry lung.

Roggli and Sanders emphasized that "differences among Groups I-III in our study were almost entirely accounted for by commercial amphiboles, primarily amosite. Indeed, commercial amphiboles were detected in 88% of cases." Because chrysotile asbestos

tends to break down after long residence in the lung and because many chrysotile fibers have a diameter less than 0.1 • m (not detected by SEM at screening magnification), SEM does not reflect past exposure to chrysotile.

Roggli and Sanders emphasized that more than 50,000 fibers of commercial amphibole asbestos (amosite + crocidolite) was detected per gram wet lung (approximately = 500,000/g dry lung) in 82% of group I patients (i.e. asbestosis) and that equal numbers of asbestos fibers were detected in only 9 cases from groups II and III. Thus, the distribution of fiber counts was bimodal and differentiated asbestosis from non-asbestosis cases. Roggli and Sanders concluded:

> "... among a selected group of primary lung cancers from the United States with some history of asbestos exposure, a markedly elevated pulmonary asbestos burden was identified among those with a pathologic diagnosis of asbestosis... Taken together, these findings suggest that an amphibole fiber burden sufficient to induce carcinoma of the lung is most often (but not invariably) accompanied by histologic evidence of asbestosis."

Pathogenesis of lung cancer in asbestos workers exposed to cigarette smoke

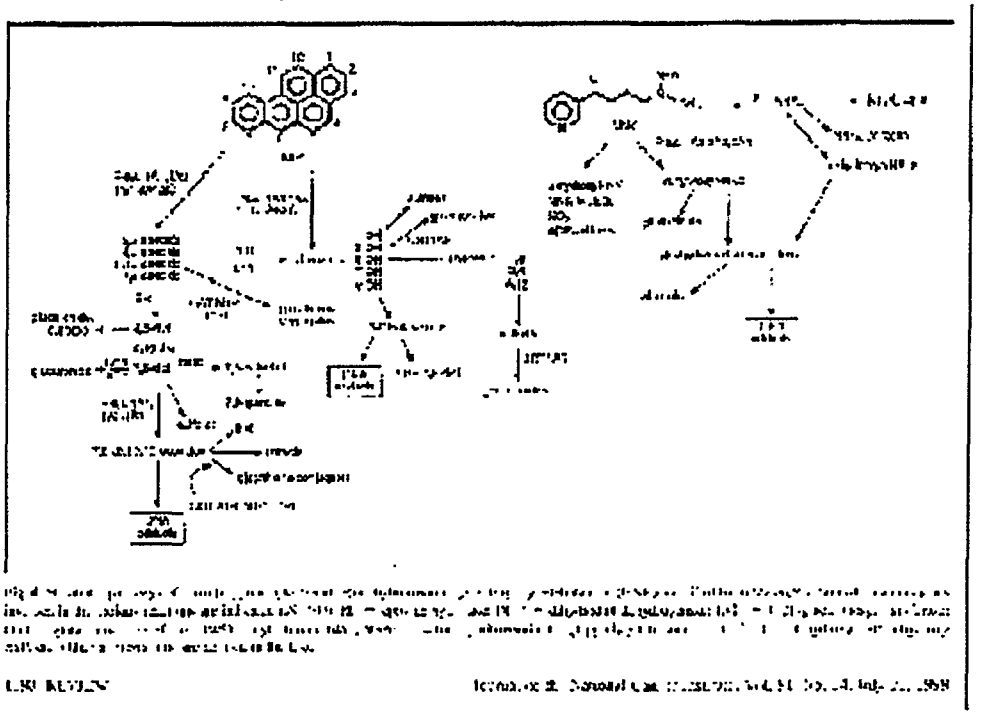
Almost all cases of lung cancer, including those which occur in asbestos workers who have asbestosis, are related to cigarette smoking. Of the 35 lung cancer cases described in 1989 by Sluis-Cremer and Bezuidenhout, 33 were current or ex-smokers. Of the 29 cases of lung cancer described in 1991 by Hughes and Weil, all were smokers. Of the 234 cases described by Roggli and Sanders (above) smoking history was available in 157 of the cases and all but 11 were smokers, i.e. 93% were current or ex-smokers.

The tobacco leaf contains a complex mixture of compounds, including starches, proteins, sugars, alkaloids, hydrocarbons, phenols, fatty acids, sterols, and inorganic minerals. When subject to burning temperatures of 830 to 890 degrees centigrade, these compounds undergo extensive pyrolytic reactions, making the cigarette a tiny "chemical factory" that generates thousands of different compounds. Mainstream cigarette smoke is a concentrated aerosol consisting of a heterogenous mixture of gases, uncondensed vapors, and about 10^{10} particles/mL. The particulate phase contains an estimated 3,500 to 4,000 different chemical compounds, including most of the carcinogens. By the late 1950's many of the compounds in tobacco smoke had been identified; many were known carcinogens,

identified earlier by Hartwell in 1951 and others and summarized in 1964 by the Surgeon General of the United States in the first report on cigarette smoking and disease[82] who observed that tobacco smoke contained at least seven, and probably many more, known carcinogens, of which benzo(a)pyrene, a polycyclic hydrocarbon, was "the most potent" and was present in the highest quantity in tobacco smoke. In addition, as remarked by the Surgeon General in 1964, other polycyclic hydrocarbons isolated from tobacco smoke were "not yet adequately tested for carcinogenicity." By 1989 the Surgeon General[83] had identified 43 compounds in cigarette smoke as known carcinogens. A 1999 review[84] published by Stephen Hecht of the University of Minnesota Cancer Center in the Journal of the National Cancer Institute identified 55 carcinogens in mainstream smoke, including 20 pulmonary carcinogens.

The two kinds of cigarette smoke carcinogens that are currently best understood are the polycyclic aromatic hydrocarbons (PAHs) including benzo[a]pyrene, and the tobacco specific nitrosamines (TSNA's) including compounds named NNN and NNK. The PAHs are delivered directly to the bronchial tubes and lung tissue by inhalation whereas the TSNAs are inhaled and absorbed and then delivered to lung and airway tissue in the bloodstream. The PAHs and TSNAs are metabolized within the body and unfortunately transform into compounds which stick or adduct to certain spots on human genes, forming "DNA adducts". These DNA adducts injure the underlying DNA, resulting in point mutation of certain essential genes which are called oncogenes such as the K-ras gene, and tumor suppressor genes including the p53, myc and rb genes. Multiple recent review articles summarize this evolving knowledge about gene mutations which are caused in almost all cases by exposure to carcinogens present in cigarette smoke.[85 86 87 88 89 90] The exact mechanisms by which certain identified cigarette carcinogens such as benzo(a)pyrene[91] and tobacco specific nitrosamines[92] cause gene mutations has also been described.

The biochemical pathways through which PAHs and TSNAs are metabolically activated and form DNA adducts were reviewed by Hecht in the 1999 Journal of the National Cancer Institute article (previously cited) and are summarized below:



Individuals vary significantly in their ability to detoxify such exogenous chemicals. To an important degree, this variability is dependent on genetically defined production of enzymes such as glutathione S-transferases (GSTs) and N-acetyltransferases (NATs) controlled by GSTM1, GSTT1 and other genes.[93 94 95 96 97 98] Recent investigations have revealed that, because tobacco carcinogens require metabolic activation before binding to DNA, "... variations in an individual's metabolic phenotype that have been detected in enzymes involved in activation and detoxification should play an essential role in the development of environmental cancer. This phenotypic metabolic variation has now been related to genetic polymorphisms, and many genes encoding carcinogen-metabolizing enzymes have been identified and cloned."[99] Variability in genetically defined production of enzymes explains the increased incidence of lung cancer in first order relatives of lung cancer patients that has been recognized for many years.

The K-ras oncogene is mutated in about 30% of adenocarcinomas, generally at codon 12, but mutated K-ras is identified less frequently in squamous cell carcinoma.[100] The p53 tumor suppressor gene is mutated in about 70% of small cell lung cancer, 65% of squamous cell, 60% of large cell and 33% of adenocarcinoma. The fundamental importance of point mutation in oncogenes and tumor suppressor genes in lung cancer is consistent with the multiple epidemiological observations that lung cancer risk is increased in cigarette smokers who are exposed to asbestos and develop asbestosis: interstitial fibrosis causes increased pulmonary cellular replication which results in the expansion of clones of cells which carry genes mutated by exposure to carcinogens such as benzo-a-pyrene. However, the question remains, does asbestos exposure itself, including exposure insufficient to result in asbestosis, cause point mutation in genes crucial to lung cancer development such as K-ras and p53? In 1995 Wang et al[101] of the Occupational Health Program, Harvard School of Public Health reported on a study of 85 lung cancers surgically removed at the Massachusetts General Hospital and suggested that p53 mutations were more common not only in patients with a heavy smoking history, but also in patients exposed to asbestos. In 1999 Nelson et al[102] of the Department of Cancer Cell Biology, Harvard School of Public Health reported on their study 84 male lung cancer patients who underwent surgical resection at the Massachusetts General Hospital between 1992 and 1996. The goal of the study was:

> "to test whether occupational asbestos exposure was associated with k-ras codon 12 mutations in lung adenocarcinoma tumors and to determine whether this was conditional on the presence of asbestosis."

The study was limited to men who had adenocarcinoma. The authors reported:

> "The prevalence of k-ras mutation was higher among those with a history occupational asbestos exposure (crude odds ratio, 4.8; 95% confidence interval,1.5-15.4) compared to those without asbestos exposure, and this association remained after adjustment for age and pack-years smoked (adjusted odds ratio, 6.9; 95% confidence interval, 1.7-28.6). An index score that weights both the dates of exposure and the estimated intensity of exposure indicated that those with k-ras mutations had significantly greater asbestos exposures than those without mutations ($P < 0.01$). Analysis of the descriptive components of exposure indicated that the duration of exposure was not associated with k-ras mutation, but that the time since initial exposure

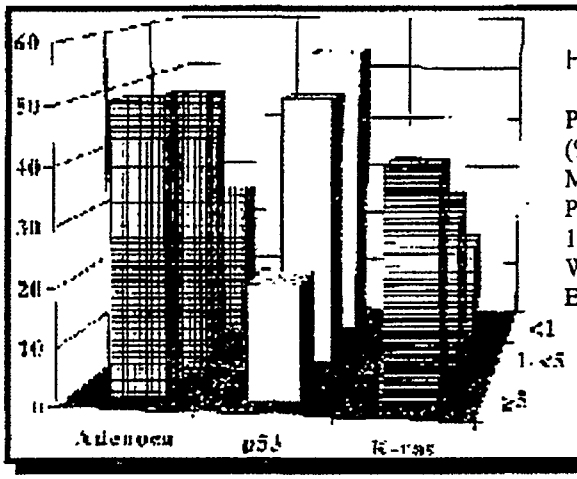
> was significantly associated with mutation status. The association of k-ras mutation and reported asbestos exposure was not dependent on the presence of radiographic evidence of asbestos-related disease. These data suggest that asbestos exposure increases the likelihood of mutation at k-ras codon12 and that this process occurs independently of the induction of interstitial fibrosis."

However, the study design of the Nelson report (above) contains serious, unexplained flaws. Asbestos exposure was determined only by history and there was no description of the presence or absence of pathological asbestosis, nor was there an attempt to correlate asbestos fiber tissue burdens with the finding of K-ras mutations. Of the 21 patients determined on the basis of history to have had asbestos exposure, 42.9%, or more simply 9 patients, were classified as having "high" asbestos exposure, and yet, only one patient was thought to have interstitial fibrosis on chest radiograph and there was no description of pleural plaque. Importantly, the authors did not indicate that the chest x-rays had been read by a NIOSH certified B reader.

A more detailed report, not limited by the above research design problems, was published in April 1999 and revealed different findings. Husgafvel-Pursiainen et al[103] of the Finnish Institute of Occupational Health reported in the American Journal of Respiratory Cell and Molecular Biology on their study of 105 lung cancer patients, nearly all of whom were cigarette smokers. Occupational asbestos exposure was determined both by history and by pulmonary parenchymal asbestos fiber burden, and 32% (33 men) of the cases were found to have a fiber burden • 1×10^6 asbestos fibers per gram dry lung (although fibers >1 µm were counted, rather than just fibers >5 µm). Scanning electron microscopy was used and chrysotile could not be identified easily; most of the fibers were amphiboles and in fact antophyllite was the most commonly identified fiber. Seven of the 33 men with a count • 1×10^6 asbestos fibers per gram dry lung were diagnosed by histology as having asbestosis. The authors reported that p53 mutation was less common in asbestos exposed than in non-exposed patients. In contrast, the K-ras mutation, which was markedly increased in patients with adenocarcinoma, was more common in cases with occupational asbestos exposure (10 of 30 cases, 33%) than in those without exposure (9 of 54, 17%); however, the authors suggested:

> "... observed differences in the frequencies of p53 and K-ras mutations between the asbestos-exposed and nonexposed lung cancer cases may, at least partially, reflect the relative increase of adenocarcinoma cell type among the exposed cases."

In other words, K-ras mutation may be more common in asbestos exposed individuals at least partially because adenocarcinoma is more common in those patients. Furthermore, the authors demonstrated a direct relationship between asbestos tissue burden and K-ras mutation:



Husgafvel-Pursiainen et al 1999:

PREVALENCE OF ADENOCARCINOMA HISTOLOGY (%), P53 MUTATIONS, AND K-RAS MUTATIONS IN MALE LUNG CANCER PATIENTS WITH PULMONARY ASBESTOS FIBER CONCENTRATIONS 1 TO < 5 X 10^6 AND 5 X 10^6 F/G DRY WEIGHT) AND WITHOUT (< 1 X 10^6 F/G) OCCUPATIONAL EXPOSURE TO ASBESTOS.

The above observations are consistent with previous epidemiological studies described earlier in this report which indicate that the increased risk of lung cancer in asbestos workers is limited to those individuals who have asbestosis or an asbestos tissue burden typical of asbestosis; furthermore, it is consistent with a newly published 1999 study[104] also from Finland which revealed a marked increase in lung cancer risk (standardized incidence ratio [SIR] = 6.7; 95% confidence interval [CI] = 5.6-7.9) in patients with asbestosis as opposed to a slightly elevated risk in patients with "asbestos-related benign pleural disease" (SIR = 1.3, CI = 1.0-1.8).

Increased risk of lung cancer in other forms of interstitial fibrosis

If the increased risk of lung cancer in asbestos workers is limited to those workers who develop interstitial fibrosis (i.e. asbestosis), then a similar pattern of increased lung cancer risk should also occur in patients with other kinds of interstitial fibrosis. The latter has been suggested for years in the medical literature, for example, in patients with scleroderma.[105] [106] [107] [108] [109] A recently published study from England provides support for this concept. Hubbard et al[110] "estimated the independent increase in lung cancer incidence in patients with cryptogenic fibrosing alveolitis [the term used in Great Britain for idiopathic pulmonary fibrosis] compared with the general population in a population-based cohort study involving 890 subjects with cryptogenic fibrosing alveolitis and 5,884 control subjects drawn from the United Kingdom General Practice Research Database." The authors indicated that their study was the largest population study on this topic published to date. Hubard et al reported:

> "The incidence of lung cancer was markedly increased among patients with cryptogenic fibrosing alveolitis (rate ratio [RR] 7.31, 95% confidence interval [95% CI] 4.47 to 11.93, $p < 0.001$), and adjustment for previous smoking history had little effect on this odds ratio (adjusted RR: 8.25, 95% CI 4.70 to 11.48, $p < 0.001$). This increase in lung cancer incidence remained when the analysis was restricted to current smokers (RR 7.36, 95% CI 1.54 to 35.19, $p = 0.012$). This study provides clear evidence that the incidence of lung cancer is increased in patients with cryptogenic fibrosing alveolitis, and that this effect is independent of the effect of cigarette smoking."

In summary, asbestos workers who smoke and who develop asbestosis are at increased risk for the development of lung cancer because:

1. Cigarette smoke is a primary carcinogen or "inducer" which stimulates mutations (i.e. malignant transformation of gene DNA) in bronchial epithelial cells resulting in dangerous alterations in oncogenes such as the K-ras gene and dysfunctional alterations in tumor suppressor genes such as the p53 gene.

2. Chronic proliferation of pulmonary cells associated with pulmonary fibrosis increases the likelihood that mutated cells will produce a malignant tumor;

3. Pulmonary fibrosis disrupts the lung's natural protective mechanisms which normally limit the proliferation of mutated cells; and,

4. Increased tissue burden of asbestos equal to or greater than the tissue burden typically associated with pulmonary parenchymal asbestosis may directly increase the incidence of at least some oncogenes such as K-ras and increase the risk of adenocarcinoma

It should be noted that despite the consistency and authority of the published medical evidence reviewed by authors such as Jones and Weiss cited above, the corroboration provided by epidemiological studies on related topics such as progression of asbestosis and non-occupational asbestos exposure, and the recently obtained understanding of lung cancer pathogenesis, some authors continue to disagree that the relationship between lung cancer and asbestos is really that originally suggested in a 1949 editorial published in the Journal of the American Medical Association[111], i.e.:

> "... the available evidence shows that the occurrence of cancer of the lung is related to pulmonary asbestosis and is not merely a possible sequella of exposure to asbestos dust...."

In the February 1999 issue of Chest which carried the Weiss report, a contrary editorial, by Banks, Wang and Parker[112] of the West Virginia University School of Medicine also appeared. (Dr. Parker is a respected official of NIOSH). Banks et al stated:

> "Thus, we can agree that both asbestosis and asbestos- related lung cancer occur at a rate commensurate with exposures, however, it appears unlikely that epidemiologic studies are adequate to convince all parties that asbestosis must be recognized in a population to place the members of that cohort at excessive risk for lung cancer."

To which I would comment that while extensive, consistent, reproducible, historical and current epidemiological data may not be sufficient to convince "all parties" that the relationship between asbestos exposure and lung cancer is due to an increased risk in those patients who have asbestosis, conclusions such as those given by Jones and Weiss derived from the epidemiological data represent the current scientifically sound consensus of medical opinion and should serve as the scientific basis for answers in medical-legal matters.

Other cancers: In the past, scientists suggested that certain cancers other than mesothelioma and primary lung cancer were associated with asbestos exposure.[113] [114] Subsequently, extensive medical and epidemiological investigations have provided strong, generally consistent evidence that other cancers are not caused by asbestos exposure. Specifically, the weight of the medical evidence indicates that the following malignancies are not associated with asbestos exposure: laryngeal cancer,[115] [116] [117] [118] [119] [120] [121] [122] [123] [124] [125] [126] [127] [128] [129] [130] [131] [132] [133] [134] [135] [136] cancers of the gastrointestinal tract[137] [138] [139] [140] [141] [142] [143] [144] [145] [146] [147] and cancers of the urinary tract.[148] [149] [150] [151] [152] [153] [154] [155] [156] [157] [158] [159] [160] [161]

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1. Mossman BT, Churg A: Mechanisms in the pathogenesis of asbestosis and silicosis. Am J Respir Crit Care Med 1998; 157:1666-1680.

2. Doll R: Smoking and Lung Cancer. Am J Respir Crit Care Med 2000; 162: 4-6.

3. Doll R, Hill AB. Smoking and cancer of the lung. Br Med J 1950; 2:739-748.

4. Cooke WE: Pulmonary asbestosis. BMJ 1927;Dec. 30:1022-1025.

5. Merewether ERA, Price CW: Report of effects of asbestos dust on the lungs and dust suppression in the asbestos industry. The occurrence of pulmonary fibrosis and other pulmonary affections in asbestos workers. J Industr 1930;12:239-257.

6. Dreesen WC, Dallavalle JM, Edwards TI, Miller JW, Sayers RR, Eason HF, Trice MF: A study of asbestosis in the asbestos textile industry. Public Health Bulletin No. 241, August 1938.

7. Fleischer WE, Viles FJ, Gade RL, Drinker P: A health survey of pipe covering operations in constructing naval vessels. J Industr Hyg Toxicology 1946;28:9-16.

8. Selikoff IJ, Churg J, Hammond EC: The occurrence of asbestosis among insulation workers in the United States. NY Acad Sci 1965:133-155.

9. Minister of Labour and National Service to Parliament by Command of His Majesty. Annual report of the Chief Inspector of Factories For The Year of 1947. London. His Majesty's Stationary Office.

10. Asbestosis and cancer of the lung. (editorial) Fishbein M. Editor JAMA 1949;134:1219-1220.

11. Doll, R: Mortality from lung cancer in asbestos workers. Brit J Industr Med 1955;12:81-86.

12. Kipen HM, Lilis R, Suzuki Y, Valciukas JA, Selikoff IJ: Pulmonary fibrosis in asbestos insulation workers with lung cancer: a radiological and

histopathological evaluation. Brit J Industrial Med 1987;44:96-100.

13. Mallory TB, Castleman B, Parris EE: Case records of the Massachusetts General Hospital, Weekly clinicopathological exercises, Case 33111. New Eng J Med 1947;236:407-412.

14. Wagner JC, Sleggs CA, Marchand P: Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Brit J Industr Med 1960;17:260-271.

15. Selikoff IJ, Hammond EC, Churg J: Carcinogenicity of amosite asbestos. Arch Environ Health 1972;25:183-186.

16. McDonald AD, Fry J, Woolley, McDonald JC: Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture. Brit J of Industr Med 1982;39:368-374.

17. McDonald AD, Fry JS, Woolley AJ, McDonald JC: Dust exposure and mortality in an American chrysotile asbestos friction products plant. Brit J of Industr Med 1984;41:151-157.

18. Liddell FDK, McDonald AD, McDonald JC: The 1891-1920 birth cohort of Quebec chrysotile miners and millers: development from 1904 and mortality to 1992. Ann Occup Hyg 1997; 41:13-36.

19. McDonald AD, McDonald JC: Chrysotile, tremolite and carcinogenicity. Ann Occup Hyg 1997; 41:699-705.

20. McDonald AD, Case BW, Churg A, Dufresne A, Gibbs GW, Sebastien P, McDonald JC: Mesothelioma in Quebec chrysotile miners and millers: epidemiology and aetiology. Ann Occup Hyg. 1997 Dec;41(6):707-19.

21. Kronenberg RS, Levin JL, Dodson RF, Garcia JGN, Griffith DE: Asbestos-related disease in employees of a steel mill and a glass bottle-manufacturing plant. Ann NY Acad Sci 1991; 643-403.

22. Lloyd JW, Cioco A: Long term mortality study of steelworkers. I. Methodology. J Occup Med 1969; 11:299-310.

23. Health Effects Institute-Asbestos Research (HEI-AR): Asbestos in Public and Commercial Buildings: A literature review and synthesis of current knowledge. Cambridge, MA 1991, page 4-12.

24. Brown, K: Asbestos-related disorders. The pathogenesis of asbestosis. Fibre dimensions. In Occupational Lung Disorders, Raymond Parkes (editor) 3rd edition, Butterworth Heinemann, Oxford, England, page 427.

25. Mallory TB (ed): CPC case 33111, NEJM 236: 407, 1947.

26. McCaughey WTE: Primary tumours of the pleura. J. Path Bact 76:517, 1958.

27. Wagner JC, Sleggs CA, Marchand P: Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Brit J Industr Med 17:260, 1960.

28. Wagner JC: Mesothelioma and mineral fibers. Cancer 1986; 57:1905-1911. (The Charles Mott Prize).

29. Selikoff IJ, Churg J, Hammond EC: Relation between exposure to asbestos and mesothelioma. NEJM 1965;272:560-565.

30. Sluis-Cremer GK: Asbestosis in South Africa - certain geographical and environmental considerations. Ann NY Acad Sci 1965;132:215-234.

31. Selikoff IJ, Hammond EC, Churg J: Carcinogenicity of amosite asbestos. Arch Environ Health 1972;25:183-186.

32. Selikoff IJ, Seidman H, Hammond EC: Mortality effects of cigarette smoking among amosite asbestos factory workers. JNCI 1980;65:507-513.

33. Sheers G, Coles RM: Mesothelioma risks in a naval dockyard. Arch Environ Health 1980;35:276-282.

34. Harries PG: Asbestos hazard in naval dockyards. Am Occup Hyg 1968;11:135-145.

35. Acheson ED, Gardner MJ, Pippard EC, Grime LP: Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. Brit J Indus Med 1982; 39:344-348.

36. McDonald AD, Fry J, Woolley, McDonald JC: Dust exposure and mortality in an American chrysotile textile plant. Brit J of Industr Med 1983;40:361-367.

37. McDonald AD, Fry J, Woolley, McDonald JC: Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture. Brit J of Industr Med 1983;40:368-374.

38. McDonald AD, Fry JS, Woolley AJ, McDonald JC: Dust exposure and mortality in an American chrysotile asbestos friction products plant. Brit J of Industr Med 1984;41:151-157.

39. Newhouse ML, Sullivan KR: A mortality study of workers manufacturing friction materials: 1941-86. Br J Industr Med 1989;46:176-179.

40. Warnock ML: Lung asbestos burden in shipyard and construction workers with mesothelioma: comparison with burdens in subjects with asbestosis or lung cancer. Environ Res 1989;50:68-85.

41. Bégin R, Gauthier JJ, Desmeules M, Ostiguy G: Work-related mesothelioma in Québec, 1967-1990. Am J Industr Med 1992;22:531-542.

42. Churg A, Wright JL, Vedal S: Fiber burden and patterns of asbestos-related disease in chrysotile miners and millers. Am Rev Respir Dis 1993;140:25-31.

43. Churg A, Vedal S: Fiber burden and patterns of asbestos-related disease in workers with heavy mixed amosite and chrysotile exposure. Am J Respir Crit Care Med 1994;150:663-9.

44. Becklake MR, Case BW: Editorial, Fiber burden and asbestos-related lung disease: determinants of dose-response relationships. Am J Respir Crit Care

Med 1994;150:1488-1492.

45. Liddell FDK, McDonald AD, McDonald JC: The 1891-1920 birth cohort of Quebec chrysotile miners and millers: development from 1904 and mortality to 1992. Ann Occup Hyg 1997; 41:13-36.

46. McDonald AD, McDonald JC: Chrysotile, tremolite and carcinogenicity. Ann Occup Hyg 1997; 41:699-705.

47. McDonald AD, Case BW, Churg A, Dufresne A, Gibbs GW, Sebastien P, McDonald JC: Mesothelioma in Quebec chrysotile miners and millers: epidemiology and aetiology. Ann Occup Hyg. 1997 Dec;41(6):707-19.

48. Berube KA, Quinlan TR, Fung H, Magae J, Vacek P, Taatjes DJ, Mossman BT: Apoptosis is observed in mesothelial cells after exposure to crocidolite asbestos. Am J Resp Cell & Molecular Biology 1996; 15(1):141-7.

49. Murname JP: Cell regulation in response to DNA damage in mammalian cells: an historical perspective. Cancer Metastasis Rev 1995; 14:17-29.

50. Levresse V; Renier A; Fleury-Feith J; Levy F; Moritz S; Vivo C; Pilatte Y; Jaurand MC: Analysis of cell cycle disruptions in cultures of rat pleural mesothelial cells exposed to asbestos fibers. Am J Respir Cell Mol Biol 1997; 17(6):660-71.

51. Dopp E, Nebe B, Hahnel C, Papp T, Alonso B, Simko M, Schiffmann D: Mineral fibers induce apoptosis in Syrian hamster embryo fibroblasts. Pathobiology 1995;63(4):213-21.

52. Hamilton RF, Li L, Iyer LL, Holian A: Asbestos induces apoptosis in human alveolar macrophages. Am J Physiol 1996; 271(5 Pt 1):L813-L819.

53. Broaddus VC: Asbestos, the mesothelial cell and malignancy: a matter of life or death [editorial; comment]. Am J Respir Cell Mol Biol 1997 Dec;17(6):657-9.

54. Frederick W. Boelter, CIH, PE, DEE, QEP dated 10/09/1996, 10/28/1996, 11/05/1996, 11/11/1996, 11/19/1996, 11/22/1996, 12/01/1996, 12/12/1996, 12/18/1996, and 12/24/1996. John W. Spencer, CIH, CSP dated 09/11/1998 prepared for A.W. Chesterton Company. Michael D. Mount and Herman L. Kitt of the McCrone Environmental Services, dated 10/12/1998. Multiple reports prepared by Carl Mangold, CIH dated 10/982, 12/1982, 11/1983, 09/1985, 01/1989, and 05/1991. Arthur Neilson dated 06/06/1980. J. LeRoy Balzer, PhD on 02/15/99. Asbestos Exposure From Gasket Operations dated 05/1978 prepared by the Naval Regional Medical Center in Bremerton, Washington.

55. Maxim Engineers, 1990, Penn Environmental Health Company, 1991, Vittorio K. Argento, Ph.D., Environmental Engineering Services, Inc., 1992, MVA, Inc., 1992, M. Douglas Mueller, BCM, 1993, Clayton Environmental Consultants, Inc., 1994, TurnKey Environmental Consultants, Inc., 1994, R.J. Lee Laboratories, Monroeville, Pennsylvania, 1997.

56. Roggli VL, Sanders LL: Asbestos content of lung tissue and carcinoma of the lung: a clinicopathologic correlation and mineral fiber analysis of 234 cases. Ann Occup Hyg. 2000 Mar;44(2):109-17.

57. Minister of Labour and National Service: Annual Report of the Chief Inspector of Factories. His Majesty's Stationery Office, London, 1947.

58. Asbestosis and cancer of the lung. (editorial) JAMA 1949; 134:1219-1220.

59. Doll R: Mortality from lung cancer in asbestos workers. Brit J Indust Med 1955; 12:81-86.

60. Hammond EC, Selikoff IJ, Seidman H: Asbestos exposure, cigarette smoking and death rates. Annals NY Acad Sci 1979;330:474.

61. Kipen HM, Lilis R, Suzuki Y, Valciukas JA, Selikoff IJ: Pulmonary fibrosis in asbestos insulation workers with lung cancer: a radiological and histopathological evaluation. Brit J Industrial Med 1987;44:96-100.

62. Liddell FDK, McDonald JC: Radiological findings as predictors of mortality in Quebec asbestos workers. Brit J Industr Med 1980; 37:257-67.

63. Berry G: Mortality of workers certified by pneumoconiosis medical panels as having asbestosis. Brit J Industr Med 1981; 38:130-7.

64. Sluis-Cremer GK, Bezuidenhout BN: Relation between asbestosis and bronchial cancer in amphibole asbestos miners. Brit J Industr Med 1989; 46:537-540.

65. Hughes JM, Weill H: Asbestosis as a precursor of asbestos related lung cancer: results of a prospective mortality study. Brit J Indust Med 1991; 48:229.

66. Wilkinson P, Hansell DM, Janssens J, Rubens M, Rudd R, Taylor AN, McDonald C: Is lung cancer associated with asbestos exposure when there are no small opacities on the chest radiograph? Lancet 1995; 345:1074-1078.

67. Jones RN, Hughes JM, Weill H: Asbestos exposure, asbestosis, and asbestos-attributable lung cancer. Thorax 1996;51:509-515.

68. Weiss W: Asbestosis: a marker for the increased risk of lung cancer among workers exposed to asbestos. Chest 1999 Feb;115(2):536-49.

69. Newhouse ML, Berry G, Wagner JC: Mortality of factory workers in East London. Brit J Ind Med 1985; 42:4-11.

70. Liddell FDK, McDonald AD, McDonald JC: The 1891-1920 birth cohort of Quebec Chrysotile miners and millers: development from 1904 and mortality to 1992. Am Occup Hyg 1997;41:13-36.

71. Oksa P, Klockars M, Karjalainen A, Huuskonen MS, Vattulainen K, Pukkala E, Nordman H: Progression of Asbestosis Predicts Lung Cancer. Chest 1998; 113(6):1517-1521.

72. Camus M, Siemiatycki J, Meek B: Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. New Eng J Med

1998;338(22):1565-1571.

73. McDonald AD, McDonald JC: Chrysotile, tremolite and carcinogenicity. Ann Occup Hyg 1997; 41:699-705.

74. Dupre JS, Mustard JF, Uffen RJ: Report of The Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario. Ontario Ministry of the Attorney General. Queen's Printer for Ontario. Toronto 1984. Page 281.

75. Doll R, Peto J: Asbestos: Effects on Health of exposure to asbestos. Health and Safety Commission. London: Her Majesty's Stationery Office 1985.

76. Huang JQ: A study on the dose-response relationship between asbestos exposure level and asbestosis among workers in a Chinese chrysotile product factory. Biomed Environ Sci 1990; 90-8.

77. Greenberg SD, Roggli VL: Carcinoma of the Lung, In Pathology of Asbestos-Associated Diseases. Little Brown & Co, 1992, p 192.

78. Roggli VL, Pratt PC, Brody AR: Analysis of Tissue Mineral Fiber Content, In Pathology of Asbestos-Associated Diseases. Little Brown & Co, 1992.

79. Roggli VL: Pathology if human asbestosis: A critical review in Advances in Pathology vol 2; 1989 pp31-60.

80. Roggli VL, Greenberg SD, Pratt PC: Pathology of Asbestos-Associated Diseases. Little Brown Co., 1992 p 322.

81. Roggli VL; Sanders LL: Asbestos content of lung tissue and carcinoma of the lung: a clinicopathologic correlation and mineral fiber analysis of 234 cases. Ann Occup Hyg 2000 Mar;44(2):109-17.

82. U.S. Department of Health, Education, and Welfare, Public Health Service. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. P.H.S. Publication 1103, 1964.

83. U.S. Department of Health and Human Services. Reducing the Health Consequences of Smoking - 25 Years of Progress: A Report of the Surgeon General. Atlanta, Georgia, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, DHHS Publication No. (CDC) 89-8411,1989.

84. Hecht SS: Tobacco Smoke Carcinogens and Lung Cancer. J Natl Cancer Inst 1999; 91: 1194-1210.

85. Husgafvel-Pursiainen K; Ridanpaa M; Anttila S; Vainio H: p53 and ras gene mutations in lung cancer: implications for smoking and occupational exposures. Occup Environ Med 1995 Jan;37(1):69-76.

86. Giaccone G: Oncogenes and antioncogenes in lung tumorigenesis. Chest 1996 May;109(5 Suppl):130S-134S.

87. Roth JA: Molecular events in lung cancer. Lung Cancer 1995 Jun;12 Suppl 2:S3-15.

88. Carbone DP: The biology of lung cancer. Semin Oncol 1997 Aug;24(4):388-401.

89. Devereux TR, Taylor JA, Barrett JC: Molecular mechanisms of lung cancer interaction of environmental and genetic factors: Giles F. Filley Lecture. 1996; Vol. 109, No. 3S, Pages 14-19.

90. Hecht SS: Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst 1999; 91:1194-1210.

91. Denissenko MF, Pao A, Tang M, Pfeifer GP: Preferential formation of bezo(a)pyrene addicts at lung cancer mutational hotspots in p53. Science 1996;274:430-432.

92. Hecht SS: Recent studies on mechanisms of bioactivation and detoxification of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a tobacco-specific lung carcinogen. Crit Rev Toxicol 1996;26(2):163-81.

93. Hirvonen A; Saarikoski ST; Linnainmaa K; Koskinen K; Husgafvel-Pursiainen K; Mattson K; Vainio H: Glutathione S-transferase and N-acetyltransferase genotypes and asbestos-associated pulmonary disorders. J Natl Cancer Inst 1996 Dec 18;88(24):1853-6.

94. Vineis P; Caporaso N: Tobacco and cancer: epidemiology and the laboratory. Environ Health Perspect 1995 Feb;103(2):156-60.

95. Rannug A; Alexandrie AK; Persson I; Ingelman-Sundberg M: Genetic polymorphism of cytochromes P450 1A1, 2D6 and 2E1: regulation and toxicological significance. J Occup Environ Med 1995 Jan;37(1):25-36.

96. Ikawa S; Uematsu F; Watanabe K; Kimpara T; Osada M; Hossain A; Sagami I; Kikuchi H; Watanabe M: Assessment of cancer susceptibility in humans by use of genetic polymorphisms in carcinogen metabolism. Pharmacogenetics 1995;5 Spec No:S154-60.

97. Hirvonen A: Genetic factors in individual responses to environmental exposures. J Occup Environ Med 1995 Jan;37(1):37-43.

98. Rebbeck TR: Molecular epidemiology of the human glutathione S-transferase genotypes GSTM1 and GSTT1 in cancer susceptibility. Cancer Epidemiol Biomarkers Prev 1997 Sep;6(9):733-43.

99. Bartsch H; Hietanen E: The role of individual susceptibility in cancer burden related to environmental exposure. Environ Health Perspect 1996 May;104 Suppl 3:569-77.

100. Vachtenheim J; Horakova I; Novotna H; Opaalka P; Roubkova H: Mutations of K-ras oncogene and absence of H-ras mutations in squamous cell carcinomas of the lung. Clin Cancer Res 1995 Mar;1(3):359-65.

101. Wang X; Christiani DC; Wiencke JK; Fischbein M; Xu X; Cheng TJ; Mark E; Wain JC; Kelsey KT: Mutations in the p53 gene in lung cancer are associated with cigarette smoking and asbestos exposure. Cancer Epidemiol Biomarkers Prev 1995 Jul-Aug;4(5):543-8.

102. Nelson HH; Christiani DC; Wiencke JK; Mark EJ; Wain JC; Kelsey KT: k-ras mutation and occupational asbestos exposure in lung adenocarcinoma: asbestos-related cancer without asbestosis. Cancer Res 1999 Sep 15;59(18):4570-3.

103. Husgafvel-Pursiainen K, Karjalainen A, Kannio A, Anttila S, Partanen T, Ojajärvi A, Vainio H: Lung cancer and past occupational exposure to asbestos. Role of p53 and K-ras mutations. Am. J. Respir. Cell Mol. Biol., Volume 20, Number 4, April 1999 667-674.

104. Karjalainen A; Pukkala E; Kauppinen T; Partanen T: Incidence of cancer among Finnish patients with asbestos-related pulmonary or pleural fibrosis. Cancer Causes Control 1999 Feb;10(1):51-7.

105. Roumm AD; Medsger TA Jr: Cancer and systemic sclerosis. An epidemiologic study. Arthritis Rheum 1985 Dec;28(12):1336-40.

106. Peters-Golden M; Wise RA; Hochberg M; Stevens MB; Wigley FM: Incidence of lung cancer in systemic sclerosis. J Rheumatol 1985 Dec;12(6):1136-9.

107. Winkelmann RK, Flach DB, Unni KK: Lung cancer and scleroderma. Arch Dermatol Res. 1988;280 Suppl:S15-8.

108. Yousem SA: The pulmonary pathologic manifestations of the CREST syndrome. Hum Pathol. 1990 May;21(5):467-74.

109. Abu-Shakra M, Guillemin F, Lee P: Cancer in systemic sclerosis. Arthritis Rheum. 1993 Apr;36(4):460-4.

110. Hubbard R, Venn A, Lewis S, Britton J: Lung cancer and cryptogenic fibrosing alveolitis. A Population-based Cohort Study. Am. J. Respir. Crit. Care Med. 2000; 161: 5-8.

111. Asbestosis and cancer of the lung. (editorial) Fishbein M. Editor JAMA 1949;134:1219-1220.

112. Banks DE; Wang ML; Parker JE: Asbestos exposure, asbestosis, and lung cancer. Chest 1999 Feb;115(2):320-2.

113. Selikoff I, Churg J, Hammond, E. Asbestos exposure and neoplasia. JAMA 188: 22,1964.

114. Selikoff IJ, Hammond EC, Seidman H: Mortality experience of insulation workers in the United States and Canada 1943-1976. Annals NY Acad Sci 1979; 330:91-116.

115. Roggli VL, Greenberg SD, McLarty JL, et al: Asbestos body content of the larynx in asbestos workers. A study of five cases. Arch Otolaryngol 1980;106(9):533-5.

116. Shettigara PT, Morgan RW: Asbestos, smoking, and laryngeal carcinoma. Arch Environ Health 1975;30:517-9.

117. Hinds MW, Thomas DB, O'Reilly HP: Asbestos, dental X-rays, tobacco, and alcohol in the epidemiology of laryngeal cancer. Cancer 1979;44:1114-20.

118. Newhouse ML, Gregory MM, Shannon H: Etiology of carcinoma of the larynx. IARC Sci Publ 1980;30:687-95.

119. Wain SL, Roggli VL, Foster WL: Parietal pleural plaques, asbestos bodies, and neoplasia. Clinical, pathologic and roentgenographic correlation of 25 consecutive cases. Chest 1984;86: 707.

120. Epstein DM: Pleural plaques - a marker for respiratory tract malignancy? Chest 1984;86:660.

121. Doll R, Peto J: Asbestos. Effects on health of exposure to asbestos. Her Majesty's Stationary Office, England, 1985.

122. Zagraniski RT, Kelsey JL, Walter SD: Occupational risk factors for laryngeal carcinoma: Connecticut 1975-1980. AM J Epidemiol 1986;124:67.

123. Brown LM, Mason TJ, Pickle LW, et al: Occupational risk factors for laryngeal cancer on the Texas gulf coast. Cancer Res 1988;48:1960.

124. Chan CK, Gee JB: Asbestos exposure and laryngeal cancer: An analysis of the epidemiologic evidence. J Occup Med 1988;30:23.

125. Edelman DA: Laryngeal cancer and occupational exposure to asbestos. Int Arch Occup Environ Health 1989;61:223.

126. Smith AH, Handley MA, Wood R: Epidemiological evidence indicates asbestos causes laryngeal cancer. J Occup Med 1990;32:499.

127. Smith AH, Shearn VI, Wood R: Asbestos and kidney cancer: the evidence supports a causal association. Am J Ind Med 1989; 16:159-66.

128. Frumkin H, Berlin J: Asbestos exposure and gastrointestinal malignancy. Review and meta-analysis. Am J Industr Med 1988; 14:79.

129. Piolatto G, Negri E, La Vecchia C, et al: An update of cancer mortality among chrysotile asbestos miners in Balangero, Northern Italy. Br J Ind Med 1990;47:810.

130. Ahrens W, Jockel KH, Patzak W, Elsner G: Alcohol, smoking and occupational factors in cancer of the larynx: A case control study. Am J Ind Med 1991;20:477.

131. Botta M, Magnani C, Terracini B, Bertolone GP, Castagneto B, Cocito V, DeGiovanni D, Paglieri P: Mortality from respiratory and digestive cancers among asbestos cement workers in Italy. Cancer Detect Prev 1991;15(6):445-7.

132. Deitmer T: [Laryngeal carcinoma and asbestos exposure. A critical review of the literature]. Laryngorhinootologie 1990;69:589-94.

133. Roggli VL, Greenberg SD, Pratt PC: Pathology of Asbestos Associated Diseases. Little Brown, 1992.

134. Muscat JE, Wynder EL: Tobacco, alcohol, asbestos and occupational risk factors for laryngeal cancer. Cancer 69: 2244, 1992.

135. Liddell FD: Laryngeal cancer and asbestos. Br J Ind Med 1990; 47(5):289-91.

136. Liddell FDK, McDonald AD, McDonald JC: The 1891-1920 birth cohort of Quebec Chrysotile miners and millers: development from 1904 and mortality to 1992. Am Occup Hyg 1997;41:13-36.

137. Greenlee RT, Murray T, Bolden S, Wingo PA: Cancer statistics 2000. CA Cancer J Clin 2000;50:7-33.

138. http://www3.cancer.org/cancerinfo/load_cont.asp?ct=12&doc=6&Language =English

139. Doll R and Peto J: Asbestos. Effects on health of exposure to asbestos. Her Majesty's Stationary Office, England, 1985.

140. Morgan RW, Foliart DE, Wong 0: Asbestos and gastrointestinal cancer. A review of the literature. West J Med 143:60,1985.

141. Hodgson JT and Jones RD: Mortality of asbestos workers in England and Wales 1971-81. Brit J Industr Med 43:158,1986.

142. Frumkin H, Berlin J: Asbestos exposure and gastrointestinal malignancy. Review and meta-analysis. Am J Industr Med 14:79,1988.

143. Weiss W: Asbestos and colorectal cancer. Gastroenterology 99:876,1990.

144. Demers RY; Bums PB; Swanson GM: Construction occupations, asbestos exposure, and cancer of the colon and rectum. J Occup Med 1994 Sep;36(9):1027-31.

145. Gamble JF: Asbestos and colon cancer: a weight-of-the-evidence review. Environ Health Perspect 1994 Dec; 102(12):1038-50.

146. Weiss W: The lack of causality between asbestos and colorectal cancer. J Occup Environ Med 1995 Dec;37(12):1364-73.

147. Kang SK, Burnett CA, Freund E, Walker J, Lalich N, Sestito J: Gastrointestinal cancer mortality of workers in occupations with high asbestos exposures. Am J Ind Med 1997 Jun;31(6):713-8.

148. McDonald JC, Liddel FDK, Gibbs GW, Eyssen GE, McDonald AD: Dust exposure and mortality in chrysotile mining. 1910-75. Brit J Indust Med 1980; 37:11-24.

149. Clemmesen J; Hjalgrim-Jensen S: Cancer incidence among 5686 asbestos-cement workers followed from1943 through 1976. Ecotoxicol Environ Saf 1981 Mar;5(1):15-23.

150. Melkild A, Langard S, Andersen A, Tonnessen JN: Incidence of cancer among welders and other workers in a Norwegian shipyard. SCAND J WORK ENVIRON HEALTH 1989;15:387-94.

151. Peto J, Doll R, Hermon C, Binns W, Clayton R, Goffe T: Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. Ann Occup Hyg 1985; 29:305-355.

152. Smith AH, Shearn VI, Wood R: Asbestos and kidney cancer: the evidence supports a causal association. Am J Ind Med 1989; 16:159-66.

153. Frumkin H, Berlin J: Asbestos exposure and gastrointestinal malignancy. Review and meta-analysis. Am J Industr Med 1988; 14:79.

154. Vineis P, Simonato L: Proportion of lung and bladder cancers in males resulting from occupation: a systematic approach [see comments]. ARCH ENVIRON HEALTH 1991; 46:6-15.

155. Vineis P: Epidemiological models of carcinogenesis: the example of bladder cancer. CANCER EPIDEMIOL BIOMARKERS PREV 1992;1:149-53.

156. Edelman DA: Does asbestos exposure increase the risk of urogenital cancer? Int Arch Occup Environ Health 1992; 63:469-475.

157. McLauglin JK, Silverman DT, Hsing AW et al: Cigarette smoking and cancers of the renal pelvis and ureter. CANCER RES 1992; 52:254-257.

158. McCredie M; Stewart JH: Risk factors for kidney cancer in New South Wales. IV. Occupation. Br J Ind Med 1993 Apr;50(4):349-54.

159. Mandel JS; McLaughlin JK; Schlehofer B; Mellemgaard A; Helmert U; Lindblad P; McCredie M; Adami HO: International renal-cell cancer study. IV. Occupation. Int J Cancer 1995 May 29;61(5):601-5.

160. Sali D; Boffetta P: Kidney cancer and occupational exposure to asbestos: a meta-analysis of occupational cohort studies. Cancer Causes Control 2000 Jan;11(1):37-47.

161. McLaughlin JK; Lipworth: L Epidemiologic aspects of renal cell cancer. Semin Oncol 2000 Apr;27(2):115-23.