

Asbestos lung burden and asbestosis after occupational and environmental exposure in an asbestos cement manufacturing area: a necropsy study

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Abstract

Objective—The largest Italian asbestos cement factory had been active in Casale Monferrato until 1986: in previous studies a substantial increase in the incidence of pleural mesothelioma was found among residents without occupational exposure to asbestos. To estimate exposure to asbestos in the population, this study evaluated the presence of histological asbestosis and the lung burden of asbestos fibres (AFs) and asbestos bodies (ABs).

Methods—The study comprises the consecutive series of necropsies performed at the Hospital of Casale Monferrato between 1985 and 1988. A sample of lung parenchyma was collected and stored for 48 out of 55 necropsies. The AF concentration was measured with a TEM electron microscope with x ray mineralogical analysis. The ABs were counted and fibrosis evaluated by optical microscopy. The nearest relative of each subject was interviewed on occupational and residential history. Mineralogical and histological analyses and interviews were conducted in 1993-4.

Results—Statistical analyses included 41 subjects with AF, AB count, and interview. Subjects without occupational exposure who ever lived in Casale Monferrato had an average concentration of 1500 AB/g dried weight (gdw); Seven of 18 presented with asbestosis or small airway lung disease (SAL). G2 asbestosis was diagnosed in two women with no occupational asbestos exposure. One of them had been teaching at a school close to the factory for 12 years. Ten subjects had experienced occupational asbestos exposure, seven in asbestos cement production: mean concentrations were 1.032×10^6 AF/gdw and 96 280 AB/gdw. Eight of the 10 had asbestosis or SAL.

Conclusion—The high concentration of ABs and the new finding of environmental asbestosis confirm that high asbestos concentration was common in the proximity of the factory. Subjects not occupationally exposed and ever living in Casale Monferrato tended to have higher AB concentration than subjects never living in the town (difference not significant). The concentrations of ABs and AFs were higher than

those found in other studies on non-occupationally exposed subjects.

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Keywords: lung burden; asbestosis; asbestos cement manufacture

The largest Italian asbestos cement factory operated in the town of Casale Monferrato (north west Italy) from 1907 to 1986. Since 1987, epidemiological studies have measured the effects of occupational, domestic, and environmental asbestos exposure, and found an increase in mortality from respiratory cancer and incidence of mesothelioma among asbestos cement workers¹ and in incidence of mesothelioma among their wives^{2,3} and in the general population without occupational exposure.³

The factory employed up to 1500 workers, produced various asbestos cement products including high pressure pipes, and used both crocidolite and chrysotile.¹ In 1981 the company reported the use of 15 000 metric tonnes of asbestos, 10% of which was crocidolite. Environmental asbestos pollution in Casale Monferrato also originated from the large use of asbestos cement products: the Town Office estimated in 1990 that asbestos cement roofs amounted to 500 000 m² in a town of about 40 000 inhabitants. The factory is about 1300 m from the centre of the town and 250 m from the closest residential areas. The town is downwind from the factory in respect to dominant winds.⁴

Measures of environmental asbestos exposure in the town of Casale Monferrato are limited in number and close in time, or subsequent to the cessation of asbestos cement production. Marconi *et al* in 1984 reported average concentrations of asbestos fibres (AFs) longer than 5 µm of 11 AF/l close to the plant and 1 AF/l in the city area farthest away from it.⁴ A study conducted between March 1990 and July 1991 by the Local Health Authority in cooperation with the ISS measured in 12 sampling sites in the town annual averages below 1 AF/l (longer than 5 µm). This threshold was exceeded in 12% of samples (Internal report, Local Health Authority of Casale Monferrato). Chiappino *et al* in 1991 found that the average concentration of AF (length >5µm and diameter >0.3 µm) was in the range 2.2-7.4 AF/l in residential areas of the city.⁵ In these studies the

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Figure 1 Microphotograph of a preparation used for counting asbestos bodies.

proportion of amphiboles ranged between 15% and 50% of AFs. The results of those studies are difficult to compare because of the different sampling and analytical methods; nevertheless, they suggest that the concentration of fibres was higher and the proportion of amphiboles was larger in Casale Monferrato than in the centre of other Italian cities.^{6,7}

No information has been presented so far on the concentration of asbestos fibres and asbestos bodies in the lung and on the prevalence of pulmonary asbestosis among persons living in Casale. Thus, we carried out a preliminary study on a set of samples of lung tissue from the necropsies performed in 1985–8 at the local hospital. On those samples we evaluated the presence of lung asbestosis and small airway lesions (SAL) and measured the concentration of AFs and asbestos bodies (ABs). These variables were related to indicators of occupational and residential asbestos exposure.

Materials and methods

The present study comprises the consecutive (unselected) series of necropsies performed at the General Hospital of Casale Monferrato between July 1985 and July 1988.

Out of 55 necropsies in the period, a sample of a lung parenchyma was available for 48. The remaining seven necropsies were conducted before December 1986 when only one of the pathologists in the hospital participated in the collection of lung samples. Necropsies were requested by the attending clinician for the elucidation of clinical questions and were not selected on exposure to asbestos. Age and sex distribution of subjects was similar to that of decedents in the hospital.

A sample of lung parenchyma was routinely collected for each necropsy, formaldehyde fixed, identified with a progressive number, and stored. Tissue collection was not optimal as only one sample was available for each person and the location had not been recorded. Each sample was then divided into two parts, which were sent respectively to the "Laboratorio di Ultrastruttura" of ISS for the identification of fibres and to the Unit of Pathology (headed by FM) of the S Giovanni Hospital for diagnosis of fibrosis and AB count.

A personal interview took place in 1994 with the nearest relative of subjects in the study to obtain information on: smoking habits, occupational history, residential history, and chest diseases. Occupational exposure in the asbestos cement industry was defined on the basis of both the interview and the nominal search in the rosters of the employees in the local asbestos cement industry.³ Occupational asbestos exposure in other activities was estimated on the basis of interview data. Among the occupations held by study subjects, those considered at definite or probable exposure were in the asbestos cement production (any job) and in the construction industry. No other asbestos related jobs were found in the study.

Both the interviews and the microscopical analyses were done blindly.

Forty one people were included in the statistical analyses. The remaining six were excluded either because the interview could not be carried out (five instances) or the sample was inadequate for fibre counting on the electron microscope (one instance). An outlier was also excluded. He was a farmer who lived in a rural village close to Casale Monferrato and had two sons working in asbestos cement production from 1960 to 1986; no occupational asbestos exposure was reported, with the possible exception of the construction of some warehouses with asbestos cement roofs in the farm courtyard; his lung burden measured 532 000 fibres/gdw (dry weight) of crocidolite and 770 ABs/gdw. He presented histological signs of SAL and died from pleural mesothelioma.

FIBROSIS AND ASBESTOS BODIES

Histological examinations and AB counts were performed by light microscopy. The ABs were measured using about 100 mg (dehydrated tissue) of lung parenchyma without pleura or bronchi: the concentration (AB/gdw) was determined by optical count after membrane filtration of the material that was obtained by hypochlorite digestion.^{8–10} Figure 1 shows a microphotograph of a preparation used to count ABs. A fragment of about 5 ml lung parenchyma was fixed and used for histological examination. Several slides (four to six usually, from one or more paraffin embedded blocks) were considered for the definition of asbestosis and SAL. Features of asbestosis were searched for on sections stained with haematoxylin-eosin and graded according to Craighead *et al.*¹¹ SAL was defined according to Wright and Churg¹² as pathological changes characterised by fibrosis with possible pigmentation of respiratory bronchioles with or without fibrosis of alveolar ducts. The diagnosis of SAL implies that ABs were not found on the examined sections, as the association of SAL and ABs is classified as grade 1 asbestosis.¹³

FIBRE COUNT AND MINERALOGICAL ANALYSES

Parenchyma samples, 40 to 200 mg of dehydrated tissue depending on the size of the original lung sample, were digested using hydrogen peroxide and sodium hypochlorite. The solution was filtered on cellulose ester filters (pore size 0.45 µm). The filters were dried,

Table 1 Descriptive information on the necropsy cases in the hospital at Casale Monferrato (1985–8) included in the present analyses

Variable	n	%
Sex:		
Men	18	43.9
Women	23	56.1
Age:		
≤49	2	4.9
50–69	12	29.3
≥70	27	65.9
Residence:		
Casale	24	58.3
Surrounding villages	4	9.8
Rest of the local health authority	8	19.5
Other	5	12.2
Birthplace:		
Casale	13	31.7
Surrounding villages	3	7.3
Rest of the local health authority	8	19.5
Other	17	41.5
Cause of death:		
Mesothelioma	4	9.8
Lung cancer	4	17.1
Other malignancies	16	39.0
Cardiovascular diseases	10	24.4
Respiratory diseases*	3	7.3
Other diseases	1	2.4

*One death from asbestosis.

covered with a thin carbon film, cut, and mounted on standard 200 mesh copper grids for transmission electron microscopy (TEM) and then exposed to acetone fumes to dissolve the filters.¹⁴

All the reagents and the solutions used in the sample preparation were filtered through Millex-GS 0.22 µm pore size sterile filters (Millipore), to avoid particulate contamination. Two blank samples were prepared in different phases of the study by filtering 50 ml sterile saline solution through 0.45 µm pore size cellulose nitrate filter. No significant contamination was found at EM analyses.

The mineral particulate on carbon films was analysed by a TEM Philips EM430 equipped with an EDAX energy dispersive spectrometer for x ray microanalysis. Accelerating voltage was 250 KeV and magnification was 10 000×. For each subject, 25 to 40 grid apertures (an aperture effective area being about 8400 µm²) in at least five different grids were examined.

The fibres and the mineral particles detected were identified by morphology, chemical composition (elements with atomic number >11), and crystalline structure. All fibres, independent of length, and all mineral particles were counted.¹⁵ Fibre and particle concentration is reported in 10⁶/gdw.

STATISTICAL ANALYSES

Data on fibre and AB concentrations are summarised by the arithmetic mean (SD). As only one necropsy sample was available for every subject it was impossible to perform repeated analyses of fibre burden.

Fibre concentration was compared over classes of exposure using Kruskal-Wallis or Mann-Whitney non-parametric tests.¹⁶ Subjects with no fibres or no ABs detected were included with the value of 0. This underestimates the value of the mean compared with the use of a fraction of the detection limit but does not affect the median and the statistical significance of the tests, which are based on ranks.

Table 2 Necropsy cases in the hospital at Casale Monferrato (1985–8)

	Occupational exposure to asbestos	
	Yes	No
Subjects (n)	10	31
Asbestos fibres (total) (10 ⁶ fibres/gdw):		
0	3	17
<0.5	2	14
0.5–<1	2	0
≥1	3	0
Arithmetic mean	1.032	0.024
SD	1.222	0.032
Median	0.563	0.0
Chrysotile (10 ⁶ fibres/gdw):		
0	10	26
0.5–<1	0	5
Arithmetic mean	0.0	0.005
SD	0.0	0.012
Crocidolite (10 ⁶ fibres/gdw):		
0	5	24
<0.5	1	7
0.5–<1	2	0
≥1	2	0
Arithmetic mean	0.706	0.010
SD	1.107	0.021
Median	0.077	0.0
Tremolite (10 ⁶ fibres/gdw):		
0	9	27
<0.5	1	4
Arithmetic mean	0.045	0.006
SD	0.142	0.016
Amphiboles (nos) (10 ⁶ fibres/gdw):		
0	8	28
<0.5	1	3
0.5–<1	0	0
≥1	1	0
Arithmetic mean	0.281	0.004
SD	0.885	0.012
Fibrosis absent	2	19
G1 asbestosis	0	0
G2 asbestosis	2	2
G3 asbestosis	2	0
G4 asbestosis	3	0
SAL	1	9
Other	0	1
Asbestos bodies (light microscope)(AB/gdw):		
0	2	6
<500	0	12
500–1000	0	7
>1000	8	6
Arithmetic mean	96285	1064
SD	117662	1797
Median	45523	321

Median is not reported when 0 in both groups.
nos=Not elsewhere specified.

Frequency distributions were compared using the χ^2 test.

Results

Study subjects are described in table 1. Average age was 71 (SD 13.3) years (range 24–92). Seven subjects (17.1%) worked in asbestos cement production and six others (14.6%) lived with a relative or the spouse working in the asbestos cement industry.

Table 2 presents the concentration of AFs, dust, and ABs and frequency of asbestosis and SAL in the 41 subjects included in the statistical analyses, according to occupational asbestos exposure. Ten subjects reported occupational asbestos exposure (seven in the asbestos cement industry). The difference between the two groups (defined as “exposed” and “non-exposed”) was significant for AFs (p<0.005), crocidolite (p=0.02), and ABs (p=0.006) as well as for the frequency of asbestosis and SAL (p<0.005). Correlation between ABs and fibres was poor (ABs and total AFs: Spearman r=0.28 among all subjects and –0.01 among

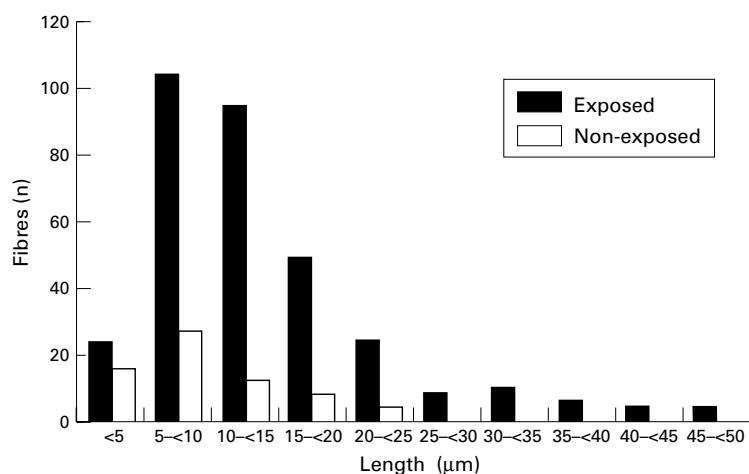


Figure 2 Frequency distribution of amphibole fibre length, according to occupational exposure.

subjects with no occupational asbestos exposure; ABs and crocidolite: Spearman $r=0.26$ and 0.19 respectively). Concentration of mineral particles was similar in the two groups (subjects with occupational asbestos exposure: mean 14.50 (SD 2.76) $\times 10^6$ particles/gdw ; subjects without exposure: mean 14.00 (SD 13.22) $\times 10^6$ particles/gdw.

No fibres were found for three subjects with occupational exposure (one in the asbestos cement industry and two in the construction industry) but in two of these subjects ABs were present.

Asbestosis was found in seven and SAL in one out of 10 subjects with occupational asbestos exposure and asbestosis was found in two and SAL in nine out of 31 subjects without occupational exposure.

Table 3 presents AF and AB concentrations according to both asbestosis and occupational asbestos exposure. In both groups (subjects with and without asbestosis or SAL) the concentration of AFs was higher among subjects with occupational asbestos exposure. Only two subjects with occupational asbestos exposure did not have asbestosis or SAL.

The total number of fibres detected in the study was 392 (83% in occupationally exposed subjects), with an average for the positive cases of 19 fibres/case (range from 2 in a subject without occupational asbestos exposure to over 100 for a subject with asbestosis). Only 4% of fibres were chrysotile, the remaining 96% amphibole. In subjects with occupational asbestos exposure the amphibole fibre burden was very much higher than the chrysotile burden (table 2) in accordance to the data

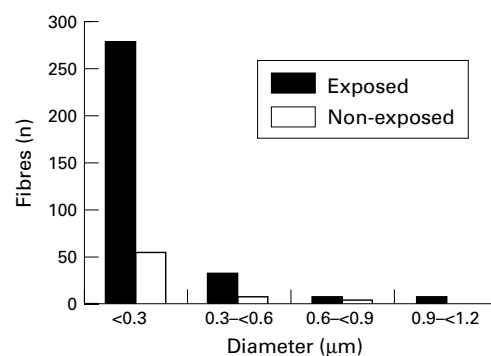


Figure 3 Frequency distribution of amphibole fibre diameter, according to occupational exposure.

reported in most studies^{17 18} on workers with exposure to mixed fibre types.

Figures 2 and 3 present the frequency distribution of amphibole fibre length (average 13.6 µm) and diameters (average 3.6 µm) separately in “exposed” and “non-exposed” groups. Eighty three per cent of fibres were in subjects with occupational asbestos exposure, who also had a higher proportion of long AFs. The average fibre length in subjects with occupational exposure was 16.3 whereas in subjects without occupational exposure it was 11.7 ($p<0.0001$). Diameter distribution was similar in the two groups (mean 0.36 and 0.40). The few chrysotile fibres showed an average length of 11.5 µm and an average diameter of 0.8 µm.

Table 4 presents the concentration of ABs among the 31 subjects with no occupational asbestos exposure, subdivided according to sex and residence (ever in life and irrespective of duration) in Casale Monferrato. In both sexes people who ever lived in Casale presented a higher AB count but the difference was not significant. Five subjects living in Casale and never resident elsewhere presented more than 1000 ABs, whereas AFs did not show remarkable differences according to residence.

Analyses of AB and AF concentrations after subdividing Casale Monferrato into smaller units and according to the distance of dwelling from the factory did not provide consistent results because of small numbers and are not presented.

Out of 18 subjects ever living in Casale Monferrato five had SAL and 2 G2-asbestosis, compared with four with SAL and none with asbestosis in the 13 subjects never living there. Both cases of asbestosis were women not occupationally exposed and never living with persons occupationally exposed (fig 4). Both had been in Casale Monferrato for over 50

Table 3 Mean (SD) necropsy cases in the hospital at Casale Monferrato (1985–8)

	No lung fibrosis			G1-G4 asbestosis+SAL		
	Occupational exposure to asbestos			Occupational exposure to asbestos		
	Yes	No	p Value	Yes	No	p Value
n	2	20		8	11	
Total asbestos fibres (10^6 fibres/gdw)	1.007 (1.424)	0.023 (0.034)	NS	1.039 (1.277)	0.026 (0.029)	0.025
Chrysotile (million fibres/gdw)	0 (0)	0.05 (0.012)	NS	0 (0)	0.006 (0.014)	NS
Total amphiboles (10^6 fibres/gdw)	1.007 (1.424)	0.019 (0.032)	NS	1.039 (1.277)	0.020 (0.023)	0.024
Asbestos bodies (AB/gdw)	0 (0)	0.461 (0.607)	NS	120.356 (120.362)	2.152 (2.633)	0.003

Table 4 Concentration of ABs according to sex and residence in Casale Monferrato among subjects with no occupational exposure to asbestos

	Residents in Casale Monferrato						p Value (ever v never)
	Ever			Never			
	n	AB/gdw		n	AB/gdw		
		mean	SD		mean	SD	
Men	5	3091	2620	4	772	931	NS
Women	13	841	1822	9	379	346	NS
p Value (men v women)	18	1466	2244	13	500	576	NS

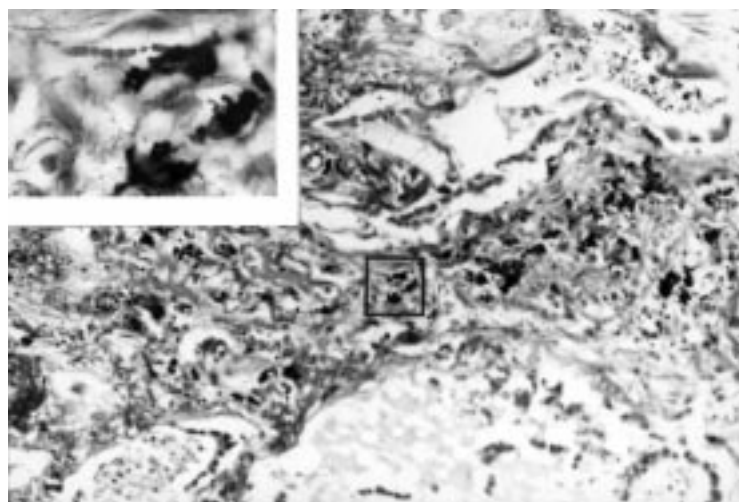


Figure 4 Microphotograph of asbestosis in a woman not occupationally exposed.

years; one was a school teacher who had been working for 12 years (1958–69) in a school close (250 m) to the asbestos cement factory; no information was available for the other. Both presented 800 AB/gdw.

Seven subjects died from lung cancer and five from mesothelioma. The mean AF concentration for cases of lung cancer was 0.50 (SD 1.25) × 10⁶ fibres/gdw, the mean concentration of crocidolite was 0.49 (SD 1.21) × 10⁶ fibres/gdw and, the mean concentration of ABs was 44.3 (SD 78.2)/gdw. Corresponding figures for mesothelioma cases were: 0.15 (SD 0.26) fibres/gdw for total AFs, 0.13 (SD 0.27) × 10⁶ fibres/gdw for crocidolite and 0.41 (SD 0.26)/gdw for ABs. In cases of mesothelioma only amphibole fibres were detected. Two cases of lung cancer and one of mesothelioma had worked in asbestos cement production. The last had 2.8 × 10⁶ fibres (only amphiboles) and 268 800 asbestos bodies. The lung fibre burdens in asbestosis cases were consistently greater than 10⁶ fibres/gdw with a mean concentration of 2.4 × 10⁶ fibres/gdw.

Discussion

The present study, albeit based on limited numbers, is unique as it includes the consecutive series of necropsies conducted in Casale Monferrato in the years immediately after the cessation of asbestos cement production. It is based on samples collected routinely for the archive of the pathology department and analysed separately. The use of these samples is a weakness as the collection was not optimal (only one sample a subject, taken from an

unspecified part of the lung): the effect could be a reduction of the fibre count in some subjects and an increased variability. By contrast, the interval between tissue collection and the analyses does not affect the results as AFs are stable in formaldehyde fixed tissues and the interval is similar for all subjects. Occupational and residential histories were collected blindly. The concentration of mineral particles is similar in subjects with and without occupational exposure, which gives an indication of the absence of bias.

Limited evidence is available on the concentration of ABs and AFs in environmentally exposed populations. Published results show large variability, because of differences in case mix, presence of occupational exposure, intensity of exposure, and analytical methods. Moreover, in some instances environmental exposure is defined in only very general terms, such as “urban” and “rural”, whereas in the present study it is clearly defined in relation to a source of occupational and environmental asbestos exposure.

The present study shows consistent (not always significant) variations in the concentration of AFs and ABs in relation to both occupational asbestos exposure and residence in Casale Monferrato.

The concentration of 1000 AB/gdw or higher can be taken as a cut off point as it is considered indicative of occupational exposure to asbestos.^{19–23} This concentration was exceeded by eight out of 10 subjects with occupational exposure (six of seven persons employed in the asbestos cement factory), by five out of 18 of those non-occupationally exposed but living in Casale and by one of 13 of those non-occupationally exposed and never living in Casale. Mollo *et al*^{8, 24, 25} and Andron *et al*⁹ in consecutive studies on unselected necropsy samples in Torino found that the proportion of subjects without occupational exposure and presenting over 1000 AB/gdw was in the range 0% to 14%. Roggli²⁶ included in a review three studies on AB concentration in “control” populations, with average values in the range 20–280 AB/gdw.

Case and Sebastien²⁷ showed a gradient in AF and AB concentration between controls and environmentally exposed subjects living in the asbestos mining areas of Quebec. There was a median concentration of 480 AB/gdw in Asbestos and 1880 AB/gdw in Thetford whereas controls presented 80 AB/gdw and subjects occupationally exposed 35 000 AB/gdw. Corresponding figures for total AFs were 0.57 × 10⁶, 1.16 × 10⁶, 0.26 × 10⁶, and 24.6 × 10⁶/gdw. Monsò *et al*²⁸ found ABs in nine out of 18 non-occupationally exposed subjects living in Barcelona (range 0 to 430 AB/gdw). Dufresne *et al*²⁹ measured ABs and AFs in the lung of residents in Asbestos never occupationally exposed and dying from diseases not related to asbestos: the average concentrations were 192 AB/gdw and 208 × 10⁶ AF/gdw. Yamada *et al*³⁰ found in 108 Japanese women a significantly higher concentration of ABs and AFs among urban than rural dwellers, measured by optical microscopy.

Several studies have been conducted to use AF burden measured by electron microscopy for estimating occupational and environmental exposure, nevertheless the variation between laboratories is still large and makes the comparison of results from different laboratories uncertain.³¹ Roggli²⁶ reviewed the published studies on AF burden in subjects not affected by asbestos related diseases: average concentrations ranged between 0.034×10^6 and 11.2×10^6 fibres/gdw. Churg,³² on the basis of these uncertainties, recommended the use of internal reference values in each laboratory but until now there is no generally accepted value of fibre concentration to distinguish between fibre burden of the "normal" population and of occupationally exposed subjects.³³ Present results are therefore compared with findings in the ISS laboratory, obtained in the city of Rome among subjects without evidence of occupational exposure to asbestos.¹⁵ Asbestos fibres were found in the lungs in nine of 18 subjects who ever lived in Casale Monferrato *v* 14 of 85 in Rome ($p < 0.003$). In addition, chrysotile fibres were present in 33% of positive subjects (those with AFs) in Casale and in 68% in Rome and corresponding values for amphiboles were 89% and 32%. Fibre concentration in Rome ranged between 0.2 and 3×10^6 AF/gdw. The range of fibre length was 1–50 μm (mean 13.6 μm) in Casale and 1–8 μm (mean 3 μm) in Rome. Diameters were similar in the two studies. These differences are consistent with the likely substantial differences in the main source and the intensity of airborne asbestos exposure in the two cities. In Casale asbestos exposure is related mostly to asbestos cement production and to the use of asbestos cement products whereas in Rome it is related to vehicle circulation and only to a lesser extent to asbestos cement used in the building industry.⁷

Concentration of chrysotile fibres in this study was low, even among occupationally exposed subjects. This finding corresponds with the results of studies on workers exposed to mixed fibres,^{17,18} on chrysotile only,³⁴ and with a lower biopersistence of chrysotile compared with amphibole fibres.

Out of 31 subjects not engaged in occupations at probable asbestos exposure, two had histological signs of asbestosis and nine of SAL, which is considered likely indicative of asbestos exposure.¹⁵ No suggestion of occupational or domestic exposure was found for the two women with asbestosis. To our knowledge, this is a new finding, which indicates high levels of environmental asbestos exposure in the past. Asbestosis in relation to environmental exposure has been reported in Turkey and attributed to high environmental levels of tremolite.³⁵ The two cases of non-occupational asbestosis had 800 AB/gdw, which is the average for women living in Casale and not occupationally exposed. In the interpretation of this value we must take into consideration that individual susceptibility plays a part in both the pathogenesis of asbestosis³⁶ and the production of ABs.³⁷ Dodson *et al*³⁷ described lung asbestosis even without finding ABs in digested lungs. Moreover, chrysotile, which is

fibrogenic but induces low production of ABs,³⁸ accounts for 50%–85% of airborne AFs, (longer than 5 μm) in the general environment of Casale.

Conclusion

We found two cases of histological asbestosis, a high prevalence of SAL, and a high concentration of ABs among people with no occupational exposure who lived in Casale Monferrato, which confirms the high prevalence of environmental asbestos exposure that was experienced in the area in relation to asbestos cement production.

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