Erionite bodies and fibres in bronchoalveolar lavage fluid (BALF) of residents from Tuzköy, Cappadocia, Turkey

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Abstract

***Objectives*—The high incidence of malignant mesothelioma in some villages of Cappadocia (Turkey) is due to environmental exposure to erionite fibres. The aim was to evaluate the fibre burden in bronchoalveolar lavage fluid (BALF) from inhabitants of an erionite village and compare it with Turkish subjects with or without environmental exposure to tremolite asbestos.**

***Methods*—Ferruginous bodies (FBs) and fibres were measured and analyzed by light and transmission electron microscopy (TEM) in the BALF of 16 subjects originating from Tuzköy.**

***Results*—FBs were detected in the BALF of 12 subjects, with concentrations above 1 FB/ml in seven of them. Erionite was the central fibre of 95.7% of FBs. Erionite fibres were found in the BALF of all subjects, by TEM, and these fibres were low in Mg, K, and Ca compared with erionite from Tuzköy soil. The mean concentration of erionite fibres in BALF was similar to that of tremolite fibres in Turks with environmental exposure to tremolite. The proportion of fibres longer than 8 µm in BALF represented 35.6% for erionite compared with 14.0% for tremolite. The asbestos fibre concentrations in erionite villagers was not different from that in Turks without environmental exposure to tremolite.**

***Conclusion*—Analysis of BALF gives information about fibre retention in populations environmentally exposed to erionite for whom data on fibre burden from lung tissue samples are scarce. This may apply to exposed Turks having emigrated to other countries.**

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Keywords: ferruginous body; asbestos body; environmental exposure; mesothelioma

Epidemiological[1] and experimental data[2–4] show that erionite fibres have the highest carcinogenic potency among any other fibres so far studied.[5] They also have a strong fibrogenic potential.[6]

Erionite belongs to the mineralogical group of zeolites. It is a complex group of hydrated aluminosilicates of alkali and alkaline earths including about 40 natural minerals. Zeolites typically occur in cavities in basic volcanic rocks and in other late stage hydrothermal environments. These minerals have a very large internal surface area resulting from the particular configuration of their crystalline lattice. They are able to lose or gain water molecules and to exchange cations without major changes to their crystalline structure, and have a catalytic activity.[5] Most of the naturally occurring zeolites are non-fibrous, whereas erionite, clinoptilolite, and mordenite are fibrous.[7]

Erionite fibres are found in rocks and soils of the Nevshehir region of Cappadocia. These fibres can also be detected in air samples and in the lungs of people living in villages in this area of Turkey. Like many other places in Cappadocia, these villages are characterised by ancient rock dwellings and caves dug in soft volcanic tuff. This type of dwelling favours the continuous exposure of inhabitants to erionite fibres, and in these villages, there is a high incidence of malignant mesothelioma.[1] Fibre concentrations up to 0.18 f/ml air were measured in school playgrounds and up to 1 f/ml air in homes and caves. The highest values were recorded after sweeping the walls of dwellings and during play in the caves.

After the description of a first case in 1975, the outbreak of malignant mesothelioma in Karain was confirmed in 1978.[8] In subsequent years the same phenomenon was reported for two other villages, Tuzköy and Sarihidir.[1] The population of the three erionite villages is around 5000 people. The mortality from malignant pleural mesothelioma among Karain villagers was estimated to be 8 deaths/1000 inhabitants/year.[1] Up to 52% of deaths in Karain between 1970 and 1994 and 36% in Sarihidir and Tuzköy between 1980 and 1994 were due to malignant pleural or peritoneal mesothelioma.[9] It also caused 14 of the 18 deaths (78%) found among a cohort of 162 Karain villagers who had emigrated to Sweden.[10] Non-malignant pleural or pulmonary changes were also described in inhabitants of the erionite villages.[1 9 11]

High concentrations of erionite fibres were found in lung tissues of several patients originating from erionite villages. Erionite fibres can form ferruginous bodies (FBs) morphologically identical to typical asbestos bodies (ABs).[12] These FBs were found more often in sputum samples of inhabitants from Karain and Tuzköy than from neighbouring villages.[13] Despite interest in gathering information about the burden of erionite fibre in the lungs and pleura of exposed subjects and comparing them with similar findings from people exposed to asbestos, the data collected over 20

Table 1 Demographic, exposure, and clinical data of the subjects

	Subjects with exposure to erionite in Turkey
n	16
Age (y)	
Mean (SD)	40.3 (9.2)
(Range)	(28–63)
20–35	4
36–40	6
41–55	4
⩾56	2
Sex ratio (M/F)	2.2 (11/5)
Duration of exposure (y, mean (SD))	28.6 (15.8)
Delay since end of exposure (y, mean (SD))	11.7 (12.0)
Subjects with lifelong exposure (n)	7
Occupation (M/F):	
Farmer or villager	3/2
Housewives	0/3
Blue collar workers	4/0
White collar workers	4/0
Disease (M/F):	
Malignant pleural or peritoneal mesothelioma	2/3
Benign pleural disease	1/5
Lung fibrosis	1/0
Pleural effusion	0
Normal findings or other disease	1/4

years about the fibre types, concentrations, and size characteristics in lung tissue of erionite villagers are limited to seven cases.[14] Further use of these data seems difficult because analyses were performed by several laboratories, each using its own analytical technique.[15]

In this study, we aimed to evaluate the FB and fibre content in bronchoalveolar lavage fluid (BALF) from 16 inhabitants of Tuzköy (E group), and to compare them with Turkish controls (C group) and Turkish subjects environmentally exposed to asbestos, mainly tremolite (T group).[16] We also compared the chemical composition of erionite fibres in BALF with that of fibres from Tuzköy soil samples.

Methods

Ferruginous bodies and fibres were counted in BALF from 16 patients originating from Tuzköy who had undergone diagnostic fibreoptic bronchoscopy at the chest department of Hacettepe University School of Medicine, between September 1991 and January 1996. Written informed consent to perform BAL was obtained from all patients.

Patients were born in Tuzköy, had lived there for at least 10 years, and were therefore considered to be environmentally exposed to erionite. All subjects were interviewed by a chest physician (LC or SE) with experience of diseases related to environmental and occupational exposure to fibres.

Sampling and preparation of BALF as well as FB and fibre counting methods have been fully described previously.[16 17] About 20 ml BALF (mean (SD) 24.3 (9.4)) was used for mineralogical analysis. Ferruginous bodies closely corresponding to the definition of a typical ABs and uncovered fibres (UFs) longer than 10 µm were counted under phase contrast light microscopy. The analytical sensitivity was 0.1 FB/ml.

Fibre counting under transmission electron microscopy (TEM) was continued until an

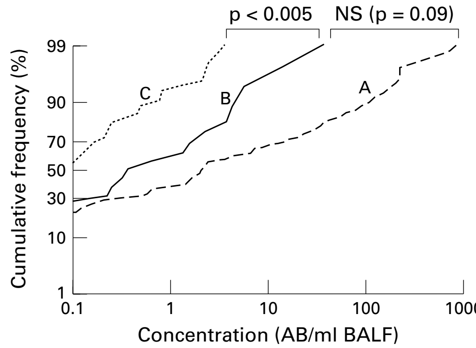

Figure 1 Light microscopy: cumulative frequency curves of concentrations of ABs in Turkish subjects environmentally exposed to asbestos (A n=64), concentrations of FBs in BALF of subjects from Tuzköy (B n=16), and Turkish controls (C n=42).

analytical sensitivity lower than 50 erionite fibres/ml BALF was obtained. Each fibre with a length of 1 µm or greater and an aspect ratio of 3/1 or more was taken into account. Fibre size characteristics and chemical composition were assessed. The chemical spectrum of each fibre was compared with reference spectra from Oregon erionite, fibres from Tuzköy soil and rock samples, and asbestos reference samples. To avoid cation leaching Tuzköy geological samples were prepared by suspension in CCl_4. The type of fibres involved in FBs of eight subjects was also examined. An object marking technique was used when the concentration of FBs was too low to allow them to be found directly by electron microscopy.[18]

Time variables are presented as mean (SD). Comparisons for age, duration of exposure, and delay since the end of exposure between the different groups were performed with Student's *t* test. Concentrations and size variables (width, length, and aspect ratio) of FBs and fibres are reported as geometric mean (GM) (GSD) and 95% confidence intervals (95% CIs). Non-detected values were given half the analytical sensitivity of the method for graphical presentation of concentrations with log scales. The Mann-Whitney *U* test was used to compare fibre concentrations and sizes. Relations between time dependent variables and concentration variables were assessed by calculating Spearman's correlation coefficient (r_s).

Results

Population characteristics and clinical data are summarised in table 1. One subject had malignant peritoneal mesothelioma. The group "other diseases" includes one case with a solitary pulmonary nodule, one with a sarcoma of the right shoulder, and three with pneumonia. When compared with the populations of T and C groups that we reported previously,[16] E group subjects were roughly 12 years younger ($p<0.005$) and their mean duration of exposure was 7.5 years shorter ($p=0.14$). None of the Tuzkoy patients reported occupational exposure to asbestos.

LIGHT MICROSCOPY

Ferruginous bodies were detected in the BALF of 12 (75%) of the subjects. The concentrations ranged from < 0.1 to 46 FB/ml, and

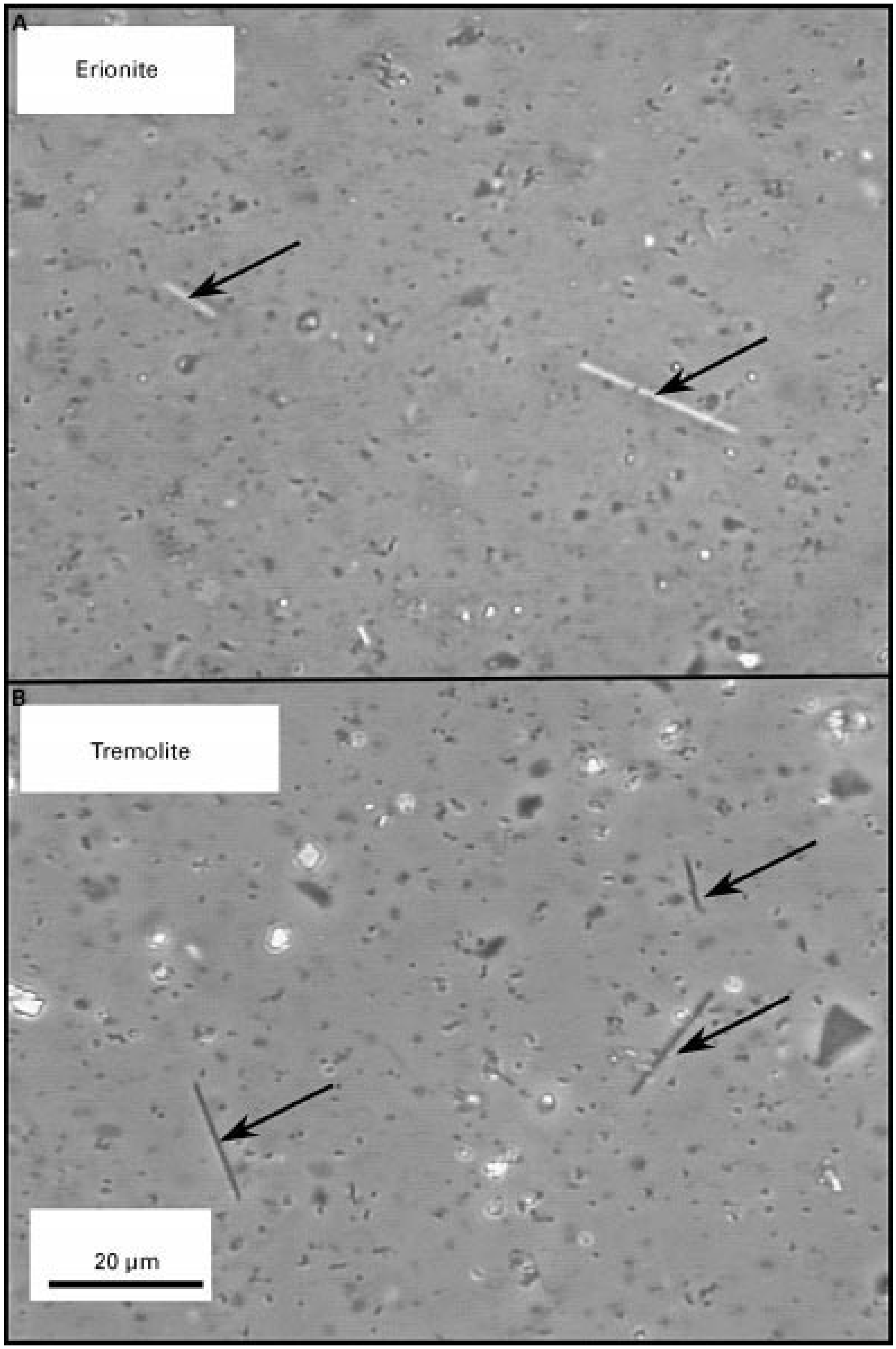

Figure 2 Phase contrast light microscopy: view of fibres recovered in the BALF of a Tuzköy subject (top) and of a Turkish subject with environmental exposure to asbestos (bottom). Due to the difference between the respective refractive indexes of erionite (1.44) and tremolite (0.61), the two types of fibres show inverted contrast and can usually be discriminated under phase contrast light microscopy.

exceeded 1 FB/ml BALF in seven samples. Geometric mean concentration of FBs was 1.33 (2.8, 0.35 to 3.04).

In figure 1, the cumulative curve for concentration of FBs in the E group is compared with the curves recorded for concentrations of ABs in C and T groups. Concentrations of FBs in the E group were higher than concentrations of ABs in the C group ($p<0.01$), but not significantly different from concentrations of ABs in the T group ($p=0.09$) although counts tended to be lower.

All subjects in the E group had uncoated fibres in their BALF, in five cases above 3 UF/ml. Erionite and tremolite fibres show an inverted contrast under phase contrast light

Table 2 Size of the central fibre of ferruginous bodies(FBs) on erionite, and of erionite, TiO_2, and other non-asbestos fibres in BALF of Tuzköy villagers and of the central fibre of asbestos bodies (ABs) on tremolite in Turks with environmental exposure to tremolite according to transmission electron microscopy

	FBs on erionite	Erionite	TiO_2	Others	ABs on tremolite
Fibres analysed (n)	89	216	29	56	294
Diameter (µm)					
GM (GSD, 95% CI)	0.37 (1.7, 0.33 to 0.42)	0.35 (2.1, 0.32 to 0.39)	0.25 (1.8, 0.20 to 0.31)	0.16 (2.3, 0.13 to 0.20)	0.31 (2.1, 0.29 to 0.35)
Range	0.06–1.1	0.04–1.80	0.06–1.20	0.02–1.3	0.03–1.65
Length (µm)					
GM (GSD, 95% CI)	37.5 (1.5, 34.4 to 41.0)	5.6 (2.2, 5.0 to 6.2)	2.0 (1.5, 1.7 to 2.3)	2.1 (1.8, 1.8 to 2.5)	33.6 (1.6, 31.8 to 35.2)
Range	14.0–105.0	1.0–65.0	1.1–8.0	1.0–8.0	10.5–140.0
Aspect ratio					
GM (GSD, 95% CI)	105 (1.8, 92 to 119)	15.8 (4.0, 14.2 to 17.7)	8.1 (1.7, 6.7 to 9.8)	13.4 (2.2, 10.9 to 16.6)	105 (2.0, 98 to 115)
Range	30–480	3.6–143	3.8–25	3.5–150	15–900

microscopy, erionite appearing as white on a grey background and tremolite as black (fig 2). The presence of the ferroprotein coating precludes the use of this distinctive criterion on FBs. The concentration of uncoated fibres had a geometric mean (GSD, 95% CI) of 2.32 (2.5, 1.04–4.40) with a maximum count of 16.3 UF/ml BALF. Concentrations of UF in the E group were higher than in C group ($p<0.01$).

ELECTRON MICROSCOPY

The central fibre from 95 FBs was analyzed, 95.7% were built on erionite, 3.2% on tremolite, and 1.1% on crocidolite. The size characteristics of the central fibre of FBs on erionite are reported in table 2. Compared with the tremolite fibres constituting the cores of ABs, erionite core fibres have the same aspect ratio ($p=0.80$, NS), but are significantly broader ($p<0.01$) and longer ($p<0.01$).

Results of TEM fibre counts are summarised in table 3. Erionite fibres were found in the BALF of all E group subjects and nine had more than 300 fibres/ml. The concentration of erionite fibres did not differ from that of tremolite fibres in the T group ($p=0.82$, fig 3). By contrast, concentrations of chrysotile, tremolite, Ti oxide, and other non-asbestos fibres in the E and C groups were similar. Only occasional amosite and anthophyllite fibres were detected. Crocidolite was not found.

No correlation was found between FB, UF, or TEM fibre concentrations in the E group on the one hand and age, duration of exposure, or delay since end of exposure on the other.

Fibre sizes for erionite, Ti oxide, and other non-asbestos fibres (various silicates and alumino silicates, carbonaceous fibres, Fe compounds) are reported in table 2. When compared with tremolite fibres present in BALF of the T group, erionite fibres were significantly thicker and longer ($p<0.001$). The size distributions of erionite and tremolite including Stanton's length and diameter criteria[19] are shown in table 4. Compared with tremolite, there are about two to three times more erionite fibres longer than 8 µm,

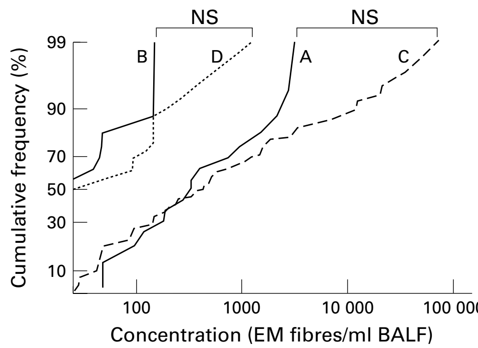

Figure 3 Electron microscopy (EM): cumulative frequency curves of (A) erionite and (B) tremolite fibre concentrations in BALF of subjects from Tuzköy (n=16) compared with tremolite fibre concentrations in BALF of Turkish subjects with (C) environmental exposure to asbestos (n=59), and (D) Turkish controls (n=16).

regardless of the diameter. The sizes of Ti oxide and other non-asbestos fibres are the same for both groups.

The ratio of the concentrations of erionite fibres/FBs in the E group was significantly higher than that of tremolite fibres/ABs in the T group (GM (GSD, 95% CI) 611 (6.5, 16 to 12 982) *v* 167 (7.5, 4 to 6374) $p<0.02$).

The chemical composition of erionite fibres from reference material, Tuzköy geological samples, and BALF are reported in table 5. Composition of soil fibres was variable, two main types can be distinguished on the basis of the K/Ca ratio. Compared with soil fibres, BALF fibres showed a narrower composition range and less Mg, K, and Ca .

Discussion

The concentration of particles in BALF can be used to estimate the past exposure to biopersistent particles.[16 17 20] It could be argued that BALF analysis only reflects recent exposures and that particles present in the lung interstitium are not sampled by lavage. Nevertheless, high concentrations of ABs and fibres can be detected in the BALF of subjects more than 20 years after exposure stopped.[21 22] This also applies to exposure to erionite, as no difference

Table 3 Transmission electron microscope (TEM) fibre concentrations in BALF of 16 subjects with an environmental erionite exposure (in fibre/ml BALF)

	Erionite	Chrysotile	Tremolite	TiO_2	Other non-asbestos
All fibres	388 (3.9, 187 to 802)	1.8 (11.7, 0 to 7.3)	5.7 (9.6, 1.0 to 21.2)	13.3 (12.8, 2.7 to 54.5)	112.1 (3.9, 48 to 262)
Maximum	3333	434	153	593	527
Fibre length ≥5 µm	130 (9.5, 38.7 to 434)	0.7 (4.6, 0 to 2.9)	ND	0.3 (2.1, 0 to 1.4)	1.2 (4.7, 0 to 4.6)
Maximum	1844	241		89	89

Concentrations reported as GM (GSD, 95% CI); ND=not detected.

Table 4 Percentage of erionite fibres in BALF of Tuzköy villagers and of tremolite fibres in BALF of Turks by environmental exposure to different dimensions of asbestos fibres

	Diameter				
	≤0.25 µm	*>0.25–0.5 µm*	*>0.5–1 µm*	*>1 µm*	*Total*
Erionite (n=216):					
Length (µm):					
<4	18.1	13.0	3.2	0.0	34.3
4–<8	10.2	10.6	7.9	1.4	30.1
8–<16	5.6	8.3	9.3	1.9	25.0
≥16	1.9	3.7	4.2	0.9	10.6
Total	35.6	35.6	24.5	4.2	
Tremolite (n=1034)[16]:					
Length (µm):					
<4	35.3	15.7	2.7	0.0	53.8
4–<8	12.3	12.9	5.9	1.1	32.1
8–<16	2.1	3.3	3.5	1.5	10.4
≥16	0.7	1.2	0.9	1.0	3.7
Total	50.4	33.0	13.1	3.5	

was found in the erionite FBs and fibre concentrations in BALF between those still living in Tuzkoy (n=7) and those who had left the village 8–36 years ago (n=9).

In sputum samples of erionite villagers examined by Sébastien *et al*,[13] FBs were detected in 41% of the subjects with maximum counts up to around 100 FB/sputum sample for two subjects. Only those older than 45 had more than 1 FB/sample. Extrapolating to what is known for ABs in sputum,[20] this can be considered as evidence of very high erionite fibre burdens in the lungs of elderly villagers. The poor sensitivity of sputum analysis[23] and the scarcity of particles collected make it unsuitable for quantitative electron microscopy studies.[13] In the present study, BALF analysis showed significant retention of erionite (more than 1 FB or 300 fibres/ml BALF) for nine of the 13 subjects of 45 or younger.

Erionite retention in BALF of erionite villagers is in the same range as tremolite retention in Turks from tremolite areas, despite these using white soil containing tremolite for whitewashing and several other procedures. The continuous indoor and outdoor exposures could therefore be more important in the build up of the lung fibre load than occasional peak exposures reached during white soil collection or whitewashing activity. The absence of whitewashing or stuccoing practices in north eastern Corsica where diseases related to environmental tremolite are also endemic supports this hypothesis.[16]

The uncoated to coated fibre ratio was higher for erionite than for tremolite. This indicates that erionite has a lower propensity to become coated than tremolite, even if a higher proportion of erionite fibres are in the length range considered to be critical for the formation of FBs.[24–26] Erionite body counts in BALF could thus correspond to higher fibre burdens than similar AB counts.

Morgan and Holmes stated that the probability of a fibre becoming coated is determined predominantly, and perhaps uniquely, by its dimensions.[25] This probability increases with length for fibres longer than 10 µm. In human lungs, there are few coated fibres below this critical length. These authors also argue that the paucity of FBs in the lungs of people exposed to erionite may be due to the thinness of the fibres. This is not supported by our data which indicate that erionite fibres in BALF are significantly broader than tremolite fibres. Other determinants than fibre dimensions, such as differences in surface properties, could thus explain the relative inefficiency of erionite to form FBs.

The similarity of the concentrations of tremolite in BALF of the E and C groups reflects the absence of any significant contact with asbestos in Tuzköy. This confirms that asbestos fibres are not contributing to the risk of mesothelioma among the inhabitants of the erionite villages.

Despite efforts made in in vivo and in vitro experimental studies,[2–4 27–29] the parameters determining the high carcinogenic potency of erionite fibres are still not well understood. Non-fibrous zeolites, which also have large surface areas, and are widely used as efficient catalysts in various industrial processes have not induced adverse health effects.[30] The fibrous morphology is an important parameter in the toxicity of erionite, but when compared with asbestos, as well as the length and width of the fibres, other factors must play a part.[27] Our chemical analyses of erionite fibres in BALF showed differences in composition between fibres from local geological samples that may correspond to an in vivo mobilisation of Mg, K, and Ca cations adsorbed on the fibres and a liberation of catalytic sites. This is associated with a high proportion of fibres in the carcinogenic range (≥8 µm length and narrow) described by Stanton *et al*.[19] Our findings thus support the idea that the high carcinogenic potential of erionite may be due to a unique combination of a high proportion of durable fibres in the critical size range amplified by an enormous surface area (200 m^2/g surface area for erionite versus 10 m^2/g for crocidolite[27]) and numerous sites of catalytic activity.

Table 5 Fibre composition of erionite in reference material, soil from Tuzköy, and fibres in BALF of Tuzköy villagers (mean (SD) weight % of oxides)

	Fibres analyzed (n)	*Na_2O*	*MgO*	*Al_2O_3*	*SiO_2*	*K_2O*	*CaO*	*TiO_2*	*FeO*
Reference samples*:									
Erionite (Oregon)	10	0.53 (0.19)	1.59 (0.12)	16.39 (0.77)	74.67 (1.42)	3.31 (1.51)	2.63 (0.44)	0.31 (0.32)	0.58 (0.41)
Soil:									
All	20	2.03 (0.82)	1.02 (0.46)	15.51 (1.08)	71.01 (3.720)	7.46 (2.76)	2.13 (1.72)	ND	0.85 (0.66)
K/Ca ≥3.5	9	2.09 (0.76)	0.85 (0.18)	15.91 (0.75)	69.28 (2.70)	9.64 (1.79)	1.26 (0.72)	ND	0.97 (0.73)
K/Ca ≤2.6	8	2.36 (0.68)	1.28 (0.61)	14.78 (1.10)	70.81 (3.24)	6.25 (2.06)	3.80 (1.36)	ND	0.73 (0.62)
BAL fibres:									
10 Subjects	83	2.80 (1.02)	0.49 (0.21)	16.82 (1.05)	73.91 (2.37)	4.54 (1.46)	0.42 (0.37)	ND	1.02 (1.21)

*Reference material was provided by Professor FD Pooley (Cardiff).
ND=not detected.

Villagers exposed to erionite have the highest incidence of mesothelioma in the world, but relevant data about the fibre burden in their lungs have been published for seven cases only.[12 14] Difficulties in obtaining lung tissue samples are a consequence of low surgery and necropsy rates combined with the small size of the exposed population. Mineralogical analysis of BALF proved to be a valuable tool in collecting data about the fibre burden in populations exposed to erionite for whom tissue samples are otherwise very difficult to obtain. This may also apply to Turkish migrants living in other countries.[10]

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