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Incidence of pleural mesothelioma in a community exposed to fibres with fluoro-edenitic composition in Biancavilla (Sicily, Italy)

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Abstract

Introduction. Amphibolic fibres with fluoro-edenitic composition characterize Biancavilla soil, including the major quarry from which building materials have been extensively extracted. These fibres induce mesothelioma in experimental animals and their *in vitro* biological action is similar to that of crocidolite.

Materials and methods. Malignant mesothelioma case series and incidence were examined to evaluate the disease burden on Biancavilla inhabitants.

Results. The incidence of pleural mesothelioma in Biancavilla is steadily higher than in the Sicilian Region, risk estimates are more elevated in women than in men, the most affected age class is constituted by subjects aged less than 50.

Discussion and conclusions. Environmental exposure to fibres with fluoro-edenitic composition appears to be causally related to the elevated mesothelioma occurrence in Biancavilla. In this frame, environmental clean-up is the main goal to be pursued in public health terms. A contribution of scientific research to public health decision making with respect to priority setting for environmental clean-up can derive from some further selected epidemiological investigations.

Key words
- fluoro-edenite
- pleural mesothelioma
- peritoneal mesothelioma
- prevention

INTRODUCTION

In the frame of the national programme of epidemiological surveillance of mortality from malignant pleural neoplasms (MPN), a proxy of pleural mesothelioma incidence, conducted by Istituto Superiore di Sanità (ISS), with reference to the time-window 1988-92, an excess risk based on four observed death versus 0.9 expected was reported in the town of Biancavilla, located in the Province of Catania (Sicily), at the slopes of the Etna volcano. Although based on a small number of cases, the excess was regarded as statistically significant since the lower limit of the confidence interval was greater than one, and thus Biancavilla was included in the list of Italian municipalities at risk of mesothelioma, where assessment of asbestos exposure was recommended [1]. The Major and the local health authorities initially challenged this inclusion, since they could easily certify that no relevant asbestos exposure occurred in that town of about 20 000 inhabitants where orange and lemon growing were the prevailing economic activities. It was anyway agreed to check if further deaths from mesothelioma had been reported, if cases were hystologically confirmed and if they had been occupationally exposed to asbestos; in about one year time (1997 and beginning of 1998) it was ascertained that further cases had been reported also between 1993 and 1997, that most of them were hystologically confirmed and that no consistent occupational exposure to asbestos was detected. Concurrently, asbestos fibres were searched in the neighbouring stone quarry of Monte Calvario where material employed in the local building industry was caved. This investigation lead to the finding of an amphibolic fibre occurring in the relatively soft material located in-between lavic rocks; that soft stone material was extensively used to produce sand, cement and plaster. Based on these results, in May 1998 the Director of the ISS wrote to the Sicilian Regional Government, to the Major of Biancavilla and to the local health authorities recommending to terminate quarrying

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activities in Monte Calvario, to remove building material by-products present near newly-constructed houses and to cover with asphalt all roads previously paved with Monte Calvario quarry waste material [2]. A detailed report on these activities was then published [3].

The Biancavilla fibre was initially regarded as an intermediate mineralogical phase between tremolite and actinolite [3]. In the meanwhile, though, a series of investigations performed by Gianfagna and coworkers lead to the identification of a new amphibole endmember, fluoro-edenite [4, 5] as extensively discussed by Bruni *et al.* in this same issue [6].

The environmental remediation process started in 2002, with the official recognition of Biancavilla as a National Priority Contaminated Site, as discussed by Bruni *et al.* [6] in this same issue. Being aware that this decision would provide in the long run a major contribution to risk-reduction in Biancavilla, epidemiologists from ISS together with colleagues from other institutions designed and realized some further studies aimed at pursuing a better insight in the health impact of environmental exposure to fibres with fluoro-edenitic composition. The main steps of this second phase of investigations can be summarized as follows.

Biggeri *et al.* [7] performed a geographic mortality study in all 36 municipalities located in the volcanic area of Mount Etna, in order to investigate the association between chronic obstructive pulmonary disease (a nosological entity in which cases of unrecognized lung fibrosis, if present, might have been allocated) and pleural mesothelioma. The association was observed, especially among women, after adjustment for urban-rural gradient and lung cancer mortality, thus suggesting an etiological role of fluoro-edenite exposure in the occurrence of non-malignant respiratory disease. Putzu *et al.* [8] performed a pilot study on the determination of fibres in the sputum of chronic bronchitis patients resident in Biancavilla as an indicator of exposure to fluoro-edenite; preliminary findings showed that six out of twelve subjects had at least one of three samples positive for fluoro-edenite. Bruno *et al.* [9] through a collaborative work with Sicilian Region Mesothelioma Registry, provided the first estimate of mesothelioma incidence in Biancavilla (5.4 x 100 000). This figure is about 10 times higher than the Sicilian incidence rate. For detailed review and critical discussion of this set of studies, the reader is referred to Bruno *et al.* [10].

The purpose of the present paper is to update the previous incidence study and to review the complete case-serie of mesothelioma cases (1988-2011), with the aim of achieving a better insight in the characteristics of fluoro-edenite induced mesothelioma.

MATERIALS AND METHODS

Biancavilla malignant mesothelioma case series

In 1997 ISS, together with Catania Local Health Unit, collected Biancavilla malignant mesothelioma cases through municipality mortality Registrar, family doctors and hospital records. If available, histology slides were collected and reviewed by a single expert pathologist. Information about clinical history, occupation, relevant behaviour and residential history were collected by Local Health Unit physicians through the subjects (if alive) or, in most cases, through next-of-kins.

Since 1998, mesothelioma incidence in Biancavilla and previous exposures of registered cases have been taken in charge by the Sicilian Operative Regional Centre (COR) of the National Mesothelioma Registry (ReNaM), a nation-wide system for malignant mesothelioma monitoring. Information have been collected through a structured questionnaire by trained interviewers.

ReNaM classifies mesotheliomas by level of diagnostic certainty:

1. "certain malignant mesothelioma" characterized by the following condition: microscopic examination on material (histological or cytological with centrifugation of the sediment) enclosed in paraffin, with characteristic morphological pattern

(1.1) with immunohistochemistry or

(1.2) immunohistochemistry not carried out or not defined;

2. "probable malignant mesothelioma"

(2.1) with histological or cytological examination with enclosure in paraffin carried out, but which did not give a result indicating mesothelioma in a clear and reliable way (doubtful case) or

(2.2) with cytological examination not enclosed in paraffin, with characteristic pattern and report expressed in terms clearly indicative of mesothelioma;

3. "possible malignant mesothelioma"

(3.1) characterized by indicative clinical and radiological data with diagnosis of discharge of mesothelioma or

(3.2) Death Certificate Only (DCO) with presence on the death certificate of the term "mesothelioma".

Asbestos exposure has been assessed and codified according to the ReNaM criteria which comprises three levels of certainty of occupational exposure (1. certain, 2. probable, 3. possible); three other modalities of exposure (4. household exposure, 5. environmental exposure, 6. non-professional exposure during leisure time activities). Other endpoints can be: 7. unlikely exposure, 8. unknown exposure (incomplete and insufficient information), 9. exposure definition in progress; 10. unclassified exposure (no information is available nor will presumably be available).

Biancavilla malignant mesothelioma incidence

Malignant mesothelioma incidence in Biancavilla municipality was compared to the regional incidence rates. Standardized Incidence Ratios (SIRs), with their 95% Confidence Intervals (95% CI) were computed, by applying the indirect standardization method by use of STATA software. For the computation of the Sicilian Region incidence rates, the population and cases resident in Biancavilla municipality were excluded. SIRs were computed for total malignant mesothelioma, pleural and peritoneal mesothelioma, in the two genders, separately. Data source for cases was the Sicilian Operative Regional Centre (COR) of the National Mesothelioma Registry. All cases diagnosed between 01/01/1998 through 31/12/2011, resident in Biancavilla at time of diagnosis, and classified as "certain", "probable" or "possible" were eligible for the study. At 05/03/2014, 24

pleural mesotheliomas and two peritoneal mesotheliomas were collected in the COR database.

RESULTS

Biancavilla malignant mesothelioma case series

Since 1988 to the end of 2011 45 cases of mesothelioma were detected among Biancavilla residents. Before 1998 a total of 17 cases of pleural mesothelioma had been collected by ISS researchers and Local Health Unit physicians (*Table 1*). For nine cases out of 17, histology slides were found and were available to be reviewed by an experienced pathologist: all diagnoses were confirmed. No certain occupational exposure to asbestos fibres was detected in any case, two subjects had been employed for a short time in industrial sectors in which asbestos might have been used. All cases but one were long-time residents in Biancavilla and eleven of them always resided in the town.

Since 1998 Sicilian COR has taken charge of the investigation on Biancavilla mesotheliomas, using standardized procedures, questionnaires and classifications [11].

Between 1998 and 2011, 28 mesothelioma cases were detected, even if two of them were not eligible to be included in the Biancavilla COR cases as they were not resident there at time of diagnosis (*Table 2*). In eight cases, only environmental exposure to Biancavilla fibres was ascertained, and an investigation to identify a concurrent occupational or non occupational exposure to asbestos fibres outside Biancavilla, if any, is ongoing for eleven cases. No one experienced a certain professional exposure to asbestos, one subject worked in an industrial sector in which asbestos had been used, and three subjects worked in industrial sectors in which asbestos presence could occur. Incomplete and insufficient information (unknown exposure), were collected for two more subjects, even if one of them, a farmer, experienced working in the quarry as a temporary job. Finally, one case refused to be interviewed (information not available). All cases were long-time resident in Biancavilla and all but five always resided there.

Twenty-six mesothelioma cases were diagnosed in subjects resident in the municipality of Biancavilla at time of diagnosis and collected by COR, 13 in men and 13 in women. In two of them, one male and one female, peritoneum was affected, the other mesotheliomas were localized in the pleura. Mean age at diagnosis was about 60 in men and 70 in women (*Table 3)*. The difference between mean age in men and women was noticeable, in particular for pleural mesothelioma. The subjects with peritoneal mesothelioma, one man and one woman, were respectively 63 and 65 years old.

Biancavilla mesothelioma incidence

Table 4 clearly shows that the Standardized Incidence Ratios (SIRs) for mesothelioma in Biancavilla were steadily high: the overall SIR was 5.76 (95% CI 3.76-8.44) respectively, 3.69 (95% CI 1.97-6.32) in men and 13.08 (95% CI 6.97-22.00) in women. An increased risk of pleural mesothelioma was also demonstrated (Overall SIR 5.65, 95% CI 3.62-8.41), both in men (SIR 3.63, 95% CI 1.87-6.34), and in women (SIR 12.75, 95% CI 6.59-22.00). The highest overall SIR was found for peritoneal cases (SIR 7.92, 95% CI 0.96-20.00), based on two observed cases.

With regard to pleural mesothelioma, when SIR estimates were stratified by age (*Table 5*), extremely high figures were shown in the younger age groups: the overall SIR in subjects less than 50 years old was 21.34 (95% CI 6.93-50 00) (four cases in men and one in a woman). These findings were strengthened by the results in the less than 40 years age group (overall SIR 62.88, 95% CI 13.00-180.00, 3 cases).

These findings are consistent with a strong excess of mesothelioma incidence among Biancavilla inhabitants

Table 1
Mesothelioma cases in Biancavilla municipality. *Ad hoc* case reports collection (before 1998)

	Year of diagnosis	Age at diagnosis	Resid years diagnosis	Gender	Level of diagnostic certainty	Known exposure to asbestos fibres	Site
1	1988	40	40	M	Indicative clinical and radiological data	0	Pleura
2	1988	55	19	M	Death Certificate Only (DCO)	Possible	Pleura
3	1991	62	62	F	Death Certificate Only (DCO)	0	Pleura
4	1992	45	45	M	Death Certificate Only (DCO)	0	Pleura
5	1992	42	42	M	Histological/cytological revised specimen	0	Pleura
6	1993	66	66	F	Death Certificate Only (DCO)	0	Pleura
7	1994	62	62	M	Histological/cytological revised specimen	0	Pleura
8	1994	44	32	M	Histological/cytological revised specimen	0	Pleura
9	1994	68	67	M	Histological/cytological revised specimen	Possible	Pleura
10	1995	63	57	M	Histological/cytological revised specimen	0	Pleura
11	1996	29	29	M	Indicative clinical and radiological data	0	Pleura
12*	1996	63	2	F	Death Certificate Only (DCO)	No information available	Pleura
13	1997	77	77	F	Histological/cytological revised specimen	0	Pleura
14	1997	68	68	M	Histological/cytological revised specimen	0	Pleura
15	1997	77	17	F	Histological/cytological revised specimen	0	Pleura
16	1997	86	86	F	Histological/cytological revised specimen	0	Pleura
17	1997	71	71	F	Death Certificate Only (DCO)	0	Pleura

* Resident in Biancavilla since two years before diagnosis.

in the absence of known occupational sources of asbestos exposure.

The cases sex ratio was 1:1, the Standardized Incidence Ratio was elevated in men and even more elevated in women. It is also important to note that a ten years lower mean age at diagnosis was experienced by the male population and to remark the extremely high SIR in the younger age groups.

DISCUSSION

The Italian National Mesothelioma Registry was created to establish a nation-wide system for malignant mesothelioma monitoring because of the massive utilization of asbestos which took place in Italy, followed by a severe health impact. ReNaM objectives are in particular centred on estimating mesothelioma incidence in Italy, and on contributing to the assessment of the effects of industrial use of asbestos and to the identification of sources of asbestos exposure; however environmental exposures to asbestos fibres have been investigated as well. In the present study, the same methodology has been used to identify or exclude occupational exposures to asbestos in Biancavilla resident cases of mesothelioma, while the definition of "environmental exposure" refers to fibres with fluoro-edenitic composition.

In vitro studies showed that fibres with fluoro-edenitic composition behave similarly to crocidolite, as discussed by Balan *et al.* in this issue [12], human lung carcinoma cells have been exposed to two different materials: prismatic fluoro-edenite and fibres with fluoro-edenitic composition. Only in the second case, they exhibit features typical of transformed cells. Most of the results for fibres with fluoro-edenitic composition were comparable to those obtained with crocidolite, used as a "positive control". Accordingly, *in vivo* studies demonstrated that the fluoro-edenitic composition fibre sample induces mesotheliomas [13].

Malignant mesothelioma (MM) incidence rates have been reported to be 1.2-9 times higher among men than among women because of occupational exposures [14]. Besides occupational settings, MM is also associated with domestic exposure in family members of asbestos workers [15]. The role of environmental exposure [16, 17] related to asbestos factories, mines, or naturally occurring asbestos (NOA) has been investigated in Greece, [18], Cyprus [19], Turkey [20-24], Corsica [25, 26], Italy [27], California, US [28], Libby, Montana, US [29] and China [30].

The sex ratio of about 1:1 both in our previous studies [3, 9] and in this issue corroborates the hypothesis

Table 2

Mesothelioma cases in Biancavilla Municipality from COR (Regional Operative Centre of National Mesothelioma Registry) (since 1998)

	Year of diagnosis	Age at diagnosis	Residence years	Gender	Level of diagnostic certainty (ReNaM)	Known exposure to asbestos fibres	Levels of certainty and modalities of exposure (ReNaM)	Site
18	1998	59	59	M	3.1	0	Not available	Pleura
19	1998	56	56	M	1.1	0*	Unknown exposure	Pleura
20	1998	39	39	M	1.2	1	Probable	Pleura
21	1999	48	48	M	1.1	1	Possible	Pleura
22	2000	87	87	M	2.2	?	Undergoing definition	Pleura
23	2002	72	72	F	3.1	0	Environmental	Pleura
24	2002	71	71	F	1.1	0	Environmental	Pleura
25	2002	70	70	F	1.1	0	Environmental	Pleura
26	2003	55	55	F	3.1	0	Undergoing definition	Pleura
27	2003	62	64	F	1.1	0	Environmental	Pleura
28	2004	66	66	F	2.2	?	Undergoing definition	Peritoneum
29	2004	77	77	F	1.1	0	Environmental	Pleura
30	2004	44	44	M	1.1	0	Environmental	Pleura
31	2005	63	48	M	1.2	?	Undergoing definition	Peritoneum
32	2005	73	73	F	1.1	?	Undergoing definition	Pleura
33	2006	84	84	M	3.2	0	Unknown exposure	Pleura
34	2006	81	81	F	1.1	0	Undergoing definition	Pleura
35	2007	74	74	F	1.1	0	Environmental	Pleura
36	2007	84	84	F	3.1	0	Undergoing definition	Pleura
37**	2009	57	53	M	=	=	=	Pleura
38	2009	27	27	F	2.1	?	Environmental	Pleura
39	2009	75	75	M	1.1	?	Undergoing definition	Pleura
40**	2009	68	28	F	=	=	=	Pleura
41	2009	61	48	M	1.2	?	Possible	Pleura
42	2009	64	64	M	1.2	?	Undergoing definition	Pleura
43	2009	90	90	F	3.1	?	Undergoing definition	Pleura
44	2011	33	31	M	1.1	?	Possible	Pleura
45	2011	57	57	M	1.1	?	Undergoing definition	Pleura

* Farmer, quarry worker as temporary job; ** Previously resident and exposed to Biancavilla fibers but not living there at time of diagnosis: data not available to the Regional Operative Centre (COR).

of an environmental exposition rather than an occupational source of asbestos exposure. In Cappadocia, Turkey, a very high incidence of pleural mesothelioma in three villages was found at the end of the 1970s. From 1970 to 1987, 108 cases of pleural mesothelioma were identified, and an annual incidence of more than 8,000 cases/million was calculated. The incidence was identical for men and women (the ratio M/W ranged between one and two), and the mean age was roughly 50, with a range of 26 to 75 years [31]. These cases of MM were caused by exposure to erionite fibers, which are not NOA, being fibrous zeolites [32]. Baris and Grandjean [33] confirmed this high incidence. Erionite fibers in pulmonary biopsy and sputum samples from mesothelioma patients were found [34, 35]. In Biancavilla six out of twelve subjects had samples positive for fluoro-edenitic fibres in the sputum [8].

In New Caledonia an excess incidence of MM was identified in a period of 10 years (1978-1987) [36]. In the same region, Baumann *et al.* [37], studying 109 MM cases recorded between 1984 and 2008, found in the Houaïlou area, where an important asbestos mining activity was located during the 1960s-1970s, a world age-standardized rate of 128.7 per 100 000 person-years [95% confidence interval (CI) 70.41-137.84]. They evaluated the presence of serpentinite on roads as a major environmental risk factor for mesothelioma.

In a case-control study conducted in the province of Sivas, Turkey, Bayram *et al.* [38] demonstrated a quantitative relationship between the risk of either malignant or non malignant pleural diseases and the proximity of the residence at birth to ophiolites, rocks known as sources of NOA.

The Biancavilla population showed excesses for pleural mesothelioma in mortality and in hospital discharges and non malignant respiratory diseases such as chronic respiratory diseases (in women) and only for hospital discharges from all respiratory diseases and in particular pneumoconiosis [39]. Diseases of circulatory system showed excess mortality among both genders.

As regards the occurrence in Biancavilla of MM cases in young people this finding is consistent with Baris *et al.* [31] findings concerning subjects exposed to erionite. In our study even the figures (four cases out 45 aged less than 40 years old, two of them in their late twenties) are surprisingly high: it needs to be considered for example that, in Australia, in 2008 out of 543 men diagnosed with mesothelioma there was only one man in his early thirties but none younger, and similarly out of 118 women diagnosed with mesothelioma there was only one woman aged in her early thirties but none younger [40].

Latency period for most of malignant mesothelioma of occupational origin is considered to be in a range between 20 to 40 years: in a review of 21 articles by Lanphear & Buncher [41] 96% had a latent period of at least 20 years and the estimated median latent period was at least 32 years after the initial exposure. Latency periods were examined in 312 cases of malignant pleural mesothelioma, diagnosed in the Trieste-Monfalcone area, Italy [42]; they ranged from 14 to 72 years (mean 48.7, median 51). Latency time analysis for 2544 cases diagnosed during the period 1993-2001 and eligible for the analysis was performed by ReNaM [43]. Median latency was 44.6 years (95% CI 44.1-45.0). Latency increased constantly during the observed period with respect to the year of diagnosis: estimated mean latency period among pleural MM cases diagnosed in 1993 and in 2001 was 41.7 and 46.2 years, respectively. In the hypothesis of an asbestos-like behaviour of the Biancavilla fibres with fluoro-edenitic composition, exposure to fibres had to occur about 30 years before the mesothelioma outbreak.

The latency period of mesothelioma in fibres with fluoro-edenitic composition has not been studied yet; if it was similar to the latency of asbestos exposed mesothelioma cases, the occurrence of pleural MM in young adults would require exposure in childhood or in teenage years. Conti *et al.* [39] in this issue showed that the mortality for malignant pleural neoplasms under 50 concerns Biancavilla and two neighbouring communities.

Table 3
Mesothelioma cases in Biancavilla Municipality: mean age at diagnosis

		Obs	Mean	Std. Dev
Pleural Mesotheliomas				
	Men	12	**58.93**	16.70
	Women	12	**70.43**	16.71
	Overall	24	**64.68**	17.36
All Mesotheliomas				
	Men	13	**59.25**	16.03
	Women	13	**70.04**	16.06
	Overall	26	**64.65**	16.65

Table 4
Mesothelioma cases in Biancavilla Municipality: standardized incidence ratios and confidence intervals

		Obs	Exp	SIR	95% CI
Pleural Mesotheliomas					
	Men	12	3.31	**3.63**	1.87-6.34
	Women	12	0.94	**12.75**	6.59-22.00
	Overall	24	4.25	**5.65**	3.62-8.41
Peritoneal Mesotheliomas					
	Overall	2	0.25	**7.92**	0.96-20.00
All Mesotheliomas					
	Men	13	3.52	**3.69**	1.97-6.32
	Women	13	0.99	**13.08**	6.97-22.00
	Overall	26	4.51	**5.76**	3.76-8.44

Table 5
Pleural mesothelioma cases in Biancavilla Municipality: standardized incidence ratios by age groups

		Obs	Exp	SIR	95% CI
Age < 40					
	Overall	3	0.05	**62.88**	13.00-180.00
Age < 50					
	Overall	5	0.23	**21.34**	6.93-50.00
Age ≥ 50					
	Men	8	3.14	**2.55**	1.10-5.02
	Women	11	0.88	**12.56**	6.27-22.00
	Overall	19	4.01	**4.74**	2.85-7.39

The disparity of ten years in mean age at diagnosis in men and in women in pleural MM observed in Biancavilla cases and the occurrence of more male cases in younger ages have to be investigated taking into account the source population, as recommended by Consonni [44]. The possible role of fibre exposure associated to outdoor recreational activities should be assessed in this frame.

This study is the first report of an excess incidence of peritoneal mesothelioma in Biancavilla, even if based on two cases; this finding in noteworthy in view of the induction of peritoneal mesothelioma in rats after intraperitoneal administration of fibres with fluoro-edenitic composition that was reported by Soffritti *et al.* [13].

An analysis of different behaviours in Biancavilla adults and children in their everyday lives could be useful to figure out the way to reduce fibres exposures.

CONCLUSIONS

In light of the evidence that was illustrated and discussed in the present paper, some conclusions appear to be warranted.

The incidence of pleural mesothelioma in Biancavilla is steadily higher than in the Sicilian Region, risk estimates are more elevated in women than in men, the most affected age class is constituted by subjects aged less than 50.

Analysis of individual data shows that the contribution of asbestos exposure to this localized high occurrence of mesothelioma is substantially irrelevant.

Amphibolic fibres with fluoro-edenitic composition characterize Biancavilla soil, including the major quarry from which building materials have been extensively extracted. These fibres induce mesothelioma in experimental animals and their *in vitro* biological action is similar to that of crocidolite.

Environmental exposure to fibres with fluoro-edenitic composition appears to be the causally related to the elevated mesothelioma occurrence in Biancavilla.

In this frame, environmental clean-up is the main goal to be pursued in public health terms.

A contribution of scientific research to public health decision making with respect to priority setting for environmental clean-up can derive from some further selected investigations concerning, namely:

- the incidence of new cases and an in-depth collection of their occupational, residential and life style histories;
- mortality and hospitalization, also in order to evaluate their temporal trends;
- mean age of mesothelioma cases in relation to the population characteristics;
- health condition profile of residents in Biancavilla to elucidate the characteristics of non neoplastic effects on respiratory system (functionality and imaging) and to study the cardiovascular diseases [39];
- investigation on modality of exposures in the environmental context in the everyday lives of adults and children [6].

The authors also recommend to adopt guidelines and rules in building sector and soil materials handling to minimize fibre dispersion.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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