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STUDIES ON SEA-SNAKE VENOMS: CRYSTALLIZATION OF ERABUTOXINS a AND b FROM LATICAUDA SEMIFASCIATA VENOM. <u>N. Tamiya* & H.Arai**.</u> *Chem. Dept., Tohoku Univ.,Japan and Med.School, Tokyo Med. and Dent. Univ., Tokyo,Japan.

The toxic principles in the venom of the sea-snake Laticauda semifasciata were separated into two components by CM-cellulose chromatography and obtained in crystalline forms by salting out with $(NH_4)_2SO_4$. They were named 'erabutoxins a and b'. The homogeneity of each toxin was shown by rechromatography, by disc electrophoresis,by ultracentrifuging, by toxicity measurements before and after repeated crystallizations and by N-terminal amino acid analysis. They had molecular weights of about 7000 as measured by

(Abstract may be extended to fill the rectangle.)

A00443

MAY 16 1978

THE INFLUENCE OF OCCUPATIONAL AND ENVIRONMENTAL ASBESTOS EXPOSURE ON THE INCIDENCE OF MALIGNANT MESOTHELIOMA IN CT.

J.C. Lewinsohn, J.W. Meigs, M.J. Teta, Ct. Cancer Epid. Unit, Yale Univ. New Haven, Ct.06510, U.S.A.

Medical, demographic, and occupational data were collected for the 229 cases of malignant mesothelioma ascertained by the Ct. Tumor Registry between 1935 and 1977 and for a random sample of approximately 700 decedents (1935-1977) from the Division of Health Statistics of the Ct. State Dept. of Health. Sources of information include the files of the CTR, death certificates, and city directories. A vital statistics tape of Ct. decedents was utilized to match spouses of cases. An asbestos-product listing with its associated industrial and employer codes has been created from the occupational histories of cases and controls. A substantial increase in registrations of mesothelioma over this 42 yr. period is evident with 85% of the cases enumerated after 1954. Changes in patterns of diagnosis and the possibility of misclassification are suggested. This hypothesis is supported by: a) only 40% of cases have autopsy diagnostic confirmation; b) discriminant function analysis performed on the 56 confirmed cases of pleural mesothelioma and the 20 cases of primary pleural tumors (not mesothelioma) with respect to age, sex, survival, stage, and number of tumors yielded 59% misclassification. Geographical clustering is evident in certain industrial cities and Labor Market Areas. Final results will include case-control comparisons with respect to occupational asbestos exposure, an analysis of the health status of spouses of these cases, and the occupational histories of spouses of non-occupationally exposed cases.

The CTR has identified 229 cases of malignant mesothelioma of the pleura (147) and peritoneum (33), other mesos (49) and 38 other pleural tumors not mesothelioma which were diagnosed in the state between 1935 and 1977.

Medical, demographic and occupational data have been collected for the cases and for their respective spouses.

Of all cases diagnosed as pleural mesothelioma, 21% (31) had unknown staging and 60% did not have an autopsy. ~~The 49 cases of mesothelioma of other or unknown site have a~~ The question of the accuracy of classification of cases of malignant pleural tumors into mesothelioma and other pleural tumors naturally arises.

I The geographical distribution of cases of mesothelioma throughout Ct shows evidence of urban clusters in the five largest cities where 30% of the cases resided at the time of diagnosis. Since these locations have comprised from ~~37 to 2~~ 20-37% of Ct's population (1940-1977) the suggested urban effect reduces to merely being a factor of population density. These five large cities are also centers of Labor Market Areas of which there are 18 in the State.

Summary

A00451

The Influence of Occupational and Environmental Asbestos Exposure on the Incidence of Malignant Mesothelioma in Connecticut

by

H. C. Lewinsohn

J. W. Meigs

M. J. Teta

The Influence of Occupational and Environmental Asbestos Exposure on the Incidence of Malignant Mesothelioma in Connecticut.

by H. C. Lewinsohn, J. W. Meigs, and M. J. Teta

Introduction

Bruckman et al. (1977a) reported that "the combined sex age-adjusted mesothelioma incidence rate (AAR) per 100,000 Connecticut population has exhibited a possible ten-fold increase since 1935..." They acknowledge that the available statistics might be subject to diagnostic error but, nevertheless, postulate that the rapid increase in the State's mesothelioma incidence rate is closely related to the increase in the State's "cumulative asbestos consumption", which includes asbestos emissions from industrial sources, motor vehicles, and building demolition.

One criticism of their study is the failure to make available complete occupational exposure histories for the 133 diagnosed (1935-1972) cases of mesothelioma drawn from the Connecticut Tumor Registry (CTR). The Air Compliance Unit of the Connecticut Department of Environmental Protection has monitored asbestos concentrations in Connecticut (Bruckman, 1977b; Bruckman, 1978) and proposed an ambient air standard for Connecticut of 30ng/m^3, measured over a thirty-day interval. The rapid increase in the State's mesothelioma incidence reported in 1977 is referred to as justification for this proposal.

The present study has been designed to re-examine the identified cases of malignant mesothelioma recorded in the CTR and attempt to determine the role of various etiological factors, such as occupational and environmental asbestos exposures. In view of the acknowledged possible diagnostic errors, which our results verify, a thorough review of available histological material will be undertaken.

Methodology

The CTR has identified 229 cases of malignant mesothelioma of the pleura (147) and peritoneum (33), other mesotheliomas, including breast, ovary, synovial membrane, testis, spermatic cord, perivesical tissue, cervical glands, brain, esophagus, bone and sternum (49), as well as 38 other pleural tumors, not mesothelioma, which were diagnosed in the state between 1935 and 1977 (Table 1). Disease topology and morphology are coded according to the ICD-0 (World Health Organization, 1976) classification. Medical, demographic, and occupational data have been collected for the cases and for their respective spouses. Similar information has been gathered for a random sample of approximately 700 decedents (1935-76) aged 20 to 98 years from the Division of Health Statistics of the Connecticut Department of Health (Table 2).

Descriptive epidemiology for this research pertains primarily to the forty-three year time interval. Statistical modeling and future case-control comparisons include cases (215) diagnosed after 1954 (Table 1), and controls (605) whose deaths occurred during this same time period. This procedure yields a case-control ratio of approximately 1:3, while reducing sources of error resulting from the limited occupational and medical data prior to 1955 and the increasing awareness of mesothelioma associated with the later time period (1955-1977).

The Price and Lee City Directories, utilized as an occupational data source for the three populations, were available for approximately sixty-six percent of Connecticut towns from 1890 to date (with the exception of smaller towns). Directories were searched for job title and name of specific employer or industry for cases, controls and spouses at 1, 10, 20, 25, 30, 40 and 50 years prior to date of diagnosis, death or until the subject was less than twenty years old. An occupational history search was attempted for spouses to coincide with these intervals for their corresponding cases.

The three-digit 1970 U. S. Census industrial and occupational codes (U. S. Dept. of Commerce, 1971) were assigned to the employment information ascertained from medical histories, death certificates, and City Directories. Industrial coding was determined on the basis of product descriptions for each specific employer which were found in the manufacturing directories of Connecticut, published by the State Department of Labor (1957, 1966, 1973) and from the Price and Lee Directories for non-manufacturing industries. From the complete listing of job and industrial codes a subset was selected by H. C. Lewinsohn, utilizing published sources indicating occupations and products associated with asbestos (Hutchison, 1976; Levine, 1978; Weston, 1976). This will form the basis for probable asbestos expsoure classifications. The City Directory data over five decades provides information on duration of exposure.

With a categorical response variable of occupational asbestos exposure, two fundamental research interests can be tested: 1. Whether cases and controls differ significantly with respect to job-related asbestos exposure (Relative Risk) and 2. The nature of the relative contributions of occupation, spouse occupation and geographical residence to the incidence of mesothelioma in Connecticut (Logistic Regression). In addition, the health experience of spouses of occupationally exposed cases and spouses of non-exposed cases can be compared.

Results

Of all cases diagnosed as pleural mesothelioma, twenty-one percent (31) had unknown staging (SEER, 1976) and sixty percent did not have an autopsy. The forty-nine cases of mesothelioma of other or unknown site have a mean age of fifty-two years and sixty-seven percent are without autopsies. The male-female ratio is approximately 1.5:1 (Table 3). The question of the accuracy of classification of cases of malignant pleural tumors into mesothelioma and other pleural tumors naturally arises. The mean ages and the male-female ratios are similar for these two groups and the "other pleural tumor" group exhibits weak diagnostic confirmation, i.e., seventy-one percent positive histology and only thirty-five percent autopsied. A discriminant function analysis of these two groups of cases (diagnosed after 1954) on the basis of age, sex, survival, time, stage, and number of tumors yields a sixty percent misclassification. This result suggests that: 1. Either these variables are not sufficiently powerful discriminators of pleural mesothelioma from other pleural tumors, or 2. The two groups, as a result of mis-assignment of a substantial number of cases to the incorrect category, now lack the heterogeneity one would expect from distinct categories.

If consideration is limited to cases identified after 1954, when recorded clinical detail in general improved, as well as an increasing awareness of this form of cancer, the number of cases with solid diagnostic confirmation and characteristics consistent with the natural history of mesothelioma are strikingly few. Of the 131 cases classified as pleural mesothelioma, 124 (95%) had histological material, (specimen from biopsy, frozen section, surgery, autopsy or D and C) examined and autopsies were performed on forty-five cases (38%). The proportion autopsied is disappointingly small.

Table 4. shows the percentages of subjects with these two diagnostic critieria for mesothelioma cases of other or unknown site, for peritoneal mesothelioma, and cases of pleural tumors, not mesothelioma.

As a result of these findings, it is imperative that a slide review and a re-examination of hospital clinical reports for all cases of mesothelioma and other pleural tumors be undertaken. A commitment has been received from an independent pathologist for this aspect of the study. The following data analyses are subject to change subsequent to this procedure.

Descriptive Epidemiology

Between 1935 and 1977, the CTR identified 229 cases of mesothelioma, yielding an overall crude incidence rate of ~~four~~ 2.2 per million. Age-adjusted incidence rates per 100,000 population (using 1950 U. S. population as a standard) for pleural and peritoneal mesothelioma consistently increase and exhibit a rapid rise beginning about 1955 - .04 (1935 - 44); .07 (1945 - 54); .18 (1955 - 64) (Figure 1.). We are in the process of generating these rates through 1977. Of these cases, 195 (85%) were reported after 1954. The male-female ratio is approximately 2:1; the mean age at diagnosis is fifty-nine years. Survival time from date of diagnosis to date of death is approximately ten months.

A logistic regression model of the form:

$$\text{Log} \left(\frac{P}{1-P} \right) = A + B_1 X_1 + B_2 X_2 + B_3 X_3.$$

was fit in order to examine the incidence of pleural mesothelioma (binary response variable) as a function of the categorical explanatory variables - time, age and sex (X_1, X_2, X_3). Connecticut population figures supplied by the Connecticut State Department of Health were used for denominator data in the estimate of disease probability ($\hat{P}$).

The three and two-way interactions of time, age and sex were found to be unimportant and the main effects model provided a reasonably good fit ($p > 0.1$).

From the estimates of the model parameters ($\hat{B}_1$, $\hat{B}_2$, $\hat{B}_3$), changes in relative risk (here approximated by the odds ratio) over time intervals, age categories, and sex groups are approximated. Persons exposed between 1975 - 77 carry 3.5 times the risk of pleural mesothelioma as those exposed between 1955 - 64. With progression across the age intervals: 45-54, 55-64, 65-74,...the individual risk of this disease is 1.5 times greater than in the preceding ten year age group. As one might expect, males have three times the risk of females. In assessing these results, the poor diagnostic confirmation outlined in Table 3 should be borne in mind.

The geographical distribution of cases of mesothelioma throughout Connecticut shows evidence of urban clusters in the five largest cities where 30% of the cases resided at the time of diagnosis. Since these locations have comprised from 37% to 20% of Connecticut's population (1940 - 1977), the suggested urban effect reduces to merely being a factor of population density.

These five large cities are also centers of Labor Market Areas (LMA) of which there are eighteen in the State. Application of the Cochran-Mantel-Haenszel Test of Average Partial Association (Landis et al., 1978) between these five LMA's and time of diagnosis (1935-77), while controlling for population age differences, suggests the following:

1. Incidence trends (i.e., the manner in which an area's cases distribute over given time intervals) are primarily the same for four out of five LMA's tested. One region suggests a greater proportion of its cases appearing in more recent years than the others (p=.04). This is readily explicable by the substantial in-migration experienced by this one area and its increasing industrialization as opposed to the other highly industrialized areas whose populations have gradually decreased over time and are, therefore, more comparable for analysis.

2. With the exclusion of this one LMA, the others indicate a similar distribution of their cases of mesothelioma over time (p=.17)

This possibly implies similar patterns of asbestos exposure for the four large industrial regions of Connecticut. Until such time as the mesothelioma incidence has been adjusted for the previously mentioned diagnostic weaknesses and possible misclassifications and until the occupationally exposed cases have been identified, it is not possible to determine the role of environmental asbestos exposure, if any, in the remaining cases.

Summary

Medical, occupational, and demographic data were collected for 267 cases of malignant mesothelioma and other pleural tumors, their spouses, and 605 controls. Methodology was developed for classification of subjects into probable asbestos exposure categories on the basis of product and job descriptions. Although disease incidence rates exhibit a rapid increase from 1955 to 1977, there remains a serious question of diagnostic reliability. A case review will be undertaken.

A0046C

Acknowledgements

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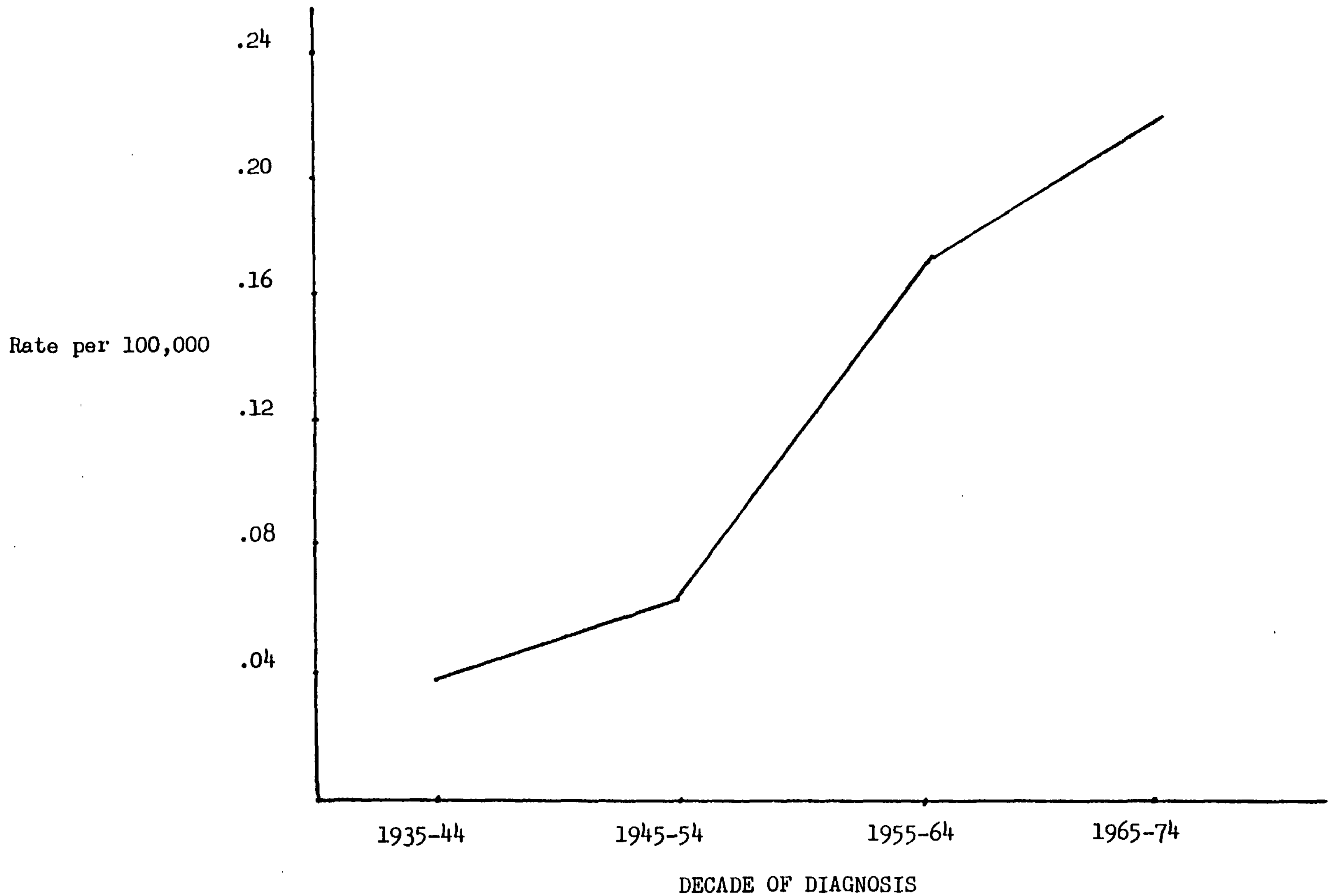
Hilton C. Lewinsohn, Corporate Medical Director, Raybestos-Manhattan, Inc. and Lecturer, Yale School of Epidemiology and Public Health
(address: Raybestos-Manhattan, Inc.,
100 Oakview Drive,
Trumbull, Connecticut 06611, U. S. A.)

J. Wister Meigs, Director, Connecticut Cancer Epidemiology Unit and Clinical Professor of Epidemiology, Yale School of Epidemiology and Public Health
(address: 30 College Street,
New Haven, Connecticut 06520, U. S. A.)

Mary Jane Teta, Associate in Research, Connecticut Cancer Epidemiology Unit, Yale School of Epidemiology and Public Health
(address: 30 College Street,
New Haven, Connecticut 06520, U. S. A.)

Figure 1. Age-adjusted Incidence Rates by Decade of Diagnosis, Pleural and Peritoneal Mesothelioma, Connecticut, 1935 - 1974



Rate per 100,000
.24
.20
.16
.12
.08
.04
1935-44
1945-54
1955-64
1965-74
DECADE OF DIAGNOSIS

A00406

Table 1.

Diagnosis	Period 1935-77		Period 1955-77	
Primary Pleural Tumors (T63)	185		151	
Mesothelioma (M905)		147		131
Other		38		20
Peritoneal Mesothelioma (T58, M905)	33		29	
Mesothelioma Elsewhere	49		35	
Site not pleura or peritoneum		37		27
Site unknown (T99)		12		8
	267	267	215	215

A00468

Table 2.

Source	Population	Variables
Ct. Tumor Registry Tape & Paper File	Cases	Demographic, diagnostic, clinical, follow-up, employment
Vital Statistics Tape of Ct. Residents, matched with case surname, first name, residence, spouse's name	Spouses	Death Cert. No., cause of death, demographic
Death Certificates (1935-1978)	Cases, Controls, Spouses	Demographic, Cause of death, employment, spouse name
Manufacturing Directories of Connecticut 1957, 1966, 1973	Cases, Controls, Spouses	Product Descriptions for specific employers
Price and Lee City Directories	Cases, Controls, Spouses	Middle initial, spouse name, address, employment product descriptions for non-manufacturing employers
1970 U. S. Census industrial and occupational codes	Cases, Controls, Spouses	Job Codes, Industry Codes

Table 3.

Diagnosis	No.	Male	Female	Mean Age	"Positive"[1] Hist.	Autopsy, if Dead
Pleural Mesothelioma	147	102	45	61	93%	40%
Pleural (not Mesothelioma)	38	24	14	62	71%	35%
Peritoneal Mesothelioma	33	20	13	58	94%	89%
Mesothelioma Other sites & site unknown	49	29	20	52	84%	33%
Total	267	175	92	59	88%	44%

1. SEER, 1976 Code/Field Number 19

A0047C

Table 4.

Diagnosis	No.	"Positive Histology"[1.]	Autopsy
Peritoneal Mesothelioma	29	96%	88%
Other mesothelioma (not pleural or peritoneal)	35	88%	40%
Pleural tumors, not mesothelioma	20	85%	36%

1. SEER, 1976, Code/Field Number 19

TITLE: The Influence of Occupational and Environmental Asbestos Exposure on the Incidence of Malignant Mesothelioma in Ct: A Retrospective Case Control Study

Investigators: J. Wister Meigs, Director, Connecticut Cancer Epidemiology Unit and Clinical Professor of Epidemiology, Yale School of Epidemiology and Public Health

Hilton C. Lewinsohn, Corporate Director, Raybestos-Manhattan, Inc. and Lecturer, Yale School of Epidemiology and Public Health

Research Plan:

1. Specific Aims of this Investigation

a. To evaluate the extent of misclassification of malignant pleural mesothelioma and other primary pleural tumors in Ct. from 1935-1977. From the entire set of primary pleural tumors a homogeneous subset will be selected on the basis of clinical, pathologic, and histologic criteria most representative of pleural mesothelioma. Comparisons will be made of these cases and those originally classified as pleural mesothelioma.

b. To bring up to date the descriptive epidemiology of all mesothelioma (pleural, peritoneal, other) and other primary pleural tumors.

c. To make case-control comparisons of occupational exposures, controlling for age, sex, and population density. Occupational histories of the population group under study will be collected in terms of job type, place of employment, and product of place of employment. Risk associated with occupational exposure of short duration will also be assessed.

d. To examine for non-occupationally exposed cases and controls the extent of risk associated with low-dose environmental exposure by utilizing information relative to occupational history of spouses and geographical distance of homes from places of asbestos manufacturing.

e. To assess the effect of occupational asbestos exposure on the disease experience of spouses.

2. Future Research Objectives

a. To examine the incidence of lung cancer, gastro-intestinal cancer, and cancer of the larynx and other cancers in Ct. in order to see whether there is any correlation between them and malignant mesothelioma in the various geographical locations which could be usefully applied to estimate the public health risk, if any.

A00507

b. To review mesotheliomas of all sites for possible relationship to asbestos in water supplies both at home and at place of employment. Cases without evidence of exposure from ambient air, occupation, or spouses' occupation can be examined regarding the waterborne asbestos hypothesis.

c. To examine the relationship of asbestos fiber type and mesothelioma by studying the extent of geographical clustering of this disease about manufacturing firms whose products have known concentrations of crocidolite, chrysotile, and amosite.

A00508

THE PROBLEM:

Studies of occupationally exposed populations have clearly demonstrated the health hazards associated with exposure to asbestos and asbestos products. (Doll, 1965; Mancuso and El-Atar, 1967; Wagner et al., 1960; Newhouse and Thompson, 1965; McDonald, 1973; Elmes, 1965) Three major lesions have been identified, namely, pulmonary fibrosis (asbestosis), lung cancer, and diffuse malignant mesothelioma of the pleura and peritoneum. In addition, an excess of deaths due to cancers of the gastro-intestinal tract have been reported in some studies and an association between asbestos exposure and laryngeal cancer has been demonstrated. It has been postulated that there may also be an increased risk of brain and renal cancers in asbestos workers but the epidemiological evidence for this is as yet unproven.

Thus far, the only positive evidence of non-occupational exposure is from living in close proximity to asbestos mining operations or factories with inadequate dust controls, and in a few isolated instances from domestic sources of contact with the clothing of relatives, friends or lodgers who were asbestos workers. Malignant mesothelioma has resulted from such exposures, but the number of such cases reported in the world literature remains very small.(Wagner et al., 1960; Newhouse, 1965; Champion, 1971; Selikoff and Hammond, 1967, 1969)

There has been great concern in recent years about a public health risk from asbestos in the general environment, but at the present time there are no data available to substantiate or refute this fear. The presence of asbestos fibers in water, beverages, drugs, and the ambient air has not been correlated with disease in the general population. In all published series of mesothelioma. there is a small proportion of cases where exposure to asbestos is considered unlikely or impossible (McDonald et al., 1970; Webster, 1972; Greenberg and Davies, 1974; Milne, 1976), but in some cases this depends upon the care with which the evidence of exposure is sought for.Another source of confusion in the attempt to isolate causative factors in the development of mesothelioma is the different biological effects of varioustypes of asbestos fibers.(McDonald,1978) Crocidolite asbestos from certain regions appears to be the most likely to produce this disease, whereaschrysotile is least likely to do so and amosite (cummingtonite-grunerite) holdsa doubtful intermediary position. On the other hand, the possibility that mesothelioma may be incorrectly attributed to asbestos exposure, must also be taken into account.In 1978 the suspicion that other materials could be partly responsible for those cases without known exposure to asbestos, was apparently verified by the finding in Turkey that asbestos related diseases mainly calcified pleural plaques, chronic fibrosing pleuritis and malignant pleural mesothelioma are endemic is some villages without asbestos deposits. These fibers were shown to be erionite type zeolite. Thus it would seem that fiber-shape and size is important in the etiology of malignant mesothelioma and fibrous minerals from sources other than asbestos mining or processing may be implicated in the epidemiology of this disease. (Baris et al., 1978)

A005U9

The reported frequency of mesothelioma has substantially increased in Ct. in the late 1950's and has continued to increase steadily since that time. One possible explanation is increased recognition on the part of pathologists and clinicians as to the existence and etiology of this disease. It has also been suggested that this increased incidence can be attributed to the tremendous growth of the asbestos industry in the U.S. In view of the long latency period for the development of mesothelioma (Selikoff, 1977; Greenberg, 1974) a continued rise in incidence until at least the end of this century is a real fear expressed by some investigators.

When the reported measurements of ambient air are studied in the literature, we see that even the highest figure for contamination of the general atmosphere is three orders of magnitude below the current hygiene standard. In considering the public health risk we must not forget the great and continuous improvement in dust control in most workplaces where asbestos is used and, therefore, a decreasing emission of dust from these sources. The emission of fibers from brake linings has been cited as a source of asbestos in ambient air and, in Ct., such measurements as have been made, indicate that this may raise the background level where traffic is dense, where brakes are applied such as toll booths or traffic intersections. (Bruckman and Rubino, 1978)

Earlier studies suggest a significant risk associated with low-dose exposures resulting from geographical residence, occupation of spouse, or occupational exposure of short duration. (Wagner et al., 1960; Selikoff, 1965; Anderson, 1976; Newhouse, 1972; Champion, 1971) A very recent publication (Whitwell et al., 1977) reports the amount of asbestos fibers in lung tissue to be associated with occupation but not with environment. No geographical cluster about asbestos manufacturers, independent of occupation, could be demonstrated. This study provides additional evidence that the development of asbestos-induced mesothelioma is dose related, an encouraging result in the evaluation of risk in the general environment.

The question which remains unresolved is whether the minute quantities of asbestos measurable in the ambient air contribute to the incidence in the general population of those diseases which have been identified in association with asbestos exposure in occupational situations. By examining in depth the mesothelioma cases which have been reported to the Connecticut Tumor Registry between 1935 and 1977 and investigating their background, if there is indeed a public health risk it should be brought to light.

MATERIALS AND METHODS:

Cases will be comprised of all malignant mesotheliomas, both pleural and peritoneal, with positive histology diagnosed in Ct. from 1935-77, with the possible addition of some or all other malignant primary pleural tumors with similar characteristics. The maximum number of cases for the study would be 248 - 210 cases of mesothelioma, 38 cases of pleural tumors, non-mesothelioma. Cases from 1935-77 will be analyzed descriptively only. Those from 1955 on (approximately 116 - 98 mesothelioma, 18 non-mesothelioma pleural) will re-ceive formal statistical analyses including comparisons with a control group of about 232 randomly selected deaths from the State of Ct. Department of Vital Statistics.(Table 1)

EXPECTED FINDINGS:

An estimate of the relative importance of various sources of asbestos exposure on the rising incidence of mesothelioma in Ct. is anticipated as a result of this research. The effect of changing trends in diagnosis and classification of this disease should also be suggested. Analyses based on cases corrected for this effect will assess the level of risk associated with low-dose exposure, namely, that which might result from residential proximity to asbestos manufacturing, an occupationally exposed spouse, or an occupational exposure of short duration.

TABLE 1

OBJECTIVE	POPULATION	DATA SOURCE	VARIABLES OF INTEREST	STATISTICAL METHODOLOGY
A	Cases(1935 to 1977)	CTR Tape & paper file	sex, age of diag.,age of death, smoking history, survival, no. of tumors, no. of primaries, grade, stage, EOD	Discriminant Analysis or Logistic Regression
B	Cases & Controls (1935-77)	CTR & State Dept. of Vital Stats.	sex; age; marital status; case survival, duration of occup. exp.,latency; incidence rates	Frequencies, ~~In~~Direct Age adjustment
C	Cases & Controls (1955-77)	City Dir. & U.S. Census	type job,place & duration of employment, product of place of employment, population density of residence	R.R., Chi-Square Test of equal risk,Var. & C.I. for R.R.
D	Non-Occ. Exp.Cases & Controls (1955-77)	City Dir. State Workers Comp.	occup. exp. of spouse & duration of, distance of usual resid. from asbestos manufact.	Chi-Square Test of Assoc. Mantel-Haenszel Stats(assoc. of resid. and disease, controlling for pop.) Geographical mapping of cases
E	Occ. Exp. Cases (1955-77)	CTR Tape & Death Tape	observed freq. of deaths for spouses by cause over time	R.R. comparisons of observed to expected

A00512