Mesothelioma: cases associated with non-occupational and low dose exposures

Gunnar Hillerdal

Abstract

Objectives—To estimate the importance of low dose exposure to asbestos on the risk of mesothelioma.

Methods—A review of the literature.

Results and conclusions—There is no evidence of a threshold level below which there is no risk of mesothelioma. Low level exposure more often than not contains peak concentrations which can be very high for short periods. There might exist a background level of mesothelioma occurring in the absence of exposure to asbestos, but there is no proof of this and this “natural level” is probably much lower than the 1–2/million/year which has been often cited.

Keywords: low exposure; asbestos; mesothelioma

Mesothelioma is an incurable disease which is almost exclusively due to inhalation of asbestos fibres. Asbestos has been extensively used in industry and construction in the 20th century, especially during and after the second world war, and even if the mineral is no longer used in most rich western countries the total world production remains high. There is a worldwide pollution with asbestos, as indicated by the finding of the mineral in samples of Greenland ice and on the Yorkshire Moors, and every citizen in the world has been exposed to some extent. Consequently, asbestos fibres can be found in most lungs at necropsy. It is thus understandable that there is concern about the risk of mesothelioma for the general population.

However, it should be remembered that mesothelioma is a rare disease with incidence in industrialised countries ranging from 1 to 5/million/year among women and values for men 5–10 times higher (see table 3). Even in cohorts with a very heavy exposure to asbestos most people will die from other causes. In people with certified asbestosis—that is, with a heavy exposure—up to 10% will develop mesothelioma; among insulators in the United States and Canada, also a heavily exposed group, 9.3% of the deaths have been due to this disease; and in amphibole miners in South Africa or Australia, this figure is 2–4% (table 1). Clearly, with exposure concentrations several magnitudes lower, as occurs in the general population, the risk is very small, often impossible to measure.

A discussion of the risks from low exposure must include the dose-response curve; the existence or non-existence of a threshold, and thus a background concentration; and should try to define low exposure and estimate to what degree this really means a low concentration. From conflicting findings and opinions attempts must be made to make a meaningful conclusion.

The different types of asbestos seem to differ considerably in their ability to cause mesotheliomas. Chrysotile is considered by many authors to be a weak carcinogen in humans, whereas the two amphiboles crocidolite and tremolite are much more dangerous according to many studies. The third of the more important amphiboles, anthophyllite, was long considered not to cause mesothelioma, but such tumours have now been reported although the risk seems to be small. There is, none the less, a minority opinion that chrysotile is in fact responsible for most of the pleural mesotheliomas in society or should at least be considered to carry the same risk. This discussion, however, falls outside the present review and is not important for the conclusions drawn here.

Definition and diagnosis of mesothelioma

Mesotheliomas are, by definition, tumours that arise from mesothelial cells and can thus arise from any body cavity: the pleura, the peritoneum, the pericardial sac, and even the tunica vaginalis testis. Pleural mesotheliomas are the most common and pathologically the best defined ones. Pleural mesotheliomas have a male to female rate of about five to one, whereas for peritoneal tumours this ratio is 1.5 to 1. Thus, either the aetiology is different, the
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Table 2  Possible risk factors and mediators of risk of mesothelioma (other than asbestos)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>Pleural scars (tuberculosis, pleurisy, therapeutic pneumothorax)</td>
<td>20</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>Single cases after Thorotrast injection or radiotherapy; causality not proved</td>
<td>21 22</td>
</tr>
<tr>
<td>Beryllium</td>
<td>Two doubtful cases described</td>
<td>18</td>
</tr>
<tr>
<td>Vegetable fibres</td>
<td>No proof in humans</td>
<td></td>
</tr>
<tr>
<td>Dietary factors</td>
<td>Provitamin A, β-carotene may decrease the risk</td>
<td>30 31</td>
</tr>
<tr>
<td>Viruses</td>
<td>Simian virus 40 DNA sequences reported in mesotheliomas</td>
<td>32</td>
</tr>
<tr>
<td>Hereditary factors</td>
<td>Familial cases (explained by common asbestos exposure?)</td>
<td>24–26</td>
</tr>
<tr>
<td>Immunological factors</td>
<td>Rapidly progressive cases in patients with HIV infection</td>
<td>28 29</td>
</tr>
<tr>
<td>Erionite</td>
<td>Very high incidence of mesothelioma environmental exposure in Turkey</td>
<td>19</td>
</tr>
</tbody>
</table>

Incidence of mesothelioma

There is a large variation in the incidence of mesothelioma in different countries and in most places a steadily rising number of cases with time. In table 3, the incidence or mortality from mesotheliomas in different countries at various times can be seen. As mortality for practical purposes is the same as the incidence for this disease, both figures have been used in the table. Some of the differences between the countries are probably due to diagnostic difficulties, but most of the variations can be explained by the use of asbestos in the particular society some decades earlier.

Dose-response and latency time

Most researchers agree that there is a positive dose-response curve for mesothelioma—the heavier the exposure to asbestos, the greater the risk. This is found in cohort studies as well as in analyses of amphibole asbestos fibres in the lungs. It was realised early that time since first exposure was of great importance, and therefore the “cubic residence-time model” was suggested by Doll and Peto in their report in 1985:

\[ I(T) = c \times F \times \left( T^4 - (T-D)^4 \right) \]

Where, \( I(T) \)=incidence at the time \( T \) after exposure; \( c=a \) constant depending on the process, \( F= \) intensity of exposure, and \( D= \) duration of exposure. This equation has been used in many studies with an acceptable fit for normal occupational exposure concentrations. \( F \) in the equation is the total exposure—a combination of fibre concentrations and exposure time—usually measured in fibre-years. (1 fibre-year = a mean of 1 fibre/ml air for 1 working year). Thus, the dose-response curve is supposed to be linear, but the result is heavily influenced by the time factor.

Unfortunately, the exact value of \( F \) is often uncertain, even in well defined highly exposed cohorts. The equation is thus rarely useful especially with low doses, in which \( F \) is usually a crude guess only. As can be seen from table 1, even with heavy exposure only up to 10% of a cohort will die from mesothelioma—so the formula is not applicable in these cases either. With very heavy exposure, most patients will die from pulmonary insufficiency due to asbestosis before there has been sufficient time to develop a mesothelioma.

Even more troublesome is the time factor \( T \), which quickly becomes very important in this equation. If the equation is correct, the risk
Table 3  Incidence or mortality of mesothelioma in various countries and areas over time (1 million inhabitants/year)

<table>
<thead>
<tr>
<th>Country or area</th>
<th>Year</th>
<th>Male</th>
<th>Female</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1968-81</td>
<td>2.1</td>
<td>0.8</td>
<td>33</td>
</tr>
<tr>
<td>North America</td>
<td>1972</td>
<td>2.8</td>
<td>0.7</td>
<td>34</td>
</tr>
<tr>
<td>Nantes-Saint-Nazaire, France</td>
<td>1985-74</td>
<td>5.2</td>
<td>0.2</td>
<td>35</td>
</tr>
<tr>
<td>Texas</td>
<td>1976-80</td>
<td>5.8</td>
<td>2.1</td>
<td>36</td>
</tr>
<tr>
<td>Selected cities, United States</td>
<td>1970s</td>
<td>4.4-11.1</td>
<td>1.2-3.8</td>
<td>37</td>
</tr>
<tr>
<td>United States</td>
<td>1986</td>
<td>7-13</td>
<td>1-2</td>
<td>38</td>
</tr>
<tr>
<td>Barcelona, Spain</td>
<td>1983-90</td>
<td>8.3</td>
<td>4.7</td>
<td>39</td>
</tr>
<tr>
<td>Great Britain</td>
<td>1968-71</td>
<td>8.4</td>
<td>2.3</td>
<td>40</td>
</tr>
<tr>
<td>Finland</td>
<td>1980-94</td>
<td>10</td>
<td>2.9</td>
<td>41</td>
</tr>
<tr>
<td>Great Britain</td>
<td>1972-76</td>
<td>12.6</td>
<td>2.8</td>
<td>40</td>
</tr>
<tr>
<td>Nantes-Saint-Nazaire, France</td>
<td>1975-84</td>
<td>17.2</td>
<td>0.8</td>
<td>35</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1983</td>
<td>17.5</td>
<td>3.2</td>
<td>16</td>
</tr>
<tr>
<td>Denmark</td>
<td>1978-80</td>
<td>14.7</td>
<td>7.0</td>
<td>42</td>
</tr>
<tr>
<td>Nantes-Saint-Nazaire, France</td>
<td>1985-92</td>
<td>19.4</td>
<td>4.0</td>
<td>35</td>
</tr>
<tr>
<td>Great Britain</td>
<td>1968-71</td>
<td>20.7</td>
<td>4.3</td>
<td>40</td>
</tr>
<tr>
<td>Great Britain</td>
<td>1982-86</td>
<td>20.3</td>
<td>4.9</td>
<td>40</td>
</tr>
<tr>
<td>Great Britain</td>
<td>1987-91</td>
<td>44.0</td>
<td>6.4</td>
<td>40</td>
</tr>
<tr>
<td>Australia</td>
<td>1994</td>
<td>49.9</td>
<td>4.8</td>
<td>44</td>
</tr>
</tbody>
</table>

would increase steeply with time, making early childhood exposure of great importance. However, there are clear indications that mineral fibres clear from the lung, albeit with different half lives for the different types of asbestos. Chrysotile has the shortest half life, and crocidolite is generally accepted to have the longest. The half life of crocidolite has been estimated to 7–8 years. This clearing of fibres would, at least theoretically, tend to actually decrease the risk of mesothelioma and other diseases with time.

In conclusion, the value of the cubic residence-time formula is in practice low and it should not be used for extrapolations, at least not at the extreme ends of exposure.

The latency time varies in different cohorts, and is dependent on how long a cohort is followed up. In 370 necropsy cases from Italy, latency time could be calculated in 312.52 Latency time was also dependent on exposure, varying from 29.6 years for insulators (with the highest exposure) to 51.7 in women with domestic exposure.

The threshold value and the background level

There have been strong arguments for the existence of a threshold value (a minimal exposure required for development of a mesothelioma). In most studies, several patients with mesothelioma do not report any occupational or other exposure to asbestos,45,50 and thus there seems to be a small spontaneous basal or background incidence of the tumour. In a large study from England, consisting of 185 cases and 159 controls who were very carefully interviewed, 5% of the cases (and 27% of the controls) seemed not to have any kind of exposure to asbestos.50 This included domestic and even residential exposure. However, it is of course possible that some of these background cases might in fact be due to occupational, domestic, or even environmental exposure, unknown to (or forgotten by) the patients themselves.

There are authors who claim that the presumed background level must be very low, and retrospective searches for the tumour in the medical literature yield no convincing cases of mesothelioma before 1946,42 although such negative evidence is of questionable value. McDonald and McDonald, in a recent review, estimated the background level to be 1-2/ million/year; they came to this figure by extrapolating backwards from epidemiological studies from various countries.52

Malignant mesothelioma can occur in children,53 and such cases can be considered as proof of non-asbestos (spontaneous) aetiology, as the latency time with necessity must be very short in these cases. Asbestos fibres have, however, been reported in the lungs of children, even in stillborn ones,54,55 showing that asbestos fibres spread in the human body and even penetrate through the placenta. Even if a latency time of only a few years is extremely rare in mesothelioma related to asbestos,56 it can occur. There are some published examples of latency times of only 5 years.60

Mesotheliomas also occur in animals, from baboons61 and domestic dogs65,75 to fish.72 Dogs are exposed environmentally to asbestos just like their human masters, which might explain some of the tumours,68 but in fish it would be difficult to blame asbestos for the tumour. Thus, as in other animals, there is probably a background level of spontaneous mesotheliomas in humans.

Levels of exposure

Although many authors write about low level exposure to asbestos, there is rarely a definition of this term. In fact, in many articles low level exposure seems to be synonymous to non-occupational exposure, which, as described later, is certainly not true in many cases. Occupational as well as non-occupational exposure can be anything from very heavy to very low.

Occupational exposure to asbestos

It must be realised that occupational exposure to asbestos occurs or has occurred not only in the “classic” industries, such as asbestos mines and factories, shipyards, insulating business, asbestos cement industry, building and construction etc, but also in very many other occupations and trades. Examples are pulp and paper industry,73 oil refineries,74 electrical industry,75 jewellery workers,76 sugar refineries,77 and cigarette filter workers.78 Seamen and fishermen can have been exposed to asbestos used as insulation in their boats. In the reprocessed textile industry, bags heavily contaminated with asbestos could be reused for various other purposes, for instance covering heaps of rags; in an Italian investigation of such an industry, mesotheliomas and lung cancer were found to be fairly common among rag sorters.79

Given the extensive use of the mineral, many people have been occupationally exposed to asbestos. This exposure can have been only brief but perhaps intense during that short period. In many or most instances the workers have no idea of the exposure and it can be impossible or almost impossible to elucidate it. Also, the level of exposure is often very difficult to estimate, should the information be available.
Non-occupational exposure to asbestos

DOMESTIC EXPOSURE

The family of an asbestos worker could be exposed to considerable amounts of asbestos brought home on his working clothes, which all too often it was the duty of the wife or daughter to clean. Pleural thickening, calcifications, and pulmonary fibrosis have been described in such cases, as well as mesotheliomas.80-82

AIR POLLUTION FROM ASBESTOS MINES, FACTORIES, DOCK YARDS, ETC

Asbestos mines used to be great environmental nuisances. They could be seen from a distance because of the dust cloud. Asbestos fibres can spread over a distance many kilometres from a mine, and the tailings from the mines were used for paving roads, parking areas, playgrounds, etc. In the crocidolite mining areas in South Africa, the incidence of mesothelioma was increased to at least 10 times that expected even among women, proving a non-occupational exposure. However, whether some of this exposure was domestic (see later) is not clear.83

Another example is the formerly active crocidolite mine at Wittenoom, Western Australia. At least 5000 people lived in the township of Wittenoom without working in the mines, and in 1993 27 cases of mesothelioma had occurred among these people.5 48-49 It has been estimated that 1.1% of child residents and 1.9% of the female residents of Wittenoom have died or will die from mesothelioma, whereas among the workforce this figure would be 6%.7

Around the chrysotile mines in Quebec, Canada, there have been at least 53 occupational mesotheliomas from the mines, nine domestic, and two with general environmental exposure only.45 In the nearby towns, the lungs of residents who have never worked in the mines have a fibre concentration which is 10 times higher than that of the average Canadian.46

Mesotheliomas have also been reported from the surroundings of asbestos factories47 and in people living near dockyards. However, the risk from residential exposure is probably low. In a large study from England, this factor accounted for only 3% of all the identified cases.48

CONSUMER GOODS

Asbestos has been introduced into various goods used by the public. Examples are wall paints and spackling and jointing compounds. Another is a hand held hair drier, of which 13 million were sold in the United States and which has been described as a “small asbestos spray gun”38. In commercially produced Kent filter cigarettes, crocidolite was used in the filters from 1952-6. The sale of these cigarettes was 11.7 billion, and in the commercials the health effects of this filter was emphasised.39 40

Once asbestos is introduced into a home, it will spread to all rooms and is almost impossible to remove even with a vacuum cleaner. It will easily be disturbed into the air from the slightest movement, and sedimentation is very slow.40

URBAN AIR POLLUTION

The air in cities contains a very low concentration of asbestos. Near to construction or demolition work the concentrations are higher. It has been suggested that the air of London during the blizz was heavy with asbestos. Asbestos is also released on braking, and close to a motorway the fibre concentrations in the air will be higher than the background, but still well below the industrial threshold values. A risk not often appreciated is in dumps. In the vicinity of a waste disposal site the concentration of asbestos fibres can be 10-1000 times above the background concentration.49

Drinking water can contain asbestos or asbestiform fibres from natural sources or pollution. The use of asbestos cement pipes can cause a considerable number of fibres in the drinking water. Small amounts of asbestos can be found in some wines, beers, liquors, and other beverages, probably deriving from the filtration process. Fibres that are ingested will to some extent also enter the blood stream as seen from animal experiments.52 53 In humans, there are few reports. However, when amphibole fibres were found in drinking water from Lake Superior, a very small portion could be traced in urine,54 and when chrysotile occurred in the drinking water amounts were again found in urine.55 However, most ingested mineral fibres will never be absorbed but will be cleared in the normal way, and the harmful effects of asbestos in drinking water or drinks is probably minuscule (and much smaller than the risk of drinking the alcohol).

Even if ingested asbestos is not dangerous, it has to be realised that it is only a very small portion of the tap water that we actually drink. Most of it is used for other purposes. Once the water has dried after washing, cleaning, taking showers etc the asbestos fibres will spread in the air. Such small amounts are small but not insignificant and will add to the normal background exposure.49

ASBESTOS IN PLACE = BUILDINGS CONTAINING ASBESTOS

A mixture containing asbestos was popular after the second world war for spraying on ceilings and walls for insulation and decoration. This was used well into the 1960s. There is now a public danger because of the plaster falling down from natural wear and tear, vandalism, or “artistic” carving in schools, etc. In many industrial buildings, asbestos was also used for spraying on the underside of the roof, and with natural wear and tear (and for instance birds building nests)!57 there is now release of fibres to the surroundings. Asbestos was also extensively used in walls or around plumbing for insulation purposes, in cement to strengthen it, or just as a cheap filler.

In a modern city, asbestos can often be found in many places: in the cellar, where steam pipes are insulated; in storage or laundry rooms; in air conditioning sets; in theatres, museums, restaurants, etc.48 Whenever there is damage to any construction or machine that contains asbestos, the possibilities of exposure, sometimes even fairly high, is there.
It has been claimed that up to 1000 premature deaths from lung cancer or mesothelioma will occur in the future among school children from schools where asbestos was used in the walls—calculations which, however, had to be built on extrapolations and assumptions. Several case reports have been published on patients with mesothelioma, in which the only exposure to asbestos that was reported was “in place” (table 4). From various cohorts with such exposure, significant increases in radiological findings from the lungs—such as pleural plaques—have also been reported, indicating exposure to asbestos, but these results are not undisputed and there is a probable overdiagnosis, as control groups are missing.127

ENVIRONMENTAL MESOTHELIOMAS FROM LOCAL DEPOSITS OF FIBROUS MINERALS

“Endemic pleural plaques” were first described from Finland and since then many such findings have been reported. In these areas, there are small local pockets of asbestos which sometimes have been quarried, often for generations, for some local use. The most common use is whitewashing of houses with tremolite, which has resulted in an extremely high incidence of mesothelioma in some villages (table 5). When the exposure is due to whitewashing of the houses the risk will disappear when this procedure is stopped, but due to the long latency time this will take many decades.128

A non-asbestos fibre, the zeolite erionite, has been found in some Turkish villages. Roads, buildings, etc, can contain this fibre in small amounts. Erionite is even more dangerous than crocidolite and the incidence of mesotheliomas in these unfortunate villages is extremely high.

Concentrations of exposure

OCCUPATIONAL CONCENTRATIONS

The concentration of exposure which the first workers exposed to asbestos have experienced can only be guessed. Estimated or recreated values from the past suggest fibre concentrations from 25 up to occasional values of 1000–2000 fibres/ml. With his own recalculations, Harries in 1970 estimated the fibre concentrations in the dockyard in 1951 as follows: sprayed asbestos insulation 171–322 fibres/cc; stripping asbestos 334; sweeping 353; adjacent passage 83; and in the passageway to the shower 25. Bagging debris 564; pipe lagging 194–200; removal of pipe lagging 171. Snap samples showed values to up to 1000–2000 fibres/cc.129 These values are similar to the ones published by McMillan in 1983, who recreated values from the past: engine room 88; delagging in boilers room 171; bagging debris 353 fibres/ml.130

Measurements from working places in the 1960s often showed peak doses of 20 fibres/ml and much less in more recent years. Where asbestos is still used, many countries have adopted a concentration of 1–2 fibres/ml as the upper legal concentration of exposure. These figures should be compared with the few available non-occupational measurements (table 6). A problem with the legal concentration is that most asbestos use today occurs in developing countries, many of which have adopted standards which they cannot enforce. As a result, actual exposures may be much higher than the standard in these countries.

NON-OCCUPATIONAL CONCENTRATIONS

The fibre concentrations in domestic exposure might in fact be as high as in occupational exposure. Brushing clothes might give peaks of >100 fibres/ml.57 Ordinary vacuum cleaning is not effective in removing asbestos fibres, which...
**Discussion**

Any asbestos fibre found in a lung must have been inhaled. As far as is known, no truly unexposed group can be found in the world.

There is no proof of a threshold value—that is, a minimal lower limit below which asbestos fibres cannot cause the tumour—and thus it is plausible that even such low exposure can cause mesothelioma (even if the risk is extremely low). Patients with mesothelioma whose lungs show fibre concentrations within the normal range cannot be dismissed as background cases,—that is, not due to asbestos.

The only way to prove such a hypothesis would be to compare the incidence of mesothelioma in a group with such background exposure with the incidence in a truly non-exposed group. This is not possible, as no such group can be found.

It is nevertheless possible that there is a background level of mesothelioma,—that is, that the tumour can occur even in the complete absence of asbestos (or erionite) fibres. However, the data reviewed here indicate that if so, this background level must be very low—probably much <1 case/million people/year. This figure comes from studies of industrialised countries, where background exposure to asbestos is unavoidable. What the true figure is can only be guessed.

What, then, are the consequences for the public health? From the studies of non-occupational exposures it seems probable that the occasional high level exposure situations are the ones that are most important. Although the background, hardly measurable, concentrations of fibres in the air cannot be completely dismissed, the cumulative risk of these exposures is probably minor—and what is more, there is no way to reduce these concentrations. It is the high concentration situations which should be avoided. By knowing where asbestos occurs, such risks could be identified. Any source of pollution by asbestos which releases significant amounts of fibres should be eliminated as soon as it is discovered, using correct equipment and techniques. Correct techniques are also necessary whenever rebuilding or tearing down of structures containing asbestos to avoid asbestos pollution of the environment.

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