A rare occupation causing mesothelioma: mechanisms and differential etiology

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Key words
Railway electrification system; mesothelioma; risk apportionment

Parole chiave
Sistema di elettrificazione ferroviaria; mesotelioma; ripartizione del rischio

Summary
Background: *In a mesothelioma lawsuit, the Public Prosecutor commissioned an expert evidence on the legal accountability for the disease, because the patient experienced multiple exposures to asbestos in both occupational and environmental settings.* **Objectives:** *To collect information on asbestos exposure from all available sources and to quantify the contribution of each source of exposure as a percentage of the total risk.* **Methods:** *We retrieved information on jobs done and asbestos exposure from a work colleague and a database maintained by the National Institute for Insurance of Occupational Accidents/Diseases, respectively. Information on environmental exposure was searched through the scientific literature. The contribution of each source of exposure was quantified with a method of risk apportionment, taking into account time elapsed since first and last exposure, intensity and frequency of exposure and carcinogenic potency of asbestos fiber mix.* **Results:** *The subject worked in the maintenance of railway electrification system. The mechanical compression stress induced on the ballast during passage of trains released chrysotile (from fragmented stones) and crocidolite (through abrasive action of crushed gravel on the underbody of rolling stocks insulated with friable crocidolite). Despite the low cumulative exposure (about 2 ff×years/cc), 99% of the mesothelioma risk was attributable to the work done because of the high content of crocidolite of inhaled asbestos.* **Conclusions:** *The report of an uncommon source of occupational asbestos exposure and a scientifically based method to allocate mesothelioma risk among multiple exposure could help to recognize mesothelioma as occupational disease in the workers employed in maintenance of the railway electrification system under the Italian National Railways.*

Riassunto
«Una rara causa professionale di mesotelioma: meccanismi ed eziologia differenziale». **Introduzione:** *In un processo penale per mesotelioma, la Procura affidò ad un esperto l'incarico di evidenziare la responsabilità legale*

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della malattia perché il paziente aveva sperimentato diverse esposizioni, occupazionali e ambientali, ad amianto. **Obiettivi:** *Quantificare la concentrazione di amianto in tutte le circostanze di esposizione e ripartire il contributo di ogni fonte come percentuale del rischio totale.* **Metodi:** *Le informazioni sulle attività svolte e sull'esposizione ad amianto sono state ottenute da un collega di lavoro e da un database dell'Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro, rispettivamente. Informazioni sull'esposizione ambientale sono state cercate attraverso la letteratura scientifica. Il contributo di ogni fonte di esposizione è stato quantificato con un metodo di ripartizione del rischio che teneva conto del tempo trascorso dalla prima e ultima esposizione, dell'intensità e frequenza di esposizione e della potenziale cancerogenicità della miscela di fibre di amianto.* **Risultati:** *Il soggetto aveva lavorato alla manutenzione del sistema di elettrificazione lungo le linee ferroviarie. Durante il passaggio dei treni, lo stress di compressione meccanica indotto sulla massicciata rilasciava fibre di crisotilo (per frammentazione del pietrisco) e di crocidolite (per azione abrasiva del pietrisco sul sottoscocca dei vagoni ferroviari coibentati con crocidolite). Il 99% del rischio di mesotelioma era attribuibile a questo lavoro, nonostante la bassa esposizione cumulativa (circa 2 ff×anni/cc), per l'alto contenuto di crocidolite.* **Conclusioni:** *Questo studio, che descrive una rara esposizione professionale ad amianto e presenta un metodo di ripartizione del rischio di mesotelioma in caso di esposizioni multiple ad amianto, può agevolare il riconoscimento del mesotelioma come malattia professionale nei lavoratori addetti alla manutenzione del sistema di elettrificazione ferroviaria delle Ferrovie dello Stato italiane.*

Introduction

In the etiologic research, legal settings and whenever a causal association between occupational or environmental exposures and disease should be assessed, the quality of exposure information must be as good as the information concerning the outcome variable. However, satisfactory exposure information is generally hard to retrieve for mesothelioma because of its long latency, with a period of interest spanning decades back in time. Additionally, given the rapidly fatal clinical course of the disease, many individuals might have died from mesothelioma before exposure information could be collected.

The occupational setting has an advantage over others because the worker is not the only potential source of information. Airborne asbestos measures or semi-quantitative estimates of asbestos exposures can be available from: plant documentation; published data on similar jobs/tasks/industries; and reports from occupational health surveillance systems (8). Furthermore, specific circumstances of exposure can be collected from work colleagues.

The present case study deals with a lawsuit where the Public Prosecutor commissioned an expert evidence on the legal accountability for mesothelioma because the patient experienced multiple exposures to asbestos in both occupational and environmental settings.

The aims were to collect information on asbestos exposure from all available sources and to quantify the contribution of each source of exposure as a percentage of the total risk.

Methods

The individual was affected by pleural mesothelioma, histologically diagnosed through thoracoscopic biopsies of diaphragmatic and parietal pleura. The individual had died before interview and the next of kin were unable to provide a detailed occupational history. Information on the occupational history was obtained from a work colleague who came to our attention unexpectedly during the investigative activities; the latter worker did the same job of the patient under study and provided information of great interest.

The main source of asbestos occupational exposure in the study subject was the document "Italian National Railways. Guidelines for technical assessment of exposure to asbestos relevant to the recognition of retirement benefits for certain categories of workers" prepared by the agency for risk assessment and prevention (Consulenza Tecnica Accertamento Rischi e Prevenzione, CONTARP) of the National Institute for Insurance of Occupational Accidents/Diseases (INAIL) after the law 257/92 (asbestos ban) (10). Several other technical reports – estimating occupational exposures company by company, department by department, job by job, period by period in the overall Italian industry – were prepared by INAIL-CONTARP in order to comply the same law that introduced additional social security benefits for asbestos workers (25).

Other details about specific occupational and environmental exposures were obtained from the literature, using Google Scholar as search engine and various combinations of "asbestos", "Casale Monferrato", "sugar factory", "green stones" and "ballast" as key words.

A targeted search was separately conducted in PubMed using as key-words "asbestos exposure", "mesothelioma risk", and "apportionment". Among the citations returned by the search engine, we selected the most interesting based on the title and abstract, and the original manuscripts were examined to look for other papers in References.

To quantify the contribution of each source of exposure as a percentage of the total risk of mesothelioma, we adopted the method described by Price (20). The general form of the model (20, 15) is the following:

$$P(T) = K_0 \times T_0^k + K_B \times f_B \times (T-10)^k + \sum_i^n K_i \times f_i \times ((T - t_{Fi} - 10)^k - (T - t_{Li} - 10)^k)$$

The model includes the calculation of the risk for spontaneous background (the symbols on the left of the "+"), which is not further considered, and separate components of risk for each specific source of exposure (the symbols on the right of the "+"). The relationship between each component of risk and the total risk (sum of these components), multiplied by 100, can be interpreted as the percentage of the total risk of mesothelioma associated to exposure to that particular component.

The calculations require numerical values for:

1. "K_i", carcinogenic potency of chrysotile (K_C), amosite (K_{Am}) and crocidolite (K_{Cr}). There is ample scientific support for the existence of a gradient of carcinogenic potency for the types of fiber. According to Hodgson (9), epidemiological studies indicated a gradient of 1:100:500 for chrysotile, amosite and crocidolite, respectively. Putting K_C=1, K_{Am}=100, and K_{Cr}=500, then: $K_{C\ \&\ Am}$ (mix 50%/50% chrysotile and amosite)=50.5; $K_{C\ \&\ Cr}$ (mix 50%/50% of chrysotile and crocidolite)=250.5; $K_{C\ \&\ Am\ \&\ Cr}$ (mix of 50% chrysotile, 25% amosite and 25% crocidolite)=150.5;
2. "k", temporal trend in carcinogenesis of mesothelioma. For mesothelioma the values of "k" estimated from studies of occupational cohorts are between 2.5 and 4.0, the value most often used in the risk model of mesothelioma is 3.0 (3, 5);
3. "f_i", annual average eight-hour daily exposure. This estimate is obtained by multiplying the average intensity of exposure (expressed as ff/cc) for two adjustment factors: "hours of exposure per day divided by 8" and "days of exposure per year divided by 240" (240 is the working days in a year);
4. the chronological variables: "T" (age at diagnosis); "t_{Fi}" (age at onset), "t_{Li}" (age at end of exposure considered).

Lastly, the Public Prosecutor, who commissioned the study, approved the manuscript and authorized the publication. Written informed consent was obtained from next-of-kin of the patient for publication of this case report.

Results

Occupational exposure

The patient was employed from 1964 to 1990 (26 years) under the Italian National Railways, in the maintenance of railway electrification system within the Compartment of Bologna (Region of Emilia Romagna, Northern Italy). His job included: checking aerial electrical lines from a lifting table rolling over the rails, after having stopped train circulation and disconnected the electrical power (task A); and inspection of traction current pylons (task B). Because pylons were at safety distance from rails and had no electrical components, task B did not involve stopping of train circulation.

There was evidence that rocks containing chrysotile asbestos (green stones) extracted from the quarries of Emilia-Romagna were used to restore the ballast throughout the railway Compartment of Bologna (1) until the Ministerial Decree of 14 May 1996 that restricted such use to rocks with a Releasing Index of less than 0.1. Despite this fact and the periodical refurbishment of ballast, in 2005 asbestos was still widespread in the railway compartment of Bologna. This evidence was supported by a written answer of Italian Secretary of Transportation to a question made on 26/1/2005 that confirmed the presence of chrysotile in the ballast of railway station of Bologna [http://ricerca.repubblica.it/repubblica/archivio/repubblica/2004/11/03/stazione-massicciata-all-amianto.html].

The gravel of ballast consisted of hard rocks (dolomite, granite, basalt, trachyte, gneiss and serpentinite) with sharp edges (21). Passage of trains induced mechanical compressive stress on the ballast, with a sliding attrition "stone against stone" resulting in fragmentation of stones. In fact, the removal of fragmented gravel and renovation with intact stones was a normal operation of maintenance according to INAIL-CONTARP (10).

The dust released by the continuous fragmentation of crushed stones resulted in persistent accumulation of chrysotile fibers on the railway ballast. Besides chrysotile, also amphibole airborne fibers could be released on the ballast, because of abrasive action of crushed gravel on the underbody of the rolling stocks that were insulated with friable crocidolite asbestos sprayed or in flakes at least until 1977-1979. Air vortex during passage of trains lead asbestos fibers airborne.

Chrysotile concentration in quarries of green stones of Emilia-Romagna was 0.02 ff/cc (1). On the other hand, amphibole fibers concentration, measured during "the work of underbody mechanical take down" of railway vehicles, was 0.65 ff/cc (10). Therefore in task A and B asbestos concentration had to be 0.67 (0.65 +0.02) ff/cc, but it was reduced by 10 times and considered equal to 0.067 ff/cc because the subject worked outdoors. Task A and B involved exposure to an average 0.067 ff/cc asbestos (50% crocidolite and 50% chrysotile) for 7 hours a day (see below), 240 days a year, for 26 years.

In the same period, the subject also worked in an electrical substation serving railway lines, employed in maintenance of electrical equipment (task C). There were 18 electrical equipment components: ultrafast circuit interrupters (with a lanyard and a tissue in friable chrysotile >95%); grounding test resistors (containing amiantite, a material composed of asbestos fibers mixed with gum); inductors (with asbestos cardboards between inductor's spires); cabinets rectifiers (with petralit panels, containing 8.5% chrysotile and 10.6% crocidolite); capacitors with harmonic absorption filter (with asbestos chrysotile cement). Maintenance was monthly (every 15 day for cabinets rectifiers) and was executed by sanding asbestos containing material (ACM). Maintenance of a single component had a 1.5 hours duration and involved, until 1993/94, exposure to 0.060 ff/cc asbestos, ranging from 0.015 to 0.160 ff/cc (10). The frequency of exposure in task C was obtained as product of: 11 (months worked per year); 1.5 (commitment time in hours for each component); and 18 (number of electrical equipment components). This gave 297 hours of work per year, about 1 hour per day. Therefore, task C involved exposure to an average 0.060 ff/cc asbestos (mainly chrysotile) for 1 hour/day, 240 days/year, and 26 years.

The subject also worked in a hydroelectric power plant (under the Italian National Railways) for three years from 1961 to 1964. Since the job did not involve asbestos exposure, it was no further considered.

Environmental exposure

The subject served in the army from 1955 to 1957 (18 months) in Casale Monferrato, where, from 1907 to 1986, was operating the largest factory of Italian asbestos cement products (slabs for roofing, pipes, tubes and ducts). Predominant fiber was chrysotile but amphiboles were also used, in particular crocidolite for high-pressure pipes. In 1984, reported concentrations were 0.01 ff/cc near the plant and 0.001 ff/cc in other urban areas (14). Therefore, the subject was exposed to 0.001 ff/cc (50% chrysotile, 25% amosite and 25% crocidolite) for 24 hours/day, 365 days/year, and 1.5 years.

From 1965 to 1991 (26 years) the subject lived in a house (owned by the Italian National Railways) located near the rails and a railway repair workshop, and 50 meters away from a sugar factory (known to entail an asbestos pollution) (13). Concerning the former source, we set: intensity at 0.0067 ff/cc (indoor concentration value 10 times lower than the occupational exposure); frequency at 8 hours/day (24 hours less 8 hours of work and 8 hours of night-time when very few trains were circulating) per 365 days/year; length at 26 years (from 1965 to 1991); and percent composition at 50% chrysotile and 50% crocidolite. Concerning asbestos exposure from the sugar factory we set: intensity at 0.001 ff/cc (equal to that of Casale Monferrato (14); frequency at 16 hours/day (not considering the 8 hours of a shift work) per 120 days/year (the usual duration of activity of sugar plants); length at 26 years (from 1965 to 1991); and percentage composition at 50% chrysotile and 50% amosite according to the literature (11).

Mesothelioma risk apportionment

Table 1 shows the chronological aspects and the intensity of asbestos exposure by source: age at the beginning and end of each exposure; age at diagnosis; time since first exposure (TSFE); time since last exposure (TSLE); asbestos concentration expressed as ff/cc; adjustment factors taking into account hours per day of exposure (over a standard of 8 working hours) and days per year (over a standard of 240 working days); the equivalent exposure (asbestos concentration adjusted for the two previous factors); and the cumulative exposure (equivalent exposure multiplied by years of duration of exposure).

Table 2 shows how the different aspects of asbestos exposure contribute to the terms of the apportionment equation: carcinogenic potency of different types of asbestos fibers; annual average eight-hour daily exposure (equivalent exposure); and chronological aspects of asbestos exposure (TSFE cubed, taking into account a minimum latency of 10 years and set to 0 if the term raised to the power k is negative; and TSLE modified in the same way). The product of these three aspects of exposure is expressed in the last column of Table 2 as a percentage of the total.

Based on these percentages of total risk of mesothelioma, we ranked the various sources of asbestos exposure as follows: 85.4% for occupational exposure (tasks A, B and C); 13.5% for residential exposure near the railway; 0.2% for residential exposure near the sugar factory; 0.7% for asbestos exposure during military service. The sum of the first

Table 1 - Chronological aspects and intensity of asbestos exposure in the different contexts (TSFE=time since first exposure; TSLE=time since last exposure)

	Age at start	Age at end	Age at diagnosis	TSFE	TSLE	ff/cc	Hours/8	Days/240	Equivalent exposure	Cumulative exposure
Military service	18.5	20	73	54.5	53	0.001	3	1.5	0.0045	0.007
Residence close to sugar factory	28	54	73	45	19	0.001	2	0.5	0.0010	0.026
Residence close to railway	28	54	73	45	19	0.0067	1	1.5	0.0101	0.261
Task A and B§	27	53	73	46	20	0.067	0.875	1	0.0586	1.524
Task C§§	27	53	73	46	20	0.060	0.125	1	0.0075	0.195

§ During maintenance of railway electrification system

§§ During maintenance in an electrical substation serving railway lines

Table 2 - Risk apportionment between different sources of asbestos exposure

	$(TSFE-10)^3$	$(TSLE-10)^3$	$(TSFE-10)^3 - (TSLE-10)^3$	Equivalent exposure	Potency	Risk components	Risk %
Military service	88121	79507	8614	0.0045	150.5	5834	0.7%
Residence close to sugar factory	42875	729	42146	0.0010	50.5	2128	0.2%
Residence close to railway	42875	729	42146	0.0101	250.5	106104	13.5%
Task A and B[§]	46656	1000	45656	0.0586	250.5	670484	85.4%
Task C[§§]	46656	1000	45656	0.0075	1	342	<0.1%
Total						784892	100%

[§] During maintenance of railway electrification system
[§§] During maintenance in an electrical substation serving railway lines

two percentages gave 99%, which is the percentage of mesothelioma risk attributable directly or indirectly to the work done under the Italian National Railways.

Discussion

In a worker affected by mesothelioma, the present study describes an occupation (maintenance of railway electrification system under the Italian National Railways) involving an uncommon asbestos exposure (chrysotile fibers released from ballast during passage of trains, and crocidolite fibers freed through abrasive action of crushed gravel on the underbody of rolling stocks insulated with friable crocidolite). An occupational origin of mesothelioma in this subject might have been disregarded since asbestos is not necessarily part of the activities and movements constituting the tasks performed. Release of fibers generally requires the necessary involvement of man; in this case, asbestos containg material was disgregated by the passage of trains.

About 29% of the stones used for ballast in Italy were found to be contaminated with asbestos, at least before 1990 (21). The percentage could have been even higher in the Compartment of Bologna given the proximity of quarries of rocks (green stones containing chrysotile asbestos) used to restore the ballast throughout. The continued fragmentation of stones at passage of trains involved release of chrysotile fibers.

The Region of Veneto (Decree of Regional Council No. 5607 of 31/10/1995) enacted an emergency plan linked with the presence of rolling stocks owned by Italian National Railways in the Region of Veneto. The Attachment A of the decree affirms that friable crocidolite asbestos was sprayed as an insulating material on the inner surfaces of the rolling stock and of the underbody, and that the insulation of the underbody had no segregating elements but was in sight. The decree prescribed to examine periodically, at least every three months, the rolling stocks (set aside in railway stations, sidings, etc.) presenting insulation in the underbody in order to detect on the ballast the macroscopic parts of the insulation detached from the underbody. The Attachment A of the decree also specifies that mechanical stress applied to rolling stocks could facilitate the release of fibers from the insulation [http://assistedil.it/Normativa/DGRV/DGRV_5607_1995.pdf].

The railway line along which the subject worked connects Central-Southern with North-Eastern Italy and is crossed daily by numerous trains in both directions, at interval of about half-hour in both directions. It is reasonable that fibers remained airborne in the short interval between the passages of two trains. There have been reported many vivid descriptions of asbestos workers who, returning home, freed asbestos fibers in the one room of their house when brushing their hair or shaking their suit working. Actual measurements, however, are scarce. Nicholson (18) using the gravimetric method, found fiber levels several times higher in the homes of chrysotile asbestos miners in Newfoundland (Canada) that in other homes in the same community. Sawyer (22) showed that crocidolite fibers can remain suspended in the air up to 3 days in a home environment and that, in these circumstances, levels of more than 100 fibers/ml have been reported following the shaking of dusty clothes (with crocidolite).

In summary, the mechanical fragmentation of gravel induced by the passage of trains resulted on the one hand in release of chrysotile fibers and, on the other hand, in release of crocidolite fibers because of the abrasive action of the gravel on the underbody. The frequent passage of trains led to keep constant the airborne mineral fiber concentrations. Our subject was therefore exposed to inhalation of asbestos fibers during Task A and B for 7 hours/day (in the remaining hour, he was employed in Task C).

Mean is the more representative value of a distribution. It is often the only value reported to characterize the concentration levels of airborne substances in a given job. A same job, however, does not necessarily involve a substantial identity of exposure. Every worker is a special case because direction and speed of air, distance from sources, frequency and timing of task and other local factors could diversify the actual exposure to asbestos (10). Rather than confidence intervals, we applied correction factors to the average concentrations found in the literature to take into account the specific circumstances of exposure of the subject. For example, in reconstructing intensity of asbestos exposure during Task A and B, we reduced up to 10 times the concentration data reported in the literature because these activities were done outdoor and in order to take into account possible differences over time for chrysotile containing rocks in the ballast and/or rolling stocks having crocidolite on the underbody. The inaccuracy could not be high, since asbestos exposure estimated in our subject is in the range of concentrations found in areas with heavy traffic or in areas near asbestos industries (12).

Our patient with mesothelioma was exposed to multiple sources of asbestos. Which one of these could be the cause of the disease? The demonstration of the causal relationship cannot be solved by using dialectical acrobatics and oratory skills (23). “Proof of causation” is actually an oxymoron because it claims to ascertain what is not certain. Man is not able to identify with certainty the cause of an event, but can only attribute to each antecedent a degree of probability. The approach, therefore, could be to reconceptualize the “harm” – considering the “risk of harm” instead of the “actual material harm” – and to estimate for each source of exposure a proportionate contribution to disease risk (7).

The latter approach calls for a probabilistic model. It is recognized from decades that cumulative exposure to asbestos and time elapsed since first exposure (TSFE) are related to mesothelioma incidence. Based on the multistage model of tumors, Newhouse and Berry (17) suggested that the risk of mesothelioma increased as power of TSFE. Although this model was supported by some authors (19), others (6) suggested that the increasing trend in the incidence of mesothelioma with TSFE was not monotonic and that incidence began to decline several years after the first exposure. Berry (4) proposed a modified model introducing a factor representing the removal of asbestos fibers from the lung. In a more recent study (2), the modified model fitted data better than the traditional model for pleural mesothelioma ($p=0.02$) but not for peritoneal mesothelioma ($p=0.22$). The different trends for pleural and peritoneal cancer was probably due to the clearance of asbestos from the lung.

The US National Research Council (16) and Moolgavkar (15) have modelled further the relationship between risk, dose and time based on plausible hypotheses about the mechanisms of mesothelioma carcinogenesis. In our study we used the model of Price (20), derived from the models of multistage carcinogenesis of Peto (19), US National Research Council (16) and Moolgavkar (15). The effort of Price (20) to develop a model of shared responsibility for the victims of mesothelioma is a crucial step towards overcoming the traditional rigid opposition between existence and non-existence of a causal relationship. The rule of “more likely than not” in specific causality was introduced in civil or administrative contexts in Italy following the judgment of the “Corte di Cassazione" (High Court of Appeal), 16 January 2009. This was followed by several decisions of the "Sezioni Unite, Cassazione Civile" (United Civil Sections of High Court of Appeal), under which the causal relationship must be established according to the principle of "more likely than not" in the context of civil liability (24). Therefore, more and more often the "experts" will be called to use epidemiological evidence to prove causation through probabilistic tools.

Asbestos exposure throughout the working life of our subject was as low as 2 ff×years/cc (table 1). Nonetheless, the subject developed mesothelioma, probably because of the high content and the high carcinogenic potency of crocidolite that showed a major weight in risk apportionment (table 2).

Conclusions

We report on an uncommon source of occupational asbestos exposure and a scientifically based method to allocate mesothelioma risk among multiple exposures. This study could help to recognize mesothelioma as occupational disease in workers employed in the maintenance of the railway electrification system under the Italian National Railways.

CONFLICT OF INTEREST

The first author (GM) was commissioned as expert by a Public Prosecutor in a mesothelioma lawsuit to evidence the legal accountability for the disease.

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