TITLE: THE HEALTH IMPACT OF NON-OCCUPATIONAL EXPOSURE TO ASBESTOS. WHAT DO WE KNOW?

Running head: Non-occupational exposure to asbestos
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Abstract

Objective: We examine the epidemiologic data that confirm the risks of pleural mesothelioma, lung cancer and other respiratory damage associated with non-occupational exposure to asbestos, in circumstances where exposure levels are usually lower than those found in the workplace: domestic and para-occupational exposure to asbestos-containing material (ACM) among people living with asbestos workers or near asbestos mines and manufacturing plants, environmental exposure from naturally occurring asbestos in soil, and non-occupational exposure to ACM in buildings.

Data synthesis: Studies concerning natural asbestos in the environment show that exposure that begins at birth does not seem to affect the duration of the latency period, but do not allow to know whether early exposure increases susceptibility; they do not suggest that susceptibility differs according to sex. Solid evidence demonstrates an increased risk of mesothelioma among people whose exposure comes from a para-occupational or domestic source. The risk of mesothelioma associated with exposure due to living near an industrial asbestos source (mines, mills, asbestos processing plants) is clearly confirmed. No solid epidemiologic data currently justify any judgment about the health effects associated with passive exposure in buildings containing asbestos. Most of the studies on non-occupational sources reported mainly amphibole exposure, but it cannot be ruled out that environmental exposure to chrysotile may also cause cancer.

Conclusion: Non-occupational exposure to asbestos may explain about 20% of the mesotheliomas in industrialized countries, but it is does not seem possible to estimate the number of lung cancers caused by these circumstances of exposure.

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Key words: environmental exposure, domestic and para-occupational exposure, exposure from geological sources, exposure in buildings

INTRODUCTION

Asbestos is a fibrous mineral of hydrated silicates, which can be divided into two groups: amphiboles and serpentine. The main varieties of asbestos within the amphibole group are anthophyllite, amosite (brown asbestos), crocidolite (blue asbestos), actinolite, and tremolite. The serpentine group comprises only chrysotile (white asbestos). These varieties of asbestos have different physical and chemical properties. It is mainly amosite, crocidolite and chrysotile, which are exploited for industrial purposes. The fibers resistance to very high temperatures and to different types of chemical attack) due to their particular physical and chemical properties have meant that asbestos have been put to many uses, for example, for the manufacture of industrial and consumer products and in the building industry. Asbestos is extracted from open pit mines, mainly in Russia, China, Canada, Brazil, Kazakhstan and Zimbabwe [http://www.economywatch.com/mineral/asbestos-production.html]. In the industrialized world, the major sources of asbestos exposure are in occupational asbestos-related occupations: mining and crushing, manufacturing of products, building and demolition of buildings, elimination of waste, servicing and maintenance work in asbestos-containing material (ACM), products or buildings. Aside of occupational sources, persons can also be exposed to asbestos in other circumstances. Domestic and para-occupational exposure to ACM occur among people living with asbestos workers or near asbestos mines and manufacturing plants; environmental exposure may come from naturally occurring asbestos in soil, and non-occupational exposure in asbestos-insulated buildings.

Asbestos is a recognized human carcinogen. It is causally related to mesothelioma of the pleura and of other sites, and lung cancer, and was recently recognized as being able to induce laryngeal cancer; associations with other cancer sites, notably the colon, have been suggested but have not been definitively established [1,2]. Asbestos also causes various non-cancerous respiratory disorders such as asbestosis and pleural plaques [3]. There is controversy regarding effects of different fiber types, some arguing that only fibers of the amphibole group are pathogenic, while other say that chrysotile asbestos exposure yields risks of the same magnitude for asbestosis and lung cancer, even it if is less potent than amphiboles in the induction of mesothelioma [4].

It is likely that the vast majority of asbestos-induced diseases in the industrialized world are caused by occupational rather than non-occupational asbestos exposure [1,2,5]. This is the legacy of the omnipresent past use of asbestos. Concern used to be focused on occupational environment, but now it is recognized that asbestos fibers are widely distributed in the general environment in many countries, cities buildings, etc. Indeed, exposure to asbestos in occupational settings has been decreasing [6], whereas this is probably not the case for non-occupational exposure. While exposure in non-occupational settings is generally much lower than in occupational settings, the levels can be not negligible, and they might be sufficient to cause disease. Due to the large difference in exposure levels usually observed in occupational and environmental settings, it is a common practice to express asbestos fiber measurements in fibers per milliliter (f/ml) in the workplace and in fibers per liter (F/L) for environmental exposure.

Studying the effects of non-occupational asbestos exposure is important for several reasons. First, it is the most direct way of ascertaining the risks posed by the widespread problem of non-occupational exposure to asbestos. Second, it provides information about the nature of the exposure-response relationship that cannot obtained from studies of workers who are mainly males, whose exposures begin in adulthood, are limited to working hours, and are typically much higher in concentration than those of non-occupationally exposed populations, whose asbestos fiber type exposure is often impossible to ascertain. See Table 1 for a summary of some of the differences in exposure conditions. Further, the current approach to assessing risks at low levels of exposure is to use risk assessment models that extrapolate from high occupational levels to low non-occupational levels. Assessing risks directly in non-occupational settings allows to validate risk assessment models [7].

The most recent review of non-occupational exposure to asbestos and cancer risk is nearly 20 years old [8], and important new evidence has accumulated. While a few of the studies analyzed here have examined the risk of lung cancer and non-cancerous respiratory conditions, most of the research focuses on the risk of pleural mesothelioma. Mesothelioma is considered to be a specific outcome of asbestos exposure, because no causal factor except for exposure to asbestos (and some other mineral fibers) [5] has been established or even convincingly suspected. Moreover, its spontaneous occurrence is very rare; the background incidence is estimated to be less than one case per million population per year [9].

In industrialized countries and in asbestos-producing regions of developing countries, occupational levels of exposure tend to dwarf non-occupational exposures, and thus make it difficult to isolate effects of the latter. Thus, the most useful studies are those in which there is an attempt to ascertain exposures at an individual rather than ecological level, in order to disentangle the different sources of potential exposure. In the following, we first review studies according to the source of asbestos exposure: natural environmental exposure to geological sources, domestic and para-occupational exposure, environmental exposures from industrial sources and passive exposure in buildings containing asbestos. Finally, we try to assess the cancer burden of non-occupational exposure to asbestos in industrialized countries.

NATURAL ENVIRONMENTAL EXPOSURE TO GEOLOGICAL SOURCES OF ASBESTOS

Beginning in the mid-1970s, the discovery of sites of endemic mesothelioma in some rural areas (Turkey, Greece, Cyprus, Corsica, and more recently New Caledonia, Sicily, China and California) has provided important information about the carcinogenicity of various mineral fibers, in temporal exposure conditions very different from those encountered in the workplace, especially as to age at first exposure and the persistence and duration of exposure. Typical time variables for occupational and environmental exposure settings are given in Table 1, and Table 2 summarizes the quantitative measurements of environmental and pulmonary samples in the principal areas of endemic pleural mesothelioma which are available.

Turkey

An excess incidence of pleural mesothelioma (13/million/year) and of lung cancer was observed during a retrospective study (1968-1976) in the Diyarbakir region (Southeast Turkey), a rural area known for its use of natural asbestos-based

materials to whitewash floors and walls [10]. A second study provided greater detail by identifying 17 cases of mesothelioma in two years, distributed roughly equally among men and women, in this area of approximately 100,000 inhabitants. Asbestos bodies identified as tremolite were found in autopsied lungs, and the percentage of chrysotile fibers was low. The mineral analysis of the whitewash used on houses showed long tremolite fibers of variable diameter, with a chemical composition similar to those found in the lungs; no chrysotile fibers were observed [11]. A radiological study showed that 6.5% of the population had pleural plaques, a frequency that increased with age (greater than 70% in subjects older than 60 years). High-resolution computed tomography was used to examine 26 subjects with multiple bilateral pleural plaques: 24 (92 percent) had signs of pulmonary asbestosis [12]. A similar site of clustered mesothelioma cases was then found in the village of Caparkayi (425 inhabitants) in central Anatolia, where mesothelioma was identified in four young women (26 to 40 years), all of whom had lived in earthen houses whitewashed with a product containing tremolite [13,14].

More recently, Metintas et al. confirmed an elevated risk of pleural mesothelioma around the town of Eskisehir in central Turkey in a study of 131 patients (59 men, 72 women) [15]. In a cohort of 1,886 villagers from villages around Eskisehir, average annual mesothelioma incidence rates were 114.8/100,000 for men and 159.8/100,000 for women (88.3 times greater in men and 799 times greater in women, respectively, in comparison to world background incidence rates) [16]. Two relatively young subjects (50 and 59 years) who had spent their childhood in this region were diagnosed with mesothelioma in Germany, where they had emigrated [17]. Fibers of tremolite and actinolite were found in the lungs of four subjects from this region [18], and soil samples from 67 villages in central Turkey contained tremolite and chrysotile [19].

Turkey was also the site of the discovery of a very high incidence of pleural mesothelioma in three villages in Cappadocia (Sarihidir, Tuzköy and especially Karain) at the end of the 1970s. From 1970 to 1987, 108 cases of pleural mesothelioma were counted in the small village of Karain (604 inhabitants in 1974) – equivalent to an annual incidence of more than 8,000 cases/million, that is, about 1,000 times the rate observed in the general population of industrialized countries. These cases were responsible for nearly half the deaths reported in this village. In Tuzköy, the annual incidence was estimated at 2,200 cases/ million. Overall, it was identical for men and women, the ratio of men/women ranged between one and two, according to series and village, and the mean age was roughly 50, with a range of 26 to 75 years [20]; a recent update confirmed this very high incidence [21]. Other authors followed a cohort of nearly 100 Karain natives who had emigrated to Sweden from the 1960s onwards. They found seven cases of mesothelioma (four women, three men); the very low mean age of the subjects (35 years, range: 25-50) argues in favor of the hypothesis that childhood exposure to was responsible for these cases [22,23,24].

Quantitative analyses of environmental samples (rocks, tuff, white stucco, whitewash, road dust, air and water) found only a few, generally short asbestos fibers (tremolite, chrysotile), most often in whitewash [25,26,27]; there were also a large number of thin natural mineral fibers named erionite, from the zeolite family. The concentrations of erionite in the outside air samples about 0.01 fibers per milliliter (f/ml)) were relatively low, but they reached 1.38 f/ml during cleaning operations [28]. Nonetheless, the numerous erionite fibers in pulmonary biopsy and sputum samples from mesothelioma patients [29,30] indicated the probability of a causal relation. Lung tissue with a similar appearance was also observed in emigrants from Karain to Sweden [23].

The comparison of subjects exposed to asbestos and to erionite shows they have very similar characteristics. The concentration of erionite fibers in the bronchoalveolar lavage fluid (BALF) of inhabitants of the "erionite villages" was similar to the concentration of tremolite fibers among the inhabitants of the "tremolite villages" [30]. Tremolite and chrysotile fibers were found in the BALF of 65 subjects from the asbestos-polluted areas [31]. In a study of 135 mesothelioma cases in Turkey from "erionite"(n=58) and "tremolite" (n=77) villages, the clinicoanatomic appearance was similar in subjects exposed to asbestos or erionite fibers, and pleural plaques were observed in all subjects. In both the erionite and the asbestos-exposed groups, one quarter of the patients were less than 40 years of age, and the mean ages were not significantly different between the two groups (respectively 46.4 and 49.7 years); age of the patients ranged from 27 to 67 years in the erionite group and 26 to 75 years in the asbestos-exposed group, suggesting that the latent period is irrespective of the type of fiber. Males and females were approximately equal in number in the erionite group (male-female ratio: 31:27); male predominance was apparent in the asbestos associated group (male-female ratio: 51:26), but the authors considered that it may be explained in part by referral bias, as populations from the three erionite villages were known as a high-risk group, and the patients are referred as soon as a presumptive diagnosis is made; in contrast, there is no equivalent system of survey in the asbestos villages where patients are not actively surveyed, but are admitted after presentation [32].

Seniygit et al. studied trends in mesothelioma incidence in various parts of southeast Turkey from 1990 to 1999. They found that this incidence diminished substantially in areas where the use of tremolite-based whitewash had stopped, but remained high in areas where the dangers of this product were not adequately publicized [33].

Greece

In 1969 and thereafter a high prevalence of endemic pleural calcification was observed in inhabitants of three villages (Metsovo, Milea, Anilio) built on sandstone rocks in a mountainous region of northwest Greece, where no industrial asbestos use has been reported. In 1980, Bazas et al. reported that the pleural calcifications of the inhabitants of these villages had increased by nearly 5% per year over the preceding 10 years [34]. The extensive pleural calcifications in 45 percent of the villagers (28% of those younger than 40, 80% in those older than 70), called "Metsovo Lung," has also been observed in other regions throughout Greece [35,36,37]. The prevalence of pleural calcifications was clearly higher than in the endemic areas in Turkey (15 to 20% of the population) [38]. The identification of long tremolite fibers with a mean diameter of 0.20 micrometers (μm) and of rare fibrils in the lungs of subjects with Metsovo Lung and in the soil sampled in the village of Metsovo led researchers to seek environmental exposures [39]. This hypothesis was confirmed by the discovery of intensive use of the soil called "luto" as a whitewashing agent [36]. Before 1940, inhabitants extracted earth from outcrops at Milea to prepare a coating material used to whitewash houses; it was also sold in Anilio. In the 1980s, nearly 10% of the villagers still used it.

Langer et al. found numerous tremolite fibers with a very high length/diameter ratio (greater than 100:1) in the luto-based coating; they were similar to those found in the lungs of Metsovo Lung patients [40]. Fiber concentrations were not high (on the order of 0.01 to 0.02 f/ml) in air samples taken from luto extraction sites, in a village, and in a house whitewashed seven days earlier; however, slightly rubbing of the whitewashed wall raised the fiber concentration in the air to 17.9 f/ml [28]. The extent of pleural calcifications was closely related to the duration of luto exposure [36]. The discovery of several cases of mesothelioma (seven in the Metsovo region [41], two in Distraton [42], five in Aridea,

Macedonia [43] suggests that exposure to the tremolite in luto does not induce only benign lesions such as Metsovo Lung. The incidence of mesothelioma, very high from 1980 through 1984 (averaging 370 cases per 1,000,000 person-years), had diminished substantially in Metsovo in 1985-1994 (140 cases per 1,000,000 person-years) [44]. This decrease was attributed to the abandonment of the use of luto whitewash by the beginning of the 1980s (92% of the population used it in 1950 and only 18% in 1980) and consider that, because of the latency period, the mesothelioma epidemic should end somewhere around 2020-2030. This conclusion was strengthened by a study conducted from 1998 to 2002, showing that the withdrawal of the use of the whitewash containing tremolite resulted in a null prevalence of pleural calcifications among young Metsovites (under 40 years old), and in a decreasing prevalence of calcifications among subjects under 60 years of age [45].

Mediterranean Islands

In Cyprus, Mc Connochie et al. found 12 cases of mesothelioma in a retrospective study; five were attributed to occupational exposure (chrysotile miners) and three to para-occupational exposure (asbestos mine workers' wives). The discovery of tremolite fibers in the lungs of two cases, one with no relation to the asbestos mine, induced the authors to seek and find natural tremolite contamination of the chrysotile deposit and of the local geological environment, in particular, the local whitewash. The analysis of the fibers in the lungs of goats grazing near the chrysotile mine confirmed the presence of thin tremolite and chrysotile fibers [46,47].
The northern part of Corsica contains many asbestos outcrops, and some chrysotile mines have been in activity in the past. An abnormally elevated frequency of bilateral pleural plaques (3.66 percent) was reported in patients born in this region and not working in the asbestos mine [48]. A quantitative study of air pollution in these villages, compared with control villages showed that the pollution levels were high (39.2 nanograms per cubic meter (ng/m3) on average), with a predominance of tremolite fibers, inside as well as outside houses [49,50]. A study of mesothelioma cases among Corsicans hospitalized in Marseilles from 1973 through 1991 identified 14 patients from this region who had no known occupational contact with asbestos. The man/woman ratio was 1.3, the mean age 69.5 years (range: 41-91 years), and calcified pleural plaques were found in 43% of the cases. Their homes and birthplaces were located in regions with asbestos deposit outcrops. The study of the pulmonary asbestos burden in five patients with mesothelioma revealed a moderate level of chrysotile fibers ($1.42 \pm 0.9\ 10^6$ fibers per gram of dry weight (f/gdw)), while elevated tremolite concentrations were found in all samples (17.15 ± 17 106 f/gdw). The annual incidence of these environmental mesotheliomas was 100 cases/million in this region [51].
An excess number of mesothelioma cases was recently identified in Biancavilla, a city on the eastern end of Sicily, associated with the construction of houses built of stone from a nearby quarry, which turned out to have large quantities of amphibole fibers; these were also found in the lung tissue of a subject with pleural mesothelioma. The amphibolic fibres were identified as fluoro-edenite, a mineral from the calcic clino-amphibole subgroup, and were found in the sputum of subjects from Biancavilla and in the lung specimens from sheep living nearby [52,53,54].

New Caledonia

The identification of 12 cases of pleural mesothelioma in a period of 10 years (1978-1987) in this South Pacific island with a population of approximately 160,000 inhabitants showed a clearly excess incidence [55,56]. From 1984 to 1993, 28 cases were identified – 13 men and 15 women [57]. In the village of Houaïlou alone, the incidence was approximately 300 times greater than expected on the basis of the whole New Caledonia rate. The lack of occupational exposure in almost all cases, the young mean age of the cases (six – two men and four women – were younger than 50 years), their concentration in the central mountain region of New Caledonia inhabited by Melanesians, and a sex ratio near one, pushed investigators to look for an environmental exposure. This was found in the use of a material, called "pö" in the local languages, for whitewashing homes; it came from rock outcrops in the local area. Analysis showed that pö contains primarily tremolite fibers, with occasionally some chrysotile fibers. Airborne samples collected in various situations confirmed the presence of tremolite fibers in the atmosphere. The highest airborne tremolite concentrations were reached during sweeping in whitewashed houses (geometric mean [geometric standard deviation] 1834 f/l [2.1]). Tremolite fibers at lower concentrations were also observed in whitewashed houses during normal activity (39 f/l [2.4]) and in outdoor samples collected near whitewashed houses (12 f/l [2.7]). Tremolite fibers were also found in lung samples from patients with mesothelioma or lung cancer. Lung concentrations of tremolite fibers were higher for subjects who reported exposure to the whitewash (5.91 [9.1] fibers/µg of dry lung and 460 [7.1] f/ml BALF) than for subjects who did not report such exposure (0,14 [3.5] fibers/µg of dry lung and 166 [1.9] f/ml BALF). [58,59]. A population-based case-control study that included incident cases of pleural mesothelioma and lung cancer between 1993 and 1995 revealed the very high risks associated with pö use, particularly among Melanesian women. The risk of mesothelioma was strongly associated with the use of the whitewash (Odds-ratio (OR) = 40.9, 95% confidence interval (CI) 5.1-325); among Melanesian women, exposure to pö was associated with an increased risk of lung cancer (OR = 4.9, CI, 1.1-21.2). In contrast, no association was noted between pö exposure and lung cancer risk among Melanesian men, probably because of lower exposure levels (a descriptive survey found that women spent on average about two more hours indoors each day than men) [60].

China

In 1983, an abnormally high frequency of pleural plaques and mesothelioma was identified in the rural province of Da-yao, in southwest China. The frequency of pleural plaques was 20% among farmers older than 40; the number of mesotheliomas averaged 3.8 cases/year from 1984 through 1995 and 9 cases/year from 1996 through 1999; this frequency is exceptionally high in view of the total population of 68,000 inhabitants. This phenomenon has been related to the presence of natural soil pollution in this region, from disseminated crocidolite outcrops. Three cohorts, defined according to their exposure to this soil pollution, were organized in this population. They showed a clear excess of lung cancer and asbestosis; in the most highly exposed cohort, 22% of the cancer deaths were due to pleural mesothelioma. Compared with a control cohort of farmers from an unpolluted area, the relative risk of lung cancer was 2.1. The mean age of mesothelioma cases was low (56 years). The male/female sex distribution was about 3:1; this is not common for purely environmental exposure, where the sex-ratio is usually close to one, and may be explained by the fact that in addition to environmental exposure, male occupational exposure occurred when some peasants made commercial products out of the crocidolite ore, by crushing the ore and making asbestos stoves and stove tubes [61].

California

A case-control study showed an increased risk of developing a malignant mesothelioma (pleural and peritoneal localizations), in relation with the distance of the residence to naturally occurring asbestos sources in California. The cases diagnosed between 1988 and 1997 were extracted from the cancer register of California; the controls were pancreatic cancers cases. Data about residence at diagnosis, and the longest occupation held were abstracted from medical records. Occupational exposure to asbestos was assessed on the basis of occupation. Naturally occurring asbestos sources were defined as ultramafic rock bodies, and geographically located using a geological map of California; residential addresses were geocoded, allowing for the calculation of the distance from ultramafic rock bodies. The main results show that there was a regular decrease of the risk of pleural mesothelioma with distance from the exposure source [62].

DOMESTIC AND PARA-OCCUPATIONAL EXPOSURE

The studies considered here concern mesothelioma cases in subjects with no known personal occupational exposure, but who lived with asbestos workers. Several case reports have attributed mesothelioma to para-occupational exposure in diverse circumstances [63,64,65,66,67,68]. Population-based case-control studies in different countries have shown cases of pleural and/or peritoneal mesothelioma attributed to regular exposure to soiled work clothes, brought home from an exposed workplace [69,70,71]. The levels of asbestos exposure in these circumstances are probably high, but cannot be quantified [72,73]. A cohort study involving more than 2,000 subjects living with asbestos-exposed workers showed an excess rate of mortality from mesothelioma [74]. The follow-up of the cohort of wives of Casale Monferrato (Italy) asbestos-cement factory workers, where approximately 10% of the asbestos used was crocidolite, revealed an excess of pleural mesothelioma: 21 observed vs. 1.2 expected (SMR = 18.00) [75]. A case-control study in this same population showed an increase in the risk of pleural mesothelioma among the workers' children (OR = 7.4; CI: 1.9-28) [76]. A population-based case-control study of pleural mesothelioma in a region of England suggested that purely household exposure might increase the risk of mesothelioma [77]. A population-based case-control study of pleural mesothelioma in three European countries (Italy, Switzerland and Spain) found an elevated risk for domestic exposure (OR = 4.8), with an exposure-response pattern [78]. Finally, a meta-analysis of eight mesothelioma studies yielded a summary relative risk of 8.1 (CI: 5.3-12) for domestic exposure [79].
Very few studies have looked at lung cancer in people in contact with asbestos workers. One showed an excess of lung cancer (Standardized mortality ratio (SMR) = 185 for the period of 20 years or longer after the first exposure). It did not however mention the current or past smoking behavior of cohort subjects. It also showed an excess of radiological abnormalities in these subjects, linked to the duration of the para-occupational exposure [74]. However, in the cohort of wives of Casale Monferrato, the mortality for lung cancer was not increased (12 observed vs. 10.3 expected; SMR = 1.17) [75].

ENVIRONMENTAL EXPOSURES TO ASBESTOS FROM INDUSTRIAL SOURCES

In the first epidemiologic study showing in South Africa a risk of pleural mesothelioma associated with asbestos exposure, published in 1960, some of the cases reported were attributed to environmental exposure [76]. Nonetheless, until recently, only a few studies had examined the risk of cancer associated with exposure to local industrial sources, and their results were discordant. More recently, diverse and better studies have clearly confirmed a risk for neighboring populations. These studies can be classified according to whether the facility involves asbestos production (mines and mills) or transformation.

Mines and mills

In 1960, Wagner *et al*. published a study of pleural mesothelioma diagnosed between 1956 and 1960 in a crocidolite-mining area in Cape Town province, South Africa. Of the 32 case subjects for whom asbestos exposure was identified (22 men and 10 women), 14 had never worked in the mines but did live near them. Since then, several studies have confirmed the risks associated with residence near asbestos mines in South Africa [76]. In a study of 232 cases of pleural mesothelioma diagnosed between 1956 and 1970 in South Africa (some of which had been included in Wagner's study); 76 of the 130 cases without identified occupational exposure had lived in areas where crocidolite is mined [77]. The analysis of mortality rates from 1968 through 1980 in South Africa, comparing mining districts (crocidolite) with neighboring control districts, showed that mortality rates from mesothelioma, asbestosis, and lung cancer were higher in the mining districts. The increase in mortality rates for these causes was of the same order of magnitude for men and women (although women have never worked in the mines), and several deaths occurred at a young age [80]. In a case-control study that included cases of pleural mesothelioma from different South African regions; the risk associated with purely environmental exposure to crocidolite from the mines in the Cape Town region was plainly higher (OR = 50.9) than that for exposure, mainly to amosite, in Transvaal province (OR = 12) [81]. A cohort study that included all whites born from 1916 through 1936 in the mining town of Prieska in Cape Town province (crocidolite mines) found a significantly excess number of cases of pleural mesothelioma and lung cancer, including among women who had never worked in the asbestos industry [82]. A case-control study including the cases of lung cancer diagnosed between 1993 and 1995 in another crocidolite mining region, the Northern Province, found an OR of 5.4 (CI: 1.3-22.5) among women who lived in mining areas [83].
Australia is another country with a large crocidolite production. The analysis of 132 cases of mesothelioma diagnosed in Western Australia between 1960 and 1982 showed that four of the 37 cases with no known occupational exposure had lived near the crocidolite mine in Wittenoom; two other cases, diagnosed from 1983 through 1986, were also classified in this category [84]. This study included one case who, as a child, had played in a plant that manufactured asbestos tiles; this anecdote illustrates the extreme diversity of situations where asbestos environmental exposure may occur and the difficulty this poses in ensuring the lack of any asbestos exposure. In a recent update, the analysis if cases of mesothelioma among residents of the town who did not work at the mine or mill, showed that the mortality rate increased with increasing residence duration, time since first exposure, and estimated cumulative exposure. The mesothelioma mortality rate was consistently lower for women, but the dose-response curve was steeper for female subjects. The rate was lower in those first exposed as children compared with those first exposed at > or = 15 years of

age (relative risk in those exposed at older ages: 2.4 (1.4 - 4.2)), both groups having similar mean residence times in Wittenoom, cumulative exposures, and lengths of follow-up. The dose-response slope for asbestos exposure and mortality from mesothelioma was not different between those who were first exposed as children than those who were first exposed at > or = 15 years of age [85]. This study is one of the few that have estimated individual exposure levels in a detailed fashion, using the available historical quantitative data.

Using an ecological design Camus *et al*. have compared the mortality from lung cancer and mesothelioma in the mining region in Quebec Province, among women aged 30 years or older residents of the towns of Thetford Mines (where tremolite-contaminated chrysotile is mined) and Asbestos (tremolite-free chrysotile mine), with that of women from 60 reference areas in Quebec over the period from 1970 through 1989. Asbestos exposure levels were evaluated and their changes since the beginning of the century; numerous potential confounding factors were taken into account in the ecological analysis (population, ethnicity, family size, educational level, income, percentage of smokers, body mass index, health-care use). Exposures were estimated at levels vastly higher than those corresponding to "normal" levels of passive environmental exposures: the authors estimated the cumulative exposure from neighborhood sources at 16 f/ml/year for the population of the mining areas; taking into account the household and occupational exposures, they reached a total of 25 f/ml/year, with a "subjective plausible" range from 5 to 125 f/ml/year. Based on 71 deaths from lung cancer between 1970 and 1989, the SMR for lung cancer revealed no excess (0.99; CI: 0.78-1.25); seven cases of pleural cancers were recorded, yielding a significantly elevated SMR of 7.63 (CI: 3.06-15.73). In all, this study appears to show that there is no risk of lung cancer associated with living near chrysotile asbestos mines. At the same time as it confirms a clear excess risk for pleural cancer; it is noteworthy that all of the pleural cancer cases occurred in Thetford Mines, where the asbestos mined is contaminated by tremolite, whereas no mesothelioma was observed in Asbestos, where there is little or no contamination of chrysotile by tremolite [7].

Populations living near anthophyllite mines have also been studied. An abnormally high frequency of pleural plaques, often bilateral, has been observed among populations who have never worked in the industry but live near anthophyllite mines in Finland [86], Bulgaria [87], and Japan [88]. To our knowledge, no cases of purely environmental mesothelioma have been reported in connection with this source of anthophyllite exposure.

Vermiculite is a naturally occurring mineral mined in different countries. Vermiculite from the mine that operated near Libby, Montana (USA) from the early 1920s until 1990 was contaminated with asbestos and other fibrous amphibole minerals. The respirable fraction of asbestiform amphiboles contaminating the Libby vermiculite has approximately 84% winchite, 11% richterite, and 6% tremolite. Reports of respiratory disease mortality among community residents and household contacts of Libby vermiculite workers suggested increased risk from ambient community exposure [89]. Cross-sectional radiographic screening revealed that 6.7% of community residents with no occupational or familial exposure have radiographic evidence of asbestos-related disease [90]. These findings suggest that there is an elevated risk from asbestos-contaminated vermiculite associated with residence in the vicinity of the mine.

Asbestos Processing Plants

Several case series looked for environmental exposures from industrial asbestos facilities. In a series of 32 mesothelioma cases with no known occupational exposure in Pennsylvania (US), eight subjects had lived or worked in the immediate vicinity of an asbestos plant (fiber type not specified) [63]. Another US series identified one case of mesothelioma in a patient who had always lived near a plant manufacturing products from only one type of asbestos – anthophyllite [91]. In the city of Hof van Twente in the Netherlands, which houses a large asbestos-cement facility, five cases of pleural mesothelioma were identified among women without occupational or household exposure to asbestos. The age at diagnosis varied from 38 to 81 years. Each case was exposed to asbestos in the direct vicinity of their residence to the factory [92]. In France, a recent study among residents near a plant where asbestos was crushed from 1938 to 1991, 4 cases of mesothelioma with no other source of exposure were identified [93].

In 1965, Newhouse and Thomson published a case-control study from the London area that examined pleural and peritoneal mesotheliomas. Among those with no occupational or domestic exposure to asbestos, there were 11 (30.6%) subjects in the mesothelioma series and five (7.6%) in the control series who had lived less than 800 meters from an asbestos plant that used crocidolite. Ten of the eleven cases were women, who were less likely to be occupationally exposed [69]. A case-control study of mesothelioma carried out in the Hamburg region (Germany), found 65 cases with no occupational exposure, 20 of whom had lived for at least five years less than one kilometer from an asbestos plant that processed crocidolite; although this information was not available for the controls in this study, the high proportion nonetheless suggests a risk associated with proximity to the factory [94]. A case-control study in three European countries found an elevated risk of mesothelioma (OR = 11.5, CI: 3.5-38.2) among people living near asbestos-cement, asbestos-textile and brake manufacturing plants, and naval shipyards [80]. Several other population-based case-control studies at national or statewide levels in the USA and in Canada, have not found any indication of a cancer risk associated with proximity to industrial asbestos facilities [70,65,71,95]. However, plants likely to induce a risk for the neighboring population are rare, and population-based case-control studies that recruit subjects from large populations over extensive geographic areas have little chance of detecting this type of risk.

Cohort studies of populations with a higher *a priori* probability of exposure may be more appropriate, even though they can lack statistical power when their sample size is insufficient, and negative results cannot be interpreted as reflecting a real absence of excess risk. An example is seen in the cohort study of mortality by Hammond *et al*., which considered the inhabitants of two areas of New Jersey (USA), one very close to an amosite plant and the other used as a control area. The follow-up included all men who had lived in these areas between 1942 and 1954 (1,779 near the factory, 3,771 in the control area), and their mortality was analyzed from 1962 through 1976. The employees of this plant had experienced high rates of both mesothelioma and lung cancer. After excluding all subjects who had worked in the factory, the authors identified one case of mesothelioma in an electrician (an occupation considered to be possibly asbestos-exposed) among 780 deaths of inhabitants of the amosite factory neighborhood, and none at all among the 1,735 deaths of control zone residents [96]. The only conclusion that can be drawn from this study is that it could help to set some upper limits on what the excess risk associated with living near the plant might be.

The study of the city and region of Casale Monferrato is of special interest because of its quality and the duration of the observation period. An asbestos-cement plant located less than 1,000 meters from the heart of downtown operated from 1907 to 1985. The factory used chrysotile, but approximately 10% of the total quantity of asbestos was crocidolite. Casale Monferrato is a medium-sized town (approximately 42,000 inhabitants in 1981); with the surrounding villages and countryside, the area includes approximately 98,000 inhabitants. The region is mainly rural, and there are no other industries involving particular asbestos exposure. Geographic mobility in this area is not especially high: for example,

of the 64 people with no known asbestos exposure who were diagnosed with mesothelioma between 1980 and 1991, 42 (roughly 70%) were born in the area [97]. A considerable proportion of the population worked in the asbestos-cement factory, which had 1,956 employees in 1960, 1,200 in 1970, and 800 in 1980. The first fiber measurements in the town of Casale Monferrato were not taken until 1984 and are certainly not representative of the pollution level in earlier decades. They revealed a mean concentration of fibers longer than 5 μm that ranged from 1 to 11 F/L, values in the range normally observed in urban areas [98]. The incidence rates of pleural mesothelioma in Casale Monferrato for 1980-1989 were compared with those from a group of nine Italian registries [97]. A substantial excess incidence of mesothelioma was found among men and women. Several features of the data suggested the role of environmental exposure: similar rates in men and women (the ratio of men to women was 1.8 for 1980-1989); approximately 10% of the cases diagnosed before the age of 50. A study of asbestos lung burden and asbestosis found a high concentration of asbestos bodies (AB) among people without occupational exposure who lived in Casale Monferrato (1,500 AB/ f/gdw [98,99,100]. The most recent publications presented the result of a case-control study that included the 103 incident cases of mesothelioma between 1987 and 1993. When the analysis was restricted to cases who had never worked in the asbestos-cement factory nor at any other exposed occupation, the risk associated with residence in Casale Monferrato was very high (OR = 20.6, CI: 6.2-68.6). Residents at the location of the asbestos-cement factory had a relative risk for mesothelioma of 10.5, adjusted for occupational and domestic exposures. Risk decreased rapidly with increasing distance from the factory, but at 10-km the risk was still 60% of its value at the source [76,101]. Finally, the Casale Montferrato study provides strong evidence that asbestos pollution from an industrial source can greatly increase the mesothelioma risk.

The meta-analysis of eight studies of various design (cohort, case-control and ecological) estimated a summary relative risk of mesothelioma of 7.0 (CI: 4.7-11), but it mixed studies considering both the risk associated with living in a mining area or near an asbestos processing plant [81].

PASSIVE EXPOSURE IN BUILDINGS CONTAINING ASBESTOS

This type of exposure, which involves subjects whose usual job does not require their direct physical contact with ACM, is at the heart of current concerns. Its health effects are controversial, but almost no epidemiologic data responds directly to the question of a possible risk. The reasons for this are multiple: the very low mean fiber concentrations that usually characterize this type of exposure, making it impossible to recruit and follow the immense cohorts necessary for a satisfactory statistical power, the difficulty in evaluating cumulative exposure at an individual level, and the relatively short time period involved (asbestos became common in building construction during the 1960s, while the average latency period for pleural mesothelioma is estimated at about 40 years [102] The available data come from case studies and from studies of the maintenance, janitorial, and renovation personnel of such buildings.

The case studies essentially concern legal situations, where plaintiffs with mesothelioma seek a legal determination that their disease was caused by exposure to an asbestos-insulated building. In 1991, Lilienfeld described the first four US cases of mesothelioma in teachers that were attributed in this context to having worked in school buildings containing asbestos. He also cited three similar cases in young people (30-45 years) whose only known exposure to asbestos was attendance as pupils at schools with ACM. These cases were attributed to this exposure because of the absence of any other known exposure [103]. Cases reports of mesothelioma in people who appear to have no other exposure except employment in asbestos-insulated buildings are published sporadically; they sometimes include biometrologic data consistent with the suspected exposure [104] It is nonetheless likely that most of the cases that occur in a litigation context are not published and are thus underestimated.

Information is also available about the custodial, cleaning, and renovation staffs of buildings containing asbestos. This heterogeneous category includes those who are occupationally exposed and others concerned by purely passive environmental exposure. Some of these cases involve personnel who actually touch asbestos containing materials very occasionally, if ever, while others do so more frequently. To our knowledge, no epidemiologic study has reported cancer cases related to asbestos exposure in this group of workers. Little information is available for assessing the asbestos exposure levels of this type of worker during normal work activity. For example, mean fiber concentrations in the atmosphere have been reported at 11.9 f/ml (brushing asbestos-flocked surfaces), 1.6 f/ml to 4 f/ml for dusting operations, and 15.5 f/ml for cleaning books in a library where asbestos debris resulted from the decay of these flocked surfaces. The levels corresponding to maintenance operations (work on ceilings, plumbing, roof and floor repair, etc.) vary from 0.006 f/ml to 0.12 f/ml [105].

Several studies analyzed the prevalence of radiological pleural and/or parenchymatous anomalies in the maintenance and custodial staff of asbestos-insulated schools. These categories include people who deal directly (at a frequency that is not reported) with materials containing asbestos, as well as those likely to be exposed only during cleaning operations and because they spend a substantial proportion of their working time in asbestos-containing facilities. In Massachusetts, of 57 school custodial employees with no known exposure to asbestos other than their jobs, 12 (21%) had radiological anomalies suggestive of pleural plaques; none showed small parenchymal opacities ≥ 1.0 (ILO coding) [106]. In California, of 315 maintenance employees with more than 10 years experience and no known past exposure to asbestos, 36 (11.4%) had parenchymal and/or pleural radiological anomalies: 18 (5.7%) had isolated small opacities ≥ 1/0, 13 (4.1%) isolated pleural anomalies, and 5 (1.6%) pleural and parenchymal anomalies [107]. In New York, of 247 school custodians with no other known asbestos exposure, 43 (17%) had small opacities ≥ 1/0, 18 pleural anomalies (7%), and 7 (3%) both pleural and parenchymal anomalies [108]. In Wisconsin, 457 employees of asbestos-insulated schools underwent radiographic examinations that showed a prevalence of pleural and/or parenchymal abnormalities that increased with duration of employment; of 27 employees who had worked there for more than 30 years, 10 (37%) had radiological anomalies suggestive of an asbestos-related disease [109]. These studies thus reveal a rather high prevalence of radiological abnormalities, although the results are contradictory, especially as to the frequency of small opacities ≥ 1/0 (0 to 17%). The interpretation of these results requires caution, however, because none of these studies included a control group, and confounding factors (age, smoking, BMI) were either ignored [108,109], or taken into account only partially. When smoking and age were mentioned [107], the radiological abnormalities compatible with a condition associated with asbestos were found in patients who were significantly older and who smoked significantly more than those with normal chest radiographs. In the only study that considered BMI [107], it was higher (not significantly) in patients with plaques. Here, one must bear in mind that the prevalence of

pleural thickening on images with an oblique view (as in the study cited) is correlated with BMI, even among subjects not exposed to asbestos [110].
A French cohort study involved the staff of a university campus in Paris ("Jussieu campus"), constructed between 1963 and 1973; the campus includes more than 200,000 m^2 of asbestos-insulated buildings hosting some 11,500 personnel. The study involved staff who regularly worked in buildings containing asbestos. A first study compared the prevalence of pleural anomalies in a group of 828 subjects who had worked on campus in asbestos-insulated buildings for at least 15 years with no other known asbestos exposure, and a group of 350 subjects who had also worked at Jussieu for at least 15 years, but in buildings without asbestos and with no known asbestos exposure. No significant difference was observed between the two groups for the prevalence of either pleural or parenchymal anomalies [111]. An update of the study compared three groups: workers (maintenance staff) occupationally exposed to asbestos because of direct contact with and work on ACM (n = 161); those who had worked at least 15 years in asbestos-insulated university buildings and who had no other known exposure (n = 416); and those who had worked at least 15 years only in buildings without asbestos and who had no other known exposure (n = 150). The study involved 727 subjects with two radiological examinations at least five years apart, and looked for small parenchymal opacities (ILO coding) and pleural thickening. The analysis took into account the confounding factors of age, smoking, BMI, and radiography quality. The results, overall, showed that in both the cross-sectional and prospective comparisons, the first group (occupational exposure) had an excess rate of pleural abnormalities relative to the other two groups, but no difference was seen between the group who had worked in asbestos-insulated buildings from those who never had. The measurements taken in diverse parts of the campus in 1975 showed concentrations on the order of 120 ng/m^3 (or approximately 60 f/L), substantially higher than those measured in the same sites in 1989 (0.1 F/L to 27.3 F/L). The buildings differed substantially in their asbestos concentrations; this implies that exposure may be heterogeneous in the group of subjects who worked in asbestos-insulated buildings. Finally, a major limitation of this study is the absence of any individual exposure reconstruction: the subjects were classified at the beginning of follow-up solely according to membership in one of the three defined groups [112]. Recently, five mesothelioma cases among campus employees born between 1934 and 1942, incident in 2001 or 2002, were identified by an organization against asbestos. Their asbestos exposure history was investigated through personal interviews using standardized and specific questionnaires revised by an industrial hygienist. The cases were vulcanologist, ultrasound physicist, mathematician, paleontologist, and engineer in oceanography. In all cases, no occupational, residential or domestic asbestos exposure could be identified, except the sporadic use of asbestos protecting devices for two of them. All cases worked from one to four years in the older part of the campus in proximity of the construction site, with potential neighborhood exposure during the spraying phases, and stayed on the Jussieu campus from ten to thirty-five years. The expected number of mesothelioma during two years in a total population of about 25,000 persons was estimated to be between 0.2 and 0.7 depending of the gender distribution: the occurrence of five cases is thus largely in excess. The fact that mesothelioma occurred almost forty years after the subjects started working in asbestos-insulated buildings is consistent with the known latency period of this cancer. Four cases got pleural plaques, typical abnormalities linked to asbestos. Three of them reported they had to remove from their desk asbestos-like dust, fallen down from a degraded ceiling several times a week. Finally, the five reported mesothelioma cases were likely to be induced by workplace passive environmental exposure to asbestos. Whether the main source of exposure came from exposure during the construction or from working in asbestos-insulated buildings is not clear [113]. To our knowledge, this is the first report of several mesothelioma cases working in the same asbestos-insulated workplace, with no other definite asbestos exposure.

SUMMARY OF THE MAJOR FINDINGS

Studies of workers in asbestos-related occupations have indicated excess risks of pleural mesothelioma, lung and larynx cancer, asbestosis, pleural plaques, and possibly other lesions. The effects are dose-related, and very likely also related to the type and size of asbestos fibers and the circumstances of exposure. While there is less knowledge concerning non-occupational exposure and its effects, the evidence that has accumulated indicates that asbestos in such settings can also be harmful.

Exposure levels

Risks induced by asbestos exposure are strongly dependant from fiber characteristics and cumulative individual exposure levels, but these data are more often missing or only partially documented in the studies of non-occupational exposure. Nevertheless, it appears that the intensity of non-occupational exposure is generally much lower than in occupational settings. While concentrations as high as 2 to 10 f/ml (i.e. 2,000 to 10,000 F/L), or even more elevated, were measured in some workplaces [1], typical exposure concentrations in different non-occupational settings are as follow [114].
Rural settings: **usually lower than 0.1 F/L; rarely above 0.5 F/L.**
Urban settings: **average concentration level (Paris, France) from July 1993 and March 1995 was 0.13 F/L; maximal level: 0.47 F/L.**
Domestic and para-occupational exposure: **this type of exposure is badly documented, except in special circumstances.**
Vicinity of industrial sources: **some measures yielded average levels of 7.8 F/L near asbestos mines, with maximal values of 20.6 F/L downwind from the mine. Near asbestos-cement factories, concentrations of 2F/L were measured at 300 meters downwind, and of 0.6 F/L at 1000 meters [114]. The earliest fiber measurements in the town of Casale Monferrato were taken in 1984 and revealed a mean concentration of fibers ranging from 1 to 11 F/L [76].**
Public and commercial buildings: **under certain conditions, asbestos-containing materials can release asbestos fibers into the air of buildings. In the USA, for ACM-containing buildings not involved in litigation, asbestos fiber concentration ranges from 0.04 to 2.43 F/L; the mean exposure value is 0.27 F/L, with 90th and 95th percentiles of 0.7 and 1.4, respectively [105].**

Effects of natural environmental exposure

The data about populations subjected to natural exposure provide useful information for understanding the problems related to other sources of exposure, especially because of its temporal characteristics: exposure start during

childhood and can be life-long; it is continuous, although occasional peaks occur. The data about environmental exposure of natural origin thus provide answers to some questions about the effect of early exposure on latency periods and on cancer susceptibility, the effect of permanent exposure, and susceptibility according to gender and fiber type.
***Effect of early exposure*: Asbestos exposure starting at birth does not seem to influence the latency period. No diagnoses before the age of 25 years were found in any of the series examined; most occurred around the age of 50. On the other hand, we do not know whether susceptibility is increased by early exposure. Some very high incidence rates suggest increased susceptibility, but the information about exposure levels, albeit fragmentary, seems to indicate concentrations that are sometimes very high and a cumulative duration of exposure more than four times higher in environmental than occupational situations (Table 1). Furthermore, natural exposures usually concern mainly amphibole fibers, which are strong pleural mesothelioma inductors. We therefore cannot know if the very elevated incidence of mesothelioma observed in some regions of the world should be attributed to early exposure, to high cumulative exposure, to the effect of amphiboles, or to some combination of these.**
***Susceptibility according to gender*: All the studies reported sex ratios (men-women) close to one. Accordingly, no arguments indicate that susceptibility differs according to gender. The strong predominance of men observed in the industrialized countries is therefore very probably due to exposure conditions that differ according to gender in these countries, in particular, the proportion of each gender occupationally exposed.**
***Fiber types:* With the notable exception of erionite in Turkey (which is not considered to be asbestos), the studies report that most exposure is to fibers from the amphibole group (tremolite especially, but also crocidolite). Nonetheless, several studies also indicate chrysotile exposure, and it is not always possible to determine from the published data the relative exposure to these two types of fibers. It is particularly interesting to note that chrysotile was found in lung samples in most of the studies. Although no study has reported exposure to chrysotile alone, the possibility that chrysotile exposure from the natural environment has a role in pleural mesothelioma cannot be ruled out.**

Effects of para-occupational or domestic source

Solid evidence demonstrates an increased risk of mesothelioma among people whose exposure comes from a para-occupational or domestic source. Although information is sparse about the types of fibers involved in these circumstances, the diversity of countries and periods in which excess levels of mesothelioma have been found is so large that it is probable that all types of fibers may cause it.

Effects of exposure to asbestos from industrial sources

Recent studies clearly confirm a risk pleural mesothelioma can be associated with exposure due to living near an industrial asbestos source (mines, mills, and asbestos processing plants). When fiber types are known, they come from the amphibole group or contain at least some amphiboles; nonetheless, some cases appear to involve mainly chrysotile exposure, and it cannot be ruled out the possibility that environmental exposure to this type of asbestos may cause mesothelioma. Some studies suggest that the risk of lung cancer might also be associated with living near an industrial asbestos source, especially in mining areas.

Effects of passive exposure in buildings containing asbestos

Currently there is only weak epidemiologic evidence about the health effects associated with passive exposure in buildings containing asbestos.

THE CONTRIBUTION OF NON-OCCUPATIONAL ASBESTOS EXPOSURE TO THE GLOBAL BURDEN OF CANCER

While the possibility of an elevated risk of mesothelioma associated with exposure to non-occupational sources is clearly documented, the risk should be regarded in relation with the individual cumulative exposure and no generalization is possible without taking into account the concentration and type of airborne asbestos fibers. Exposure in non-occupational settings is generally much lower than in occupational settings and it is likely that the vast majority of asbestos-induced diseases in the industrialized world are caused by occupational rather than non-occupational asbestos exposure. However, albeit very scarce data are available on individual lifelong cumulative exposure in non-occupational settings, it the may not be negligible in some circumstances, and sufficient to cause cancer.
Exposure to asbestos in occupational settings has been decreasing [6], whereas this is probably not the case for non-occupational exposure. For instance, the prevalence of pleural thickening approximately doubled from the National Health and Nutrition Examination Survey (NHANES) I (1971-1975) to the NHANES II (1976-1980) in the USA: the increase may be due to occupational asbestos exposure, but it is so large as to suggest some contribution from environmental, non-occupational asbestos exposure [115].
Estimating the contribution of non-occupational exposure to the burden of cancer in a given population is complicated by two factors. First, most studies on the risk of cancer from residential or household asbestos exposure have addressed specific exposure circumstances (e.g., natural sources of amphibole fibers), and the application of the risk estimates to other populations is problematic. Second, it is generally unknown which proportion of a given population is exposed to levels comparable to those addressed in the available studies, or how the risk can be extrapolated to circumstances of low – yet not null – exposure. To our knowledge, in no country data on the numbers of persons exposed to non-occupational sources in the general population, the type of asbestos fiber, the level and duration of exposure are available. Available data from X-ray or biological specimen studies do not allow either to derive reliable estimates of the general population exposure to asbestos. For instance, a WHO report estimated that 5% of the European population experienced in the 1980s non-occupational exposure to asbestos [116], yet one cannot match this figure with the risk estimates derived from studies conducted among populations exposed at relatively high level [117]. Population-based case-control studies might be more adequate, since they integrate the effect of different exposure circumstances experienced by a given population. As quoted above, some population-based case–control studies tried to estimate the proportion of mesothelioma attributable to non-occupational circumstances, but such studies are rare. In a study carried out in three European countries, no evidence of occupational exposure to asbestos

was found for 53 out of 215 cases, yielding 24.6% non-occupational cases [80]; in a case-control nested within the French National Mesothelioma Surveillance Program [118], the percentage of non-occupational cases was 18% (84 out of 466 cases). Among the 198 mesotheliomas with a histological diagnosis for which exposure was defined in the Italian National Mesothelioma Register, 73 (37%) had no occupational exposure [119].
When considering the potential impact of non-occupational exposure to asbestos on the total number of cancers in a population, the available data do not allow for a direct estimation. An alternative approach is thus to assume that, given that the incidence of mesothelioma in absence of asbestos exposure is almost nil [9], and other established causes account for a very small proportion of cases, most or all cases of mesothelioma without occupational exposure to asbestos are attributable to non-occupational exposure. Based on the results of the three population-based studies quoted [80,118,119], this would imply that in industrialized countries about 20% of the mesotheliomas could be caused by environmental exposure to asbestos. This approach, however, depends on the quality of exposure assessment, whose sensitivity is notoriously low, and in most of the population-based surveys, there is a fraction of mesothelioma without any identified exposure to asbestos, whatever the route (occupational or non-occupational). For instance, in the European study, among the 41 subjects with no evidence of occupational exposure to asbestos with sufficient exposure data, 9 (22%) were classified as having no exposure to domestic or environmental sources [80]; in the French study [118], no exposure to domestic or environmental sources was found for about 60% of the non-occupational cases, and the figure for the Italian National Mesothelioma Register was 29.5% [119]. According to the population under study and the methods of exposure ascertainment, this proportion of cases without any identified exposure to asbestos is usually in the range of 10-20% among men, and much higher among women (50-60%) [*Medioni J, Goldberg M. Mesotheliomas without Asbestos Exposure: Reality or Methodological Problem? Unpublished report*].
Data from industrializing countries are inadequate for an estimate. Furthermore, it is unclear whether the ratio between asbestos-related mesothelioma and lung cancer cases estimated in occupational cohorts can be extrapolated to estimate the number of lung cancers caused by non-occupational exposure.

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Table 1. Typical time variables for occupational and environmental exposure situations

	Occupational	Environmental
Age at first exposure	Adult	Birth
Years/life	40	Life-long
Hours/week	40	168
Frequency	Intermittent	Continuous

Table 2. Quantitative measurements of environmental and pulmonary samples in the principal areas of endemic pleural mesothelioma

COUNTRY (references)	ENVIRONMENT		LUNGS (unit: 10^6/g dry tissue)	
	Materials sampled	Airborne samples	Humans	Animals
Turkey "erionite-villages" (Baris et al. 1988a ;Metintas et al. 1999 ; Baris et al 1991)	Rocks, tuff: zeolite, tremolite traces Dust routes: idem + rare chrys. Stucco, house whitewash: zeolite, tremolite	Street: < 0.01-0.02f/ml (60-80% zeolite), tremolite traces Schools playgrounds: 0.01-0.175 f/ml (playing) Cave houses: 0.01-1.38f/ml (sweeping)	Zeolite: 17, 39 Chrysotile: 2, 15 Tremolite (1-5% vol) BALF[a]: erionite ferruginous bodies	Zeolite: 0.13 Chrysotile: 4.27
"tremolite-villages" (Yazicioglu et al. 1980; Baris et al. 1988a ; Metintas et al. 2002; Zeren et al. 2000; Baris et al. 1979; et al. 1998)	House whitewash, soil, road dust: tremolite, chrysotile	Tremolite chrysotile Indoor: 0.009-0.28 f/mL Whitewashed houses: up to 200 f/mL (rock crushing), 0.02-17.9 f/mL (sweeping floors)	Tremolite, actinolite, rare chrysotile BALF[a]: tremolite and chrysotile ferruginous bodies	
Greece (Sichletidis et al. 1992; Constantopoulos et al. 1985 ; Langer et al. 1987)	Earth: rare tremolite, chrysotile traces whitewash: tremolite	Exterior: 0.01-0.02 f/ml Whitewashed house: 0.01 and 17.9 f/ml (rubbing)	Tremolite Rare chrysotile	

Table 2 (ctd). Quantitative measurements of environmental and pulmonary samples in the principal areas of endemic pleural mesothelioma

COUNTRY (references)	ENVIRONMENT		LUNGS (unit: 10^6/g dry tissue)	
	Materials sampled	Airborne samples	Humans	Animals
Cyprus (McConnochie et al. 1987, McConnochie et al. 1989)	House whitewash: chrysotile and tremolite Roof dust: idem		Tremolite: 220 Chrysotile: 115	Tremolite: 0.02-7 Chrysotile: 7.8-78.5
Corsica (Boutin et al. 1989; Billon-Galland et al. 1988 ; Rey et al. 1993)		Exterior: (ng/m3), tremolite: 12 ± 6.6, chrysotile: 15.5 ± 10.9 Interior: (ng/m3): tremolite: 59.8 ± 48, chrysotile: 14.3 ± 15.7	Tremolite: 1.4-62 Chrysotile: 0.3-3.4	52-82 (5% tremolite, 95% chryso
Sicily (DeNardo et al. 2004; Putzu et a;. 2006)	Quarry and building stones: fluoro-edenite		Fluoro-edenite	Fluoro-edenite
New Caledonia (Luce et al. 1994 ; Goldberg et al. 1995; Luce et al. 2004)	Whitewash, rocks: tremolite, chrysotile	Exterior: tremolite: 0.2 -12 F/L: chrysotile: 0-1 F/L Road dust: tremolite 0-5 F/L, chrysotile: 0-9 F/L Whitewashed houses: tremolite 4-1834 F/L (cleaning), chrysotile: 0-11 F/L (cleaning)	Tremolite: not exposed to the whitewash: 0.14 (3.5)[b] exposed to the whitewash: 5,91 (9.1)	
China (Liu et al. 2003)	Earth: crocidolite			

a: BALF : Bronchoalveolar Lavage Fluid
b: geometric mean (geometric standard deviation)