FILE NAME: Asbestos Mining (ASMI)

DATE: 0000

DOC#: ASMI032

DOCUMENT DESCRIPTION: Unpublished Draft Report - Critique of Braun-Truan Report [Limitations Which Lead to False Negative Findings]

Critique Braun-Truan Report

Limitations Which Lead to False Negative Findings

I. The period of follow-up of the cohort 1950 was too short, six years, to meet the requirements of the latent period for lung cancer. It was basic medical knowledge then at the time the study was conducted, and confirmed from many studies, that although occupational cancer can occur following a short latent period, usually the clustering of the majority of lung cancers occurs after an interval of 20 years or more, usually an interval of 25 or 30 years or more. (For example, in the study of chromate workers, the majority of the lung cancers occur after an interval of 26-36 years and may extend to 42 years.) The long latent period has been observed by Selikoff and others in asbestos workers, where most of the lung cancer cases occurred after an interval of 20 years.

In the Braun-Truan Study, the cohort was of those who were working in 1950 who had worked five years or more--which would mean a period of 11 years for the cohort as a whole.

In essence, the design of the study limiting the period of subsequent observation to six years, had a built-in limiting factor in the study which would prevent and severely limit observations pertaining to lung cancer which required a much longer latent period. The limited follow-up period represented a fundamental flaw in the study, which severely limited any positive findings relative to lung cancer--because the interval of time of observation follow-up was too short for the interval in years required for the development of the majority of the lung cancers.

This was evident to the investigators themselves--as clearly shown in the designation of years of employment for each of the lung cancer cases, shown in Tables 6 and 7 on page 642 of the published paper. (Example: Excluding one case of 16 years, of the total of 12 lung cancer cases, 11 had an employment of 20 or more years, which means that the interval of time for these lung cancers since start of employment was 20 or more years.) There is no recognition or admission made in the Summary of the paper that the design of the study had a self-limiting factor to make such observations less meaningful. In essence, the design of the study increased markedly the probability of false negative findings and increased the probability that the investigators would come up with artificial, incorrect, low association of lung cancer and asbestos exposure.

Further, the investigators state that 133 members of the cohort could not be found. If the 133 were found and only one or two lung cancers had been located, the conclusion of the study--even in its limited state--would be in the direction of positive rather than negative findings.

II. The second limiting factor relates to obvious questionable and inappropriate classification of the cohort by categories of degree of exposure into I, II, III.

Evidence of this classification of exposure is reflected in both the pre-publication report and in the published report.

On page 33 of the pre-publication report, tables show the years of employment for the nine proven lung cancers and three

8. Schlieff on Exposure Category

We must mark that the Exposure Category had some merit with Category II being twice as dusty as Category I and Category III, 3 times as dusty.

I should then I wanted the views of Mills on Both East Broughton and asbestos, Quebec, I was told that the men did not stay on one job in the asbestos mine as much as in the others more and Thus the Category II was very misleading"

Yours

See Schlieff exhibit 14 -
Center of Hospitals
Not published - no Hospital Study
Post mortems rarely done

Yes

"suspected" primary cancers of the lung, classified by exposure.

	Proven		Suspected
	Asbestos cohort	Thetford	
Exposure Category I	34 years 37 years	32 years 16 years	
Exposure Category II	26 years	22 years 30 years	42 years
Exposure Category III		33 years 28 years	32 years 33 years

The table demonstrates that for all the workers (who had lung cancer) those with the longest and therefore highest period of employment exposure to asbestos, 34 years and 37 years in the asbestos cohort, were assigned to the lowest category of Exposure I.

Three of the total of nine proven lung cancer cases, ~~all of~~ which had 32 years or more exposure employment, were classified as Category I.

For Category II classification of exposure, the highest exposure occurring in terms of years of employment of all categories and all lung cancers was 42 years in the Thetford mines. All four lung cancers had 22 or more years of employment; three of the four had 26 or more years of employment exposure.

In the comparison of the four lung cancers in Category III with Category I for both asbestos cohort and Thetford mines, the Category I had equal or higher number of employment exposure years in three of the four comparisons with Category III.

It is readily apparent that there are basic flaws in whatever process was used in the assignment of exposure categories, as evidenced by the categories assigned to the lung cancer cases.

Anyone at all acquainted with work processes would recognize that the constant dust exposure each day, week, month, for 25 or more years for the miners represents a tremendous accumulation of dust exposure over those years. Even employment exposure of 16 years, the lowest number of years for any of the lung cancer cases, would represent a tremendous cumulative dust exposure.

In industrial studies, the usual classification of employment exposure is 0-1 years, 1-2 years, etc. But never in the history of industrial medicine has dust exposure of 34, 37, 32 years been classified Category I, as lowest exposure.

The contradiction in the classification exposure comparisons of the lung cancer cases in I, II, III relative to number of years employment exposure, make the analysis of such data unreliable and therefore the conclusions unreliable.

In order for any one to really be able to designate work exposure, it would have been necessary to know by air sampling and measurement the dust concentration for each week, month, year for the 30 plus years, for each work area. Since no such measurements were made, and in face of the great many years of employment in Category I, it must be concluded that the dust exposure categories made cannot be justified and are misleading, and that there is a basic weakness and fallacy relative to the classification of the work exposure to asbestos. This is important because the authors rely upon this classification of exposure as the basis for their conclusion of negative findings, because there was no correlation, no increase in death rate for lung cancer by increase in exposure

categories. Obviously, if the classifications are in error to begin with, the correlations themselves are meaningless.

III. Another built-in limitation in the analysis of the data and therefore limitations of the findings, relates to comparison of data in the pre-publication with that in the published article pertaining to the dilution of the cohort, as shown in the percentage distribution by age and percentage distribution by length of employment.

In the 12 lung cancer cases, 11 had employment of 20 or more years. Only one of the 12 had employment of less than 20 years. Eight out of nine proven lung cancer cases had over 20 years duration of employment, and seven out of the nine had 25 or more years of employment. This means, according to their study, that the increased risk for lung cancer in their particular miner cohort, occurs after 20 years of employment.

The limitation factor is the dilution factor as shown on page 28 of the preprint, Table 2--77% of the asbestos cohort and 67% for Thetford mines had less than 20 years of employment. It is obvious that a dilution factor of 70%, in the cohort of employees, tremendously lessens the possibility of any observations pertaining to lung cancer, which as previously shown required 20 years duration of employment.

IV. Another misleading classification in the study relates to the classification of heavy smokers as those who smoked five

cigarettes or more a day, which is not the classification definition of the major published studies pertaining to cigarette smoking and lung cancer: Richard Doll--50 or more a day; Wynder and Graham--35 or more a day; Sodowsky and Gilliam--41 or more a day; Breslow--40 or more a day.

It is obvious that the criteria for heavy smoking, stated as 5 cigarettes or more a day by Braun and Truan is incorrect and therefore the analysis that was conducted and reported in the publication relative to smokers (5 cigarettes or more versus none) are invalid. When the designation of heavy smokers is set at 5 cigarettes or more as was done in this study, it mixes up the truly heavy smokers, those of 40 cigarettes or more a day, with the moderate smokers and very light smokers.

Further, there is no way to determine how the smoking histories were obtained--no information relative to age at start of smoking, nor duration of period of smoking.

Again in Table 4 of the pre-publication report, the percentage of smokers is shown to be:

	Asbestos Cohort	Thetford Mines
Smokers	85%	74%

However, in Table 20 the lung cancer rate of the Cohort Asbestos Miners is 22.1/100,000 while the Thetford Miners proved 27.3/100,000. The total suspected is 41.0.

According to the table, the asbestos miners cohort, with 85% smokers, had the lower lung cancer death rate, 22.1 compared to Thetford miners which had the higher rate for lung cancer of 27.3,

with the lower percentage of smokers, 74%. According to these tables, the more you smoke the less is the lung cancer rate. They do not bring this out in the analysis or in the findings.

(V.) There is another limiting factor, and this relates to the use of the "combined" rates, the averaging effect when the two individual mining facilities are combined in the presentation of the death rates. The comparison of Table 20 in the pre-publication report with Table 16 of the published report illustrates the problem of the averaging effect, where a higher rate is submerged in the average combined rate.

In the prepublished report, Table 20--asbestos cohort had a rate 22.1 proven lung cancer and Thetford miners had a rate of 27.3 and for the total lung cancers 41.0. When they combined the proven cases of 22.1 and 27.3, the combined rate became 25.3 which is less than the higher rate observed of 27.3. It is that average combined number which is compared to the Province rate of 22.5. In essence, the higher rate of 27.3 is submerged in the average of 25.3.

Similarly, the higher rate of 41 is submerged in the average of 33.8, which would be statistically significant compared to 22.5. This is mentioned because in the published document, it is stated that 33.8 is close to being statistically significant. Obviously, rates above 33 are going to reach that point.

By using the combined figures as was done in that report, it lessens the difference between the observed and the control group, which is the Province rate. Whenever an investigator lowers the numbers in the observed group, this of course lessens the chances of noting any positive findings.

VI. Further, in the pre-publication, page 29, Table 3, the distribution by exposure category of the asbestos mining cohort and the Thetford area differ substantially and therefore, any combination of the two would be inappropriate. This was actually done in the study.

Exposure Category	In Asbestos City	Thetford	Combined
I	969 / 43%	1062 / 29%	34%
II	564 / 25%	1586 / 43%	36%
III	735 / 32%	1037 / 28%	30%
Unknown	5 x	0 --	--
	100%	100%	100%

It is noted that in Exposure Category I, asbestos miners cohort had 43% and Thetford miners had 29%. The reverse occurred in Exposure Category II: asbestos cohort had 25% and Thetford 43%. When you combine the two mining facilities who have such marked differences in percentages, by exposure classification, the investigators are actually mixing weighted populations in different categories and then combining them as one.

It is obvious that the use of the combined exposure percentage is not accurate because it submerges important differences. Therefore, the exposure group combinations and designations are misleading.

VII. In the lead-off to the Braun-Truan Report, the authors try to convey the impression that the prior epidemiological work or

prior reports relative to asbestos and lung cancer had certain limitations, and as a means of demonstrating that, they were going to overcome the limitations by having a total population that was followed over a period of time. Their critique in effect said that the prior publications, because they related to autopsies of individuals and groups of individuals, were dealing with selective groups and therefore, in their terms, their study would be much better because of the fact that they were going to take a total population and study that total population. What they did not say and what they did not include in their analysis was an analysis of their own data in Tables 6 and 7 of the published report.

Table 6 refers to proven cases of the primary cancer of the lung; it specifies the exposure, meaning the years that the individual was employed; it specifies whether the individual had an autopsy; and the column to the right specifies whether there was an asbestosis or not. Of the nine cases of proven lung cancers, there were seven autopsies and there were four cases of asbestosis, which gives you approximately a percentage of 57 percent of lung cancers having asbestosis.

Moving to Table 7, and adding to Table 6 the suspected lung cancer cases and the additional autopsies, you find eight autopsies and five observed cases of asbestosis, for a percentage of 62 percent.

What has happened here, and what Braun-Truan unfortunately neglected to emphasize, was that they proved and confirmed all the prior studies of the relationship of asbestosis and lung cancer by overcoming the difficulties they had previously cited other authors had had, by using the method which they called a representative

sample, a representative population of all the asbestos miners, which they took, and they found all the lung cancers in their particular study and determined those who had autopsies of the lung cancers and found 57 percent in one category and 62 percent in the other. Consequently, this was much higher than even the 14 percent and 16 percent and 17 percent and 13 percent previously reported by other authors, which were significant in comparison to the percentage of lung cancers observed among individuals exposed to silicosis.

according to Enterline, Paul Buell's Journal paper just 1965 Fed Proc

Lung cancer with asbestos exposure ... Statistical computation ... then computed ... Enterline (1964)

(VIII) Braun + Truan in the development of the comparison of observed lung cancer cases w Expected as derived from the death-genetic Province - Selectively used years 1954-1955 years to calculate the Expected rates. ... death rates for the years of 6 years 1950-1955 representing the period of the study which is the proper + customary way of deriving Expected rates.

By arbitrarily using 1954-1955 - they got a Expected of 6 lung cancer cases ... 0.12 ... (Dav) ... But By using the proper technique covering The years of 6 years of study 1950-1954 the Expected was (4) ...

Enter here

"Importantly, no data were presented to support the authors belief that chromosome aberrations in the marrow appeared between the Population Studied and the population from which irradiated rats were derived. As a result doubt is cast on the conclusion that cosmic rays and lung cancer are not associated"!

MR. HENDERSON: No. I think that we want to finish it. You asked him about Braun-Truan, and he has a response for you that's as complete as he has it; and he wants to do it and I want him to do it.

Q All right, Dr. Mancuso. Did you observe anything else in comparing the draft Braun-Truan Report with the final published report?

A Yes, I did. I'm referring now to the published document of the Braun-Truan Report, and I'm referring specifically to Tables 6 and 7. I'm ~~mixing~~ inserting it within the following context and for the following reason: In the Braun-Truan Report in the lead-off of his document in the preparation he tries to try to convey the impression that the prior epidemiological work or prior reports relative to asbestos and lung cancer had certain limitations, and as a means of demonstrating that he was going to overcome these limitations by having a total population that was followed over a period of time, his critique in effect said that the prior publications, because they related to autopsies of individuals and groups of individuals, he

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implied and stated that this was a selective group and therefore, in his terms, his study would be much better because of the fact that he was going to take a total population and study that total population; but what he did not say and what he did not include in his analysis was an analysis of his own data on Tables 6 and 7.

Q Is that in the final report, Doctor?

A His final report published in the Archives of Industrial Health, and in Table 6 it refers to proven cases of the primary cancer of the lung, it specifies the exposure, meaning the years that the individual was employed, it specifies whether the individual had an autopsy, and the column to the right specifies whether there was an asbestosis or not. In looking at that table, Table 6, showing nine cases of proven lung cancers, of those nine lung cancers there were seven autopsies and there were four cases of asbestosis, which gives you approximately a percentage of 57 percent of lung cancers had asbestosis.

If you move down then to Table 7 and you add then to Table 7 the suspected lung cancer cases

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and you add then the additional autopsies, you find eight autopsies and observed cases of five cases of asbestosis, for a percentage of 62 percent.

So what has happened here and what Braun-Truan had unfortunately neglected to emphasize was that he, in effect, had proven and confirmed all the prior studies of the relationship of asbestosis and lung cancer by overcoming the difficulties that he had previously cited the other authors had, by doing the method in which he said was a representative sample, representative population of all the asbestos miners, which he took, and he found all the lung cancers in his particular study and determined those who had autopsies of the lung cancers and found 57 percent in one category and 62 percent in the other. Consequently, this was much higher than even the 14 percent and 16 percent and 17 percent and 13 percent previously reported by other authors, which were significant in comparison to the percentage of lung cancers observed among individuals exposed to silicosis.

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