National Institute of Occupational Safety and Prevention

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LABORATORY OF OCCUPATIONAL
EPIDEMIOLOGY AND HEALTH STATISTICS

THE NATIONAL MESOTHELIOMA REGISTRY (ReNaM)

(art. 36 of Legislative Decree 277/91)

<u>First Report</u>

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FOREWORD

The *raison d'être* of the Registry of Mesothelioma cases among the population may be summed up borrowing the terms used by William Farr in 1840 to explain the objectives of the establishment of the *Registrar General* in Great Britain:

> "It is easier to prevent than to treat diseases, and the first step towards prevention is the discovery of … the cause. The *Registrar* will recognise… these causes, measure their intensity… in the two sexes, for different ages and (identify) the influence of… occupation, place of residence, season… in generating diseases and causing death, thus improving public health".

The etiology of mesothelioma cases is relatively simple. Apart from the various forms of asbestos and high doses of *in situ* emissions, other causes are unknown (this greatly simplifies confounding controls in etiological studies). In the industrial society, for less than one quarter of persons contracting pleural or peritoneal mesothelioma, it is quite difficult to identify in the case history (providing it is accurately recorded) any previous exposure to asbestos, mainly in the workplace but also in the general or domestic environment. The risk of contracting this disease depends on the level of exposure and the period that has elapsed since the beginning of exposure. The association is valid for all forms of asbestos, and is 2-3 times greater for exposure to amphiboles than with chrysotile. There is no satisfactory mathematical model to describe the relationship between the level of exposure and the risk of mesothelioma (partly because of the difficulty in applying a model upon the occurrence of mesothelioma to persons exposed to asbestos – with relatively low concentrations - as a pollutant of the non-occupational atmosphere, such as in Casale Monferrato). Instead, it is generally accepted a model which correlates the risk of mesothelioma to the third power of the period elapsed since the beginning of exposure, ignoring the ten years prior to the diagnosis.

What will the ReNaM be used for? Firstly, for the identification of geographic non-uniformity and clustering of cases as a first step towards pinpointing the sources of exposure to asbestos. This procedure has already been tested with the use of mortality statistics for malignant tumours of the pleura, but compared with the ReNaM is much less powerful (because of the greater reliability of diagnoses vis-à-vis certifications on the cause of death, as well as the supplementing of recorded cases with their residential and professional history). Secondly, as

some years have passed since the cessation of all forms of mining, manufacture, trading and exporting of asbestos or asbestos-based products, it is important to have instruments to monitor the consequences of the ban imposed. Unfortunately, because of the latency of mesothelioma cases, we shall probably have to wait a little longer before being able to observe and quantify the beneficial effects of Decree Law 257/92.

The ReNaM, as a health surveillance instrument, helps in assessing the harmlessness of fibrous products now used in production as a replacement for asbestos, even if, on the basis of their properties, they are considered less harmful than the various forms of asbestos.

We should not underestimate the cultural contribution made by any form of pathology registration system which adopts high-quality methodologies, such as the one proposed by the ReNaM to regional operating centres. This helps not only to keep the level of professional competence in the registration phase, up to high standards, but also to create a basis of data to be used for scientific studies whenever any hypotheses on biological mechanisms of pleural and peritoneal carcinogenesis are developed (currently very little is known about the factors for individual susceptibility to asbestos carcinogenesis). Then, the way from the databases to the access to biological sample (and possibly to the creation of real banks of biological samples) may be quite short.

Finally, there is the clinical implication to consider. Although the prognosis of primary serosa tumours is currently very poor, it is likely that - as with other tumours - increasingly effective therapeutic protocols will be developed. The population-based survival estimate (one of the basic aims of cancer registries) will make it possible to monitor the occurrence of inequalities in the administration of the most effective protocols, in other words, preventing inequality with regard to access to therapies. This role, to eliminate social inequality in the health sphere, is one of the target pursued by our country’s health authorities at the start of the new millennium.

Benedetto Terracini

ABSTRACT

The origins of the National Mesothelioma Registry (ReNaM) may be found in art. 17 of Community Directive 83/477, which sets out that "*for Member States a registry shall be established for confirmed cases of asbestosis and mesothelioma*". Implementing a series of Directives protecting workers against risks deriving from exposure to physical, chemical and biological agents, including Directive 83/477, Legislative Decree 277 was promulgated in Italy on 15 August 1991. Art. 36 - "Cancer registry" - states that "*ISPESL establishes a registry of confirmed cases of asbestosis and asbestos-related mesothelioma*". The law provision refers to a subsequent Prime Minister's Decree implementing "*executive models and procedures*" for the ReNaM. This decree is not yet be promulgated.
ISPESL, aware of the fact that the incidence and forecasts of temporal trends for malignant mesothelioma in Italy place this neoplasia among those of priority interest in terms of primary prevention, has pursued a two-step strategy in recent years: firstly, elaboration of the draft executive decree and consequent presentation of this decree to the competent ministries and to the State-Regions Conference for its approval, and secondly, creation of an ad hoc information system which enables, even in the absence of precise legislative references, to record cases in a thorough and exhaustive manner conforming to fixed quality standards.
With reference to the establishment of the ReNaM, first of all the main objectives were fixed, namely estimate of the incidence of malignant mesothelioma cases in Italy, collecting information on past exposure to asbestos, impact and spread of the disease among the population and identification of unexpected or unknown sources of contamination. Secondly, the architecture of the information system was established. To ensure the thoroughness and quality of collected information it was decided to set up Regional Operating Centres (CORs) for the collection, implementation and filing of information, partly through active research, on all cases diagnosed or treated in the area of competence, with special reference to the definition of diagnosis and the possible history of asbestos exposure. A summary of the principal information pertaining to each recorded case is regularly sent by the CORs to ISPESL for the creation and updating of the ReNaM. The Institute, in addition to acquiring and processing the information received, activates "return" flows to CORs on the cases received. To ensure a level of homogeneity in the collection, definition and transmission of cases to ISPESL, the Institute, in conjunction with regional experts having a considerable experience in this subject, has drawn up operating Guidelines for defining reference diagnostic protocols and exposure to asbestos. For the latter activity a standard questionnaire

has been drafted, to be compiled directly by the patient, if still alive, or to any next of kin, for defining the type of exposure to asbestos using predetermined and uniform criteria. The Institute's Guidelines have been approved by a Technical Committee appointed within the ISPESL organisation, made up of pathologists, epidemiologists, clinicians, hygienists, representatives of CORs and of other interested public institutions; the Committee performs steering and liaison activities for all ReNaM activities. The Technical Committee, expired the first three-year term of office, is waiting for next reappointment.

On the basis of an agreement entailing the adoption of ISPESL reference standards, the Institute has acted in accordance with the CORs of Piedmont, Liguria, Emilia-Romagna, Tuscany and Puglia to set up a systematic and one-to-one information flows for the acquisition and update of cases recorded and defined in each regional area. These regions represent 31% of the Italian population in terms of resident population and 45% of all Italian cases in terms of mortality due to malignant tumours of the pleura.

ISPESL-COR collaboration has enabled to set up a database which, for the period from 1993 to 1996, includes 991 cases, 792 of which confirmed by histological diagnosis (around 80%) and 80 by cytologic diagnosis (a little over 8%). Of those cases with histological diagnosis, 747 are pleural malignant mesothelioma.

The mean age of cases is 64.5 ± 11 (std dev.); 47.3% of affected persons are below the age of 65 for all sites, and 46.6% for pleural mesothelioma; 568 cases refer to men, 221 to women, with a male-female ratio of 2.57:1 for those cases confirmed by histological diagnosis, and 2.72:1 for pleural mesothelioma only. Worthy of note is the unexpected presence of a large number of female cases.

The annual standardised incidence rate amounts to 1.09 per 100,000 inhabitants (1.61 men and 0.60 women) for all sites and to 1.03 for pleural mesothelioma (1.54 men and 0.54 women). The highest values have been recorded for men in Liguria (5.99 per 100,000) and in Piedmont (2.25 per 100,000).

Exposure to asbestos has been investigated and defined in over 55% of cases, while other cases are still to be studied. Of the 438 cases with defined exposure, 291 (66.4%) proved to be cases of “ascertained”, “probable” or “possible” occupational exposure. For each CORs this percentage varies from 53.1% to 79.5%. There are numerous cases of environmental exposure (9.1%, where homes are close to potential sources of contamination), followed by domestic exposure (3.9%, contamination is transmitted through the clothing of exposed workers) and “hobby-related” exposure (1.8%).

Considering occupational exposure, the sectors most at risk are confirmed as those traditionally associated with shipbuilding and dockyard activities and with the asbestos cement industry. A relevant percentage of cases were due to exposure in production sectors such as iron and steel, metal and mechanical engineering, plastic and rubber industry and the sector of hydraulic and thermohydraulic systems, but the evidence, even if well documented

in literature, does not appear to be as well established as the previous examples of exposure. The great “fragmentation” of the remaining cases in many other productive activities highlights the widespread and even ubiquitous presence of asbestos in our country. What also clearly emerges is the dangerousness of contamination sources still present as an environmental pollutant in numerous workplaces.
As far as the future is concerned, with the Regional Operating Centres of Lombardy, Marche, Sicily, Veneto, Basilicata and Campania commencing or about to commence operations, we expect to consolidate and implement existing flows and to encourage the start-up of similar initiatives in the rest of the country.

PART ONE - FRAME OF REFERENCE

GENERAL ASPECTS

Malignant Mesothelioma

Malignant mesothelioma is a primary tumour of the mesothelial cells that arises most frequently from serosas of the pleura and peritoneum and, more rarely, of the pericardium and the tunica vaginalis of the testicle [1].

The diagnosis is complex from a clinical viewpoint since it is not easy to distinguish between primary tumour and the metastasis of other cancers [2], and from a morphological stance, since malignant mesothelioma may be of an epithelioid type, sarcomatoid type or mixed types [3].

Malignant mesothelioma is contracted from inhaling asbestos fibres. Recent studies suggest that there is no evidence of an exposure threshold below which risk is absent [4]. Till now no other causes for this disease have been found, apart from ionising radiation [5]. Recently the presence of virus SV40 DNA has been found in mesothelial cells [6] but their etiological significance has not yet been studied [7].

Since the appearance of mesothelioma is practically always associated with asbestos exposure, this disease is considered as a “sentinel event” indicating past exposure to asbestos [8].

It is assumed that asbestos behaves as both an initiator and promoter, even though in some cases the role of promoter is emphasised. The risk of mesothelioma depends on the time elapsed since the first exposure, the type of fibre and the intensity of exposure [9] [10].

Estimates of the frequency of past exposure to asbestos in cases of pleural mesothelioma vary in literature between 75% and 80% [10] [11] [12] [13]. Most cases of professional exposure are observed in persons aged over 65. Below the age of 45 and for women in general, there are more frequent cases of environmental or para-occupational exposure [14] [15] [16].

The median latency period is very long, and has been estimated to be around 32 years for cases with occupational exposure [17]. An important variability of the latency period has been discovered for various occupational groups [18].

Since the cumulative threshold dose below which the possible carcinogenic action of asbestos can not be defined, a slight and short exposure may cause malignant mesothelioma [9] [4].

Recent studies state that the “natural level” of mesothelioma cases, in the absence of asbestos exposure, may be equal or below 1 or 2 cases per year per million inhabitants [4] [19].

Exposure to asbestos

At the present time, following the banning of asbestos and promulgation of executive decrees regarding risk prevention, occupational exposure is limited to workers assigned to insulating/lagging activities, handling of waste containing asbestos and to the ordinary and extraordinary maintenance of plants or buildings where the asbestos is still present [20]. Productive sectors that in the past made an extensive use of asbestos in the production cycle and inside the plants were chiefly the shipbuilding industry, the asbestos cement production, the textile industry, the chemical and petrochemical industry, the iron and steel industry, the thermoelectric plants, the manufacture and maintenance of rolling stock and sugar-refineries.

Recently the CAREX study published an estimate of 350,000 workers exposed to asbestos in the industrial and construction sector in Italy for the period 1990-1993 [21], while ISPESL published a list of firms with a possible presence of asbestos, reconstructed in accordance with the productive sectors specified by the Presidential Decree of 8 August 1994 [22].

It has been calculated that asbestos has been utilised in 3,000 different ways in several industrial sectors [20]. In Italy the annual output of asbestos in the 1980s was between 100,000 and 130,000 tons [14].

The environmental contamination is caused by the release of fibres from materials containing asbestos owing to wear and tear, mechanical stress, accidental damage, maintenance and the action of atmospheric agents; these fibres remain suspended in the air or, when they are present as sediments, they rose with a great concentration in urban areas.

Past emissions have been identified from mines (in particular that of Balangero, now cast-off) and plants for the production of materials containing asbestos, stockpiling resulting from the clean-up of large-sized plants containing insulation for tubing and tanks, warehouses with asbestos cement roofs, buildings having surfaces sprayed with materials containing asbestos.

Mortality rates, incidence and forecasts in Italy and in the world

Mortality

In our country there were 998 deaths in 1994 (654 men and 344 women) owing to tumours of the pleura, with a standardised ratio (reference population: Italy 1991) of 1.28 per 100,000 inhabitants (Table 1). The regional distribution of these rates (Table 2) shows, for the period 1988-1994, a peak in Liguria (annual standardised ratio 3.66), followed by Friuli-Venezia Giulia (1.86) and Piedmont (1.99) [23]. Mortality rates from tumours of the pleura based on ISTAT data represent a good indicator of the number of mesothelioma cases in Italy [24].

Table 1. *Mortality from malignant tumour of the pleura in Italy (1988-1994)*
(Reference population: Italy 1991)

	Men		**Women**		**Total**	
Year	**Cases**	**Standard. rate. (x100,000)**	**Cases**	**Standard. rate. (x100,000)**	**Cases**	**Standard. rate. (x100,000)**
1988	487	1.47	267	0.73	754	1.12
1989	506	1.50	286	0.76	792	1.12
1990	527	1.54	302	0.79	829	1.16
1991	597	1.69	313	0.81	910	1.24
1992	589	1.67	354	0.88	943	1.27
1993	638	1.76	337	0.83	975	1.28
1994	654	1.76	344	0.83	998	1.29

Source: Di Paola M, Mastrantonio M, Carboni M, Belli S, De Santis M, Grignoli M, Trinca S, Nesti M, Comba P. *Exposure to asbestos and deaths due to malignant tumour of the pleura in Italy (1988-1994).* Istisan reports 00/9.

Table 2. Mortality from malignant tumour of the pleura in Italian regions (1988-1994) (Reference population: Italy 1991)

	Men		Women		Total	
Region	**Cases**	**Standard rate (x100,000)**	**Cases**	**Standard rate (x100,000)**	**Cases**	**Standard rate (x100,000)**
Piedmont	535	3.37	357	2.06	892	2.70
Val d'Aosta	4	0.99	4	0.92	8	0.96
Liguria	565	7.82	175	2.12	740	4.89
Lombardy	695	2.56	534	1.71	1229	2.12
Trentino	37	1.35	29	0.92	66	1.13
Veneto	283	2.03	164	1.05	447	1.53
Friuli-Venezia Giulia	182	4.07	49	0.93	231	2.46
Emilia-Romagna	280	1.79	130	0.75	410	1.26
Marche	94	1.66	49	0.86	143	1.25
Tuscany	267	1.89	137	0.89	404	1.38
Umbria	31	0.92	21	0.63	52	0.77
Latium	138	0.85	86	0.51	224	0.68
Campania	238	1.64	133	0.86	371	1.24
Abruzzo	42	0.91	27	0.59	69	0.74
Molise	8	0.63	4	0.31	12	0.47
Basilicata	9	1.82	16	0.87	25	1.33
Puglia	208	1.39	96	0.86	304	0.67
Calabria	50	0.80	44	0.72	94	0.76
Sicily	240	1.54	106	0.72	346	1.12
Sardinia	84	1.74	36	0.76	120	1.24

Source: Di Paola M, Mastrantonio M, Carboni M, Belli S, De Santis M, Grignoli M, Trinca S, Nesti M, Comba P. *Exposure to asbestos and deaths due to malignant tumour of the pleura in Italy (1988-1994).* Istisan reports 00/9.

Incidence

With reference to incidence data of mesothelioma cases (Table 3), Italian cancer registries, which cover around 15% of the Italian population [25], show 201 cases for Genoa (161 men and 40 women) in the five-year period 1988-1992 and 69 cases for Trieste (63 men and 6 women) over the same period. Standardised rates for male population (reference population: world 1988-1992) vary from 0.2 (per 100,000) for Latina to the highest rates for Genoa (5.0) and Trieste (6.4). The female population has much lower rates, with a maximum again in Genoa (0.9). The data for the latter two cities are among the highest in the world for both genders [25] [26]. The establishment of the Registry of Mesothelioma cases in Liguria in 1996 has pointed up the high incidence of pleural tumours in La Spezia [27].

Table 3. *Standardised incidence rates (per 100,000 inhabitants) of mesothelioma cases* (Reference population: world 1988-1992)

REGISTRY	Men	(SE)	Women	(SE)
Turin	**0.9**	0.17	**0.5**	0.11
Genoa	**5.0**	0.41	**0.9**	0.17
Varese	**1.4**	0.24	**0.4**	0.11
Padova	**1.2**	0.17	**0.4**	0.09
Trieste	**6.4**	0.84	**0.6**	0.25
Parma	**1.0**	0.25	**0.2**	0.09
Modena	**0.6**	0.16	**0.3**	0.11
Ferrara	**0.9**	0.41	**-**	-
Forlì-Ravenna	**1.3**	0.25	**0.4**	0.12
Macerata	**1.5**	0.54	**0.2**	0.17
Florence	**0.5**	0.12	**0.3**	0.08
Latina	**0.2**	0.13	**0.1**	0.1
Ragusa	**0.6**	0.26	**-**	-

Source: Zanetti R, Crosignani P, Rosso S. (eds): "Cancer in Italy. Incidence data from cancer registries". Il Pensiero Scientifico Editore, Rome 1997

Trends

With regard to future scenarios on the spread of malignant mesothelioma, Julian Peto et al. estimated through an age/birth cohort model, for six Western European countries (Great Britain, France, Italy, Germany, Holland and Switzerland), a number of male deaths due to mesothelioma of 5,000 in 1998, rising to 9,000 in 2018, before beginning to decline after that date [28]. For Italy an evaluation of the effects of cohort and births did not detect a decline for younger cohorts, suggesting further increases in deaths due to malignant tumours of the pleura in coming years [29] [30] [31]. In particular, Peto's study for Italy estimates 940 cases per year in the peak period for the spread of the neoplasia, likely between 2015 and 2019. These projections are in line with a previous estimate that gave a peak of 1,300 cases for Great Britain in 2010 [32]. Epidemiological studies conducted in other Western European countries confirm this hypothesis. For France the number of deaths for the period from 1996 to 2020 was estimated at about 20,000 men and 2,900 women [33]. As far as Holland is concerned, again on the basis of an age/birth cohort regression model, an estimate of 20,000 male cases over the next 35 years was predicted, with a peak in deaths of around 700 in 2018, dropping to roughly 450 cases in 2030 [34].

All of these analyses assume that the great use made of asbestos in Western Europe in the 1960s and 1970s led to intense exposure for men born in more recent cohorts (1946-1950 and 1951-1955).

The situation is different for those countries (e.g. United States) where the use of asbestos came at an earlier stage than in Western Europe. It appears that a peak in deaths due to mesothelioma has already been reached in the US, with a forecast of approximately 2,300 male cases prior to 2000 and a tendency to fall over the next 15-20 years up to reach about 500 deaths at the end of that period [35]. In the same way, in Finland the number of mesothelioma cases grew rapidly from 1975 to 1990. Incidence trends slowed down in the 1990s, and will probably continue to do so over the next decade. Basing forecasts on Finnish cancer registries, Karjialainen has estimated 40-50 new cases per year for men and 10-20 cases for women for the years around 2010 [36].

<u>The National Registry of Mesothelioma cases (ReNaM) in the current legislative context</u>

The Directive promulgated on 27 November 1980 (80/1107/EC) constitutes the first European framework legislation on the protection of workers against exposure to major chemical, physical and biological agents, including asbestos.

Five European directives issued between 1980 and 1988 were implemented in Italy on 15 August 1991 with the promulgation of Legislative Decree 277 [37] concerning the protection of workers against risks arising from exposure to physical, chemical and biological agents in the workplace, with special attention to lead, asbestos and noise. The new law introduced general concepts that were firmly established in the Community, such as risk evaluation, accumulated doses, threshold values.

In detail, on the basis of article 17 of Directive 83/477/EC, in which the first paragraph sets out that "for member States a registry of verified cases of asbestosis and mesothelioma shall be established", Legislative Decree 277 states in article 36 that "ISPESL shall set up a registry of confirmed cases of asbestosis and asbestos-related mesothelioma".

Due to the nature of the two pathologies in question, two separate registries would have to be established, with different management methods and information systems. Reference standards to be adopted in the ReNaM and in the information network should be fixed by law referred to a subsequent executive Prime Minister's Decree, which has not yet been promulgated. The lack of a law promulgation establishing a reference model has thwarted the actual application of the art. 36.

In these years ISPESL has in part got around this problem by drafting Guidelines [38] regarding reference standards for diagnoses and case histories and by developing, on the basis of selected operating models, collaboration with regional registration systems pre-existing in Italy. In particular, on the basis of specific agreements, adopting common methodologies and procedures, Piedmont, Liguria, Emilia-Romagna, Tuscany and Puglia, named Regional

Operating Centres (CORs), have established their own registries of mesothelioma cases and set up information flows relative to the acquisition and study of cases with ISPESL.
The Institute's actions to promote the initiative and set up a national system for monitoring mesothelioma, combined with the awareness and cooperation shown by all the regional organisations involved, are beginning to give results, and it is hoped that new collaboration relationships may rise and reach levels of established territorial experiences.

Why have a ReNaM?

In Italy, as in many other industrial countries, there is an ongoing epidemic of tumours caused by asbestos, the proportions of which are growing constantly. In particular, the frequency and temporal trends of mesothelioma cases have placed these cancers among the priorities of primary prevention [25]. There are a host of exposure risk situations and new at-risk categories are emerging with unexpected clarity, making it necessary to consider the emergence of mesothelioma as extensive and ubiquitous [39] [4] [15].
Furthermore, the epidemiological scale of asbestos-related mesothelioma cases is likely underestimated in Italy [39]: the high percentage of cases registered in regions, strongly motivated, mainly depends on a more accurate identification and registration of ongoing cases in those regions without ruling out particular exposure scenarios.
It is accordingly essential to record every new confirmed or suspected case and carry out suitable anamnestic analyses. In particular, it is important to set up a system of epidemiological surveillance: this entails the systematic and continuous collection of data to check and monitor exposure risk factors and associated harmful effects, as opposed to public health actions based on spasmodic reporting and *a posteriori* analyses [40].
Such a monitoring system for mesothelioma enables to assess the frequency, trends and reasons for the emergence of mesothelioma in the country, and constitutes a prevention tool of fundamental importance in deciding upon effective public health policies and for the optimal allocation of resources [41]. Of course, it is important to broaden the field of observation to a national level in a coordinated and standardised manner in all areas of the country at the same time, with the aim of improving our knowledge, strengthening the network of cooperation and disseminating information to more people.

Systems for recording cases of Mesothelioma in other countries

The first cases of mesothelioma correlated with asbestos exposure were published by Wagner in 1960, relative to South Africa and followed by further studies confirming this evidence in many countries. Afterwards, surveillance programmes focusing on asbestos-related occupational diseases were set up and legislation was introduced in accordance with the evolution of scientific knowledge, paying attention to monitoring programmes of lung-related occupational diseases. Finally in Europe a draft agreement was reached for the banning of

asbestos after exhausting talks with the most reluctant countries: Spain, Greece and Portugal [42].
In Great Britain, France, Germany and Holland, as well as in Australia and New Zealand, specific mesothelioma registries were created, while in the United States and Scandinavian countries, the same data have been recorded through the system of population-based cancer registries (PCRs).

Great Britain
The Registry of Mesothelioma cases, established in UK in 1967, is the most important part of Mortality Registries due to Special Pathologies (such as mesothelioma, asbestosis and hepatic angiosarcoma). Data have been collected by the Medical and Epidemiology Statistics Unit, which belongs to the Health Policy Division of the HSE (Health Safety Executive). These registries also contain information obtained from death certificates.
The main sources for the Registry of Mesothelioma cases are data on national mortality of the OPCS (Office of Population Censuses and Surveys) and the GRO(S) (General Registrar's Office for Scotland). The two offices send copies of death certificates to the HSE. Supplementary sources of information include cancer registries received via the OPCS from regional registries. These are used to complete and control the correctness of OPCS data. For each case is collected gender, area of residence at the time of death, last full-time occupation and site of mesothelioma (pleura, peritoneum, or unspecified). Up to 1993, in the case of insufficient information on a death certificate to complete a proper code, the ONS (Office for National Statistics) sent a medical inspector to the certifying physician for further information. This practice was suspended for deaths registered after 1993.
Annual data on deaths due to mesothelioma are published in the HSE Statistics Report. The annual number of deaths caused by mesothelioma in Great Britain has grown rapidly since 1968, going from 153 deaths in the first year of the Registry to 1,330 in 1997. The growth rate appears to have slowed down in recent years: in 1997 the number of deaths rose by only 2%, and in 1996 the number fell to 1%.
The number of female deaths has always been lower than the number of male deaths, and the male/female death ratio rose from 3:1 in 1974 to 7:1 in 1997, reflecting the quicker growth rate among men in that period.
Projections for mesothelioma cases given in previous versions of H&S statistics are currently being reviewed using the most recent available data.
The mortality rate for mesothelioma (per million inhabitants) for the three periods 1989-1991, 1992-1994 and 1995-1997 grew constantly, being respectively for men 29.57, 36.71 and 40.93 and for women 4.67, 4.98 and 5.77. Data for the two most recent periods are provisional [43].

France

In France, the idea of a national registry of mesothelioma cases was launched in 1975, but this registry was created only for five "departments" and two regions. In January 1998 the "Registry of mesothelioma cases" was turned into the National Mesothelioma Surveillance Programme (PSNM), partly funded by the Department of Labour Relations and partly by the General Health Directorate of the Ministry of Employment and Solidarity [44].

The PSNM currently covers the population of twenty departments in France (out of a total of about 90), corresponding to about 15 million inhabitants, including 4 million inhabitants from high-risk zones. The programme sets out to estimate the incidence of mesothelioma in France, starting out from the exhaustive recording of cases of pleural mesothelioma [45].

The sources selected for the reporting of mesothelioma cases are pathologic anatomy laboratories and clinics (pneumologists, thoracic surgeons, oncologists, etc.). Cooperation with the national pathologies insurance fund is being planned in order to encourage the participation of companies' physicians in reporting cases. A procedure for the confirmation of the histological diagnosis (experience of the Mésopath group, French College of pathologists, mesothelioma specialists) is applied to each case. A comparison of incidence data with mortality data from the national registry of death cases (SC8 INSERM) will provide an estimate of the national incidence of mesothelioma and its evolution over time.

In addition to incidence analysis, the PSNM sets out to look into the etiological aspects of mesothelioma, studying the risk of mesothelioma attributable to asbestos exposure both inside and outside the workplace, as well as potential risk factors (other fibres, ionising radiation, SV40 virus, other industrial carcinogens).

The estimated number of cases in 1998 for the 17 departments included in the initial study, using data from the FRANCIM network, was 112 cases. The number of cases notified in 1998, now in course of diagnostic confirmation, was 128. Based on these results, the incidence rate in 1998 in the PNSM geographic zone, including both men and women, was 1.18 per 100,000 inhabitants (CI 95% [0.97;1.38]). The gender ratio was 5:1 in favour of men. The average age of notified cases was 71 for men and 72 for women [45].

It is generally accepted that the incidence of mesothelioma in industrial countries has risen by 5-10% per year from the 1950s onwards. As far as France is concerned, the FRANCIM network of French cancer registries estimates an increase of more than 25% every three years from 1979 to 1990. [44].

The incidence of mesothelioma in France is relatively low compared with other industrial countries, but this difference, due to a later use of asbestos in France, is going to diminish because the incidence is constantly rising while in other countries the trend is slowing down. Thus there is likely to be an increase in the annual number of cases until 2010-2020 [44].

Germany

The German Registry of Mesothelioma cases was created in 1987 by the Institute of Pathology of the Ruhr University Hospital of the University of Bochum, supported by the German Federation of Commercial Professional Associations (Sankt Augustin) [<www.uv.ruhr-uni-bochum.de>].

The project deals with the morphological, epidemiological, experimental and medical-legal issues regarding pulmonary and pleural diseases caused by asbestos (asbestosis, mesothelioma, bronchial carcinoma caused by asbestos). The Registry acquires documentation at a central level, registries and assesses the mentioned pathologies. Macroscopic, microscopic, histochemical and immunohistochemical tests are performed on samples sent by the various institutes of pathology of the old and new regions of the Federal Republic of Germany, as well as by professional associations.

It is not possible to have a picture of national incidence of the pathology, since only partial data have been published, such as the recording of peritoneal mesothelioma cases for the period 1992-1998 [46] and some incidence data of occupational tumours in Germany [47].

Holland

In Holland the Netherlands Mesotheliomenpanel was created in 1969 by the Dutch Cancer Institute.

Using data from the Eindhoven Cancer Registry, studies have been conducted on incidence and survival rates for malignant mesothelioma in the southern part of the Netherlands, from 1970 onwards [48]. It is assumed that asbestos exposure in this area has been limited. Most mesothelioma cases were for the pleura (119 cases, 88%) as compared with 15 cases (11%) for the peritoneum and 2 cases for the tunica vaginalis. Compared with other European countries, the incidence rate for the southern part of the Netherlands was lower in the second half of the 1980s. Between 1975 and 1994, incidence rates for pleural mesothelioma (taking age into account) have doubled (from 10 to 19 per million persons/year for men and from 2.4 to 3.8 for women); while for peritoneal mesothelioma remained constant. The relative general survival rates for 6 months, 1 year and 3 years remained at 68%, 42% and 8% respectively. The incidence rate for men was four times women's one. The incidence of mesothelioma in the southern part of the Netherlands will probably remain low [48].

Finland

In Finland there is no specific registry of mesothelioma cases, but this disease is included in the Cancer Registry. Data are compared with the Finnish Registry of Occupational Diseases. Combining the yearly statistics of the two Registries, it is possible to evaluate incidence trends for mesothelioma as an occupational disease. The registration system is practically comprehensive. In addition to reports sent by occupational safety authorities, the Registry of

Occupational Diseases is notified of each new case reported as an occupational disease to insurance companies, regardless of the decision taken to grant any indemnities. The incidence trend appears to have slowed down from the 1990's onwards [36].

Sweden

In Sweden there is no specific registry of mesothelioma cases. Such cases are identified through the Swedish Cancer Registry. In Sweden the first laws governing the use of asbestos were introduced in 1964, and in the mid-1970s the importing of raw asbestos was drastically cut. In 1995 about 80 cases of pleural mesothelioma were attributed to occupational exposure to asbestos. In recent years incidence has grown by birth men cohort. The incidence is a lot higher for men born between 1935 and 1944, compared with men born in previous years. At the present time, there are no results to prove that preventive measures have reduced the risk of contracting pleural mesothelioma. The long latency period indicates that the effects of preventive measures in the 1970s will be assessable only around the year 2005 [49].

Denmark

A Danish study to identify cases of pleural mesothelioma for the period 1983-1990 made use of the Danish Cancer Registry (there is no specific mesothelioma registry in Denmark). The data thus obtained were crosschecked with the Registry of Occupational Pathologies and with the registries of the National Agency for Industrial Accidents. The clinical records of patients not included in the Registry of Occupational Pathologies were requested from hospitals, and occupational exposure levels were assessed. The frequency of cases of pleural mesothelioma rose from 43% in the period 1983-1987 to 53% for the period 1988-1990 [50].

United States

Following the introduction of OSHA (Occupational Safety and Health Act) legislation in 1970, responsibility for the collection of statistics on occupational diseases and accidents was delegated to the BLS (Bureau of Labour Statistics). The BLS's annual Review, drafted in cooperation with participating public agencies, is a collection of data from a sample of around 250,000 industrial plants per year. Practically all private companies are included. From 1992 the review was broadened, enabling a more detailed classification of respiratory pathologies [Work-related Lung Disease Surveillance Report – 1999. Division of Respiratory Studies – NIOSH. Available from Website <www.cdc.gov/niosh/publistd.html>].

There are a number of data sources, from the Annual Survey of Occupational Injuries and Illnesses of the BLS to the Multiple Cause of Death Data, the National Hospital Discharge Survey, the Occupational and Environmental Disease Surveillance Database and the specific Sentinel Event Notification Systems for Occupational Risks (SENSOR) of the NIOSH.

Mesothelioma cases are not recorded in a separate section, thus there is a limited possibility to assess the specific disease. Malignant tumours of the pleura led to around 400 deaths in 1968. The number rose above 500 in 1984, and peaked at over 550 deaths in the period 1989-1992; from 1993 to 1996 there was a decline in trends [Work-related Lung Disease Surveillance Report – 1999. Division of Respiratory Studies – NIOSH. Available from Website <www.cdc.gov/niosh/publistd.html>].

Australia

The Australian Mesothelioma Registry is kept by the Epidemiological Unit of the National Occupational Health and Safety Commission at Camperdown in the State of New South Wales. Australia has a very high and growing incidence rate. The Australian Mesothelioma Surveillance Programme started up in January 1980. For each reported case, a thorough reconstruction of the person's occupational and environmental history was required, on the basis of the direct evidence of the patient or any next of kin. In January 1986 a new, less detailed notification system came into force, using a brief questionnaire; only histologically confirmed cases are recorded. Crosschecks are regularly carried out with cancer registries and reports are published on annual incidence rates.

The tenth report (1998) of the Australian Mesothelioma Register [National Occupational Health and Safety Commission – The Incidence of Mesothelioma in Australia 1993 to 1995 – Australian Mesothelioma Register Report, 1998] includes data on cases notified to the registry and diagnosed in 1993, 1994 and 1995, about which full confirmation was obtained from all cancer registries. Studies of incidence rates in 1996, 1997 and 1998 are pending controls with these registries, but reports of cases for 1996, 1997 and 1998 totalled 463, 318 and 390 respectively (through November 1998).

Australia was a producer of asbestos and has one of the highest mesothelioma incidence rates in the world. Incidence is still rising and is expected to continue to grown for the next 10-20 years. In 1996 a study was conducted to examine past and future incidence rates for the disease in a given number of industries and occupations as a basis for estimating future trends. The occupational histories of a total of 3,758 cases of mesothelioma collected by two national sequential projects (Australian Mesothelioma Surveillance Programme (1979-1985) and Australian Mesothelioma Registry (1986-1995) have been coded by the authors. The mean latency between initial exposure to asbestos and diagnosis of the pathology proved to be 37.4 years for cases notified between 1979 and 1985, and 41.4 years for those between 1986 and 1995 [51].

New Zealand

The National Asbestos Registry was created in New Zealand in 1992 following the recommendation of the Asbestos Advisory Committee (created in 1990) to report to the Labour Ministry on the effects of the use of asbestos on health in New Zealand [52].

The Registry contains the reports of persons significantly exposed to asbestos, and is split up into two parts: the first part records those exposed to asbestos, while the second part lists those having contracted an asbestos-related disease.

Following an information campaign in March and April 1992, the increased interest in the problem produced a high response rate. Reports of exposure to asbestos came from individuals, trade unions, physicians, associations and large-sized firms. These data were collected in the Asbestos Exposure Registry. A Registry of Pathologies was also created for reports of persons contracting asbestos-related diseases, limited to cases reported by physicians, all cases of asbestos-related diseases, before being recorded, are checked out by experts of the Asbestos National Medical Panel.

Of the 554 cases of asbestos-related pathologies reported in the period March 1992 - October 1997, 96 (17%) proved to be cases of mesothelioma. The mean latency from first exposure was 42 years (range 12 -74) [52].

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THE NATIONAL REGISTRY OF MESOTHELIOMA CASES (ReNaM)

Aims of the National Registry

The establishment and management of the *National Mesothelioma Registry* has entailed the set up of an information system, designed as an organisational and working structure consisting of a number of interdependent parts working towards shared goals. On this basis, and in order to identify the requirements of the information system, the following aims were set:

- to estimate the incidence of malignant mesothelioma cases in Italy;
- to collect information on past exposure to asbestos;
- to evaluate the effects of the industrial use of asbestos in order to analyse the impact and spread of the pathology among the population and to plan preventive measures;
- to identify unexpected sources of contamination;
- to promote research projects on the relation between environmental exposure to asbestos and the emergence of mesothelioma.

Standard information contained in the Registry

On the basis of the above aims the standard information collected in the National Registry for each Mesothelioma case is:

- personal data of patient;
- cancer site;
- date and type of diagnosis;
- patient's work history;
- information on relatives, certainly or probably, exposed;
- information on plants for the production and/or manufacture of asbestos products located near the house;
- information sources.

Statistical collection units

The statistical collection units, conceived as the primary input of the procedure, are all cases of malignant mesothelioma of the pleura, peritoneum, pericardium and tunica vaginalis of the testicle, including suspected cases.

System architecture and Regional Operating Centres

The flow of information linked to the acquisition of mesothelioma cases and definition of exposure proceeds along a series of predetermined information channels through which it is possible to raise the informational value of elementary data obtained in the initial phase of the procedure. The system architecture provides for the role of *Regional Operating Centres*

(CORs) as a sort of link between the reporters of cases and the *National Institute of Occupational Safety and Prevention.* These Units act as a hub for information coming from different source archives and ensure the thoroughness and quality of this information. In five Italian Regions (Piedmont, Liguria, Emilia-Romagna, Tuscany, Puglia) the Regional Health Departments have already identified the CORs responsible for reporting mesothelioma cases and verifying past exposure to asbestos. CORs are preferably established within *Regional Epidemiological Observatories* or other epidemiological Services or through *Local Mesothelioma Archives, Population-based Cancer registries* or other similar structures already operational.
The activities performed by CORs are briefly as follows:

Acquisition, processing and filing of information
Since the coming into force of DPCMs (Prime Minister's Decrees), all sources with special interest - public hospitals and private clinics, university departments, pathologic anatomy services and institutes, local health authorities, national higher institutes, etc. - send to the CORs of the Region in which the available documentation pertaining to each case (including suspected cases) of malignant mesothelioma is located. In tandem with this passive activity, CORs conduct active research on cases from potentially suitable sources through the direct consultation of archives.

Diagnostic definition of cases
The relative rarity of malignant mesothelioma and the complexity of histological aspects make the diagnosis of such cases rather tricky. For this reason reference *Diagnostic protocols* have been drafted to permit, whenever possible, the standardised diagnosis of mesothelioma. A standard interpretative grid allows a breakdown of cases into classes or groups depending on the degree of diagnostic approximation. The application of a minimum admissibility criterion makes it possible to extrapolate confirmed cases in order to move on to the next phase, exposure definition to asbestos. At the same time, consistency controls have been fixed, i.e. criteria and procedures aimed at assessing diagnostic uniformity through a critical revision of the diagnoses received or recorded. In many cases CORs avail themselves of a local Panel of pathologists, which reviews histological studies.

Definition of asbestos exposure
The study of the patient's professional case history, together with information on lifestyle and residential history, is conducted in accordance with a specific protocol comprising the compilation of a standard questionnaire, for which the interviewer has been trained in advance. The interview is with the patient himself/herself (direct interview) or, having verified his/her unavailability, with a relative (indirect interview) that is able to supply

information on the subject's work and life history. Interviews with work colleagues from firms in which the person has performed his/her working activity may be of considerable interest. The supervisory authority of the National Health Service, which mostly is the Occupational Prevention Operating Unit, may be able to supply important information about the firms in question (possible site inspections or simple requests for information from firms) or possess (useful) data that can be used to analyse the information collected through interviews. CORs thus make use of the collaboration of local health and public hygiene structures and of occupational prevention, hygiene and safety services for the acquisition of data on the occupational and residential exposure of identified cases. The level of exposure is classified by an industrial hygienist who, depending on the content of documents and his own knowledge of productive sectors, has the duty to establish whether the working activity, personal life history or possible environmental conditions were the cause of asbestos exposure. Since the quality of information collected does not always allow to define exposure with absolute certainty, a reference standard has been drawn up to assess the presence (or absence) of asbestos exposure. This standard enables to assign each case to various levels of probability in relation to asbestos exposure, resulting from the combination between the information obtained by the interviewer and the knowledge of the hygienist. If the information acquired through the questionnaire does not permit a precise and unmistakable judgement about environmental or occupational exposure, a further phase of study is conducted. The opinion on the thoroughness and reliability of acquired information is verified through a process of revision and critical appraisal of the questionnaires compiled by CORs. The classification of occupational exposure sets three levels of probability (ascertained, probable, possible) so that the hygienist can form a judgement in all those situations in which the interviewee has not expressly declared to be exposed because either the composition of materials or products used during his/her working life was not perfectly known, or information is not backed up by details useful to define the exposure. This usually happens when a person other than the patient is responding. In some historical periods and in particular productive sectors, knowledge about the utilisation of asbestos is quite advanced, but it should be pointed out that because of the extreme diffusion of this material, the discovery of the most unusual and peculiar use appears to be a never-ending process.

National Institute of Occupational Safety and Prevention (ISPESL) and Guidelines.

To deal appropriately with all the reports coming from CORs, the Institute has set up a procedure for the acquisition, processing and filing of information received. On the basis of criteria fixed by the Technical Committee, ISPESL elaborates and regularly updates *reference standards* for the detection and registration of cases. On this point, reference Guidelines have been drawn up for the implementation of the information network and for the diagnostic and anamnestic definition of cases. The Institute acts as a sorting office for information among

CORs in cases of health migrations (i.e. persons resorting to health centres operating in regions different from the residence) and, moreover, provides CORs with useful elements for reconstructing the working history of subjects through an agreement with social security Institutes. ISPESL also intends to encourage the work performed by CORs, promoting epidemiological studies on quantitative assessments of risks for exposed populations (both working and non-working), the identification of worker categories exposed to asbestos for whom exposure has so far gone unrecognised, and the identification of other agents that might be the cause of mesothelioma.
ISPESL, having acquired single regional flows, periodically sends to CORs a general summary of data present in the Institute's archives.

<u>The Technical Committee</u>
A *Technical Committee* has been set up within the *National Institute of Occupational Safety and Prevention (ISPESL)*, made up of pathologists, epidemiologists, clinicians, hygienists and representatives of CORs, trade unions and employers associations as well as of other public institutions. This *Committee* has the tasks of:

- establishing and updating standards for the acquisition of information *(procedures, information flows)*;
- determining processes for verifying the quality of diagnoses and working histories;
- drawing up plans for periodical checks on information procedures;
- fixing methods for the processing of information in accordance with the objectives to be achieved;
- defining the ways in which information is disseminated and its availability for further researches in compliance with confidentiality constraints.

In carrying out these tasks, an ongoing debate is conducted within the *Committee* on these issues, with the aim of making the best use of what has been learnt over time about the pathology and its correlation with asbestos exposure. Expiring the first three-year term of office, the Technical Committee is waiting to be reappointed.

PART TWO - EPIDEMIOLOGICAL DATA

– Statistical methods

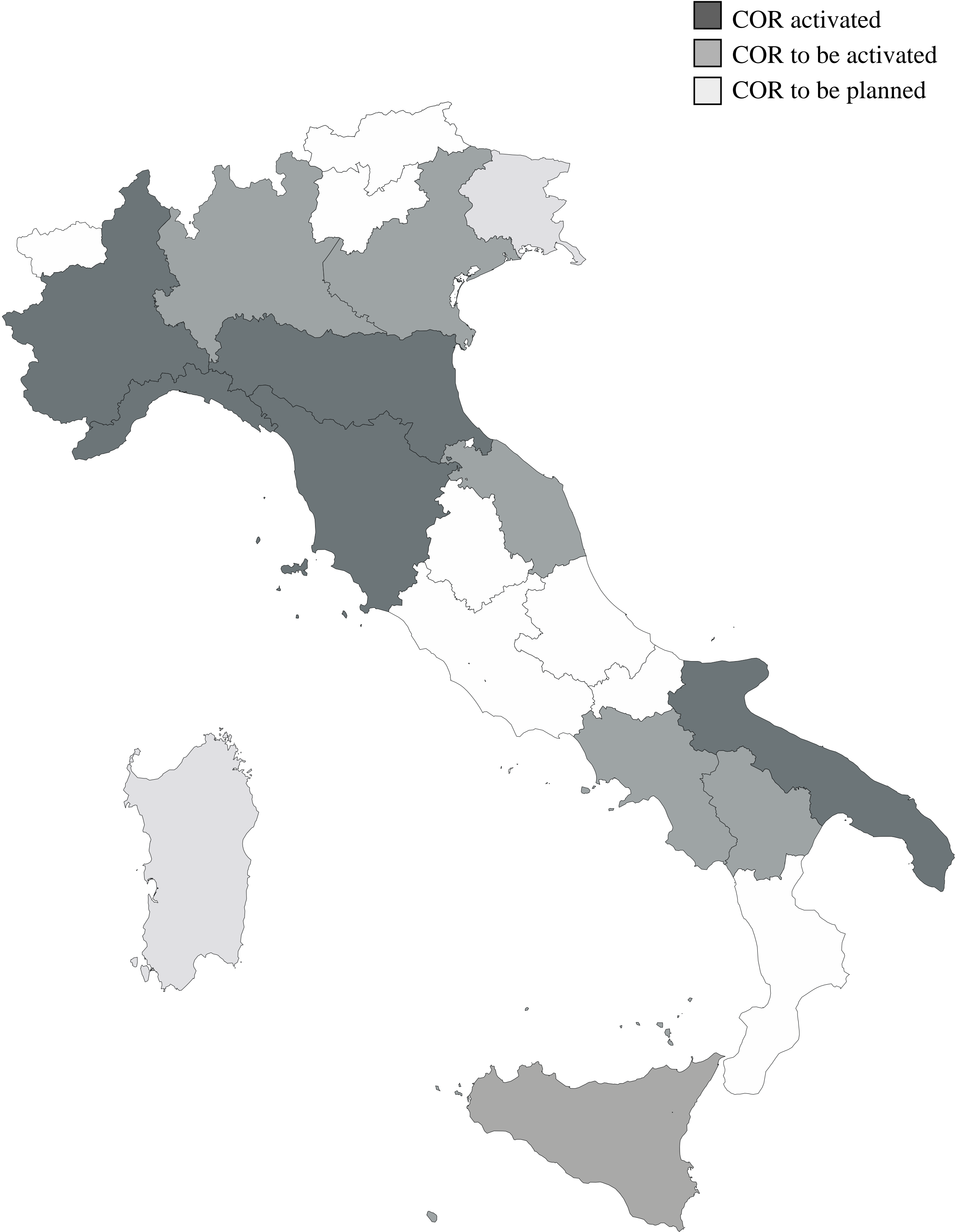
– Table I. absolute data by diagnosis and COR
– Table II. absolute data by site and morphology
– Table III. absolute data by year of incidence and COR
– Table IVa. absolute data by gender, age class and COR (all sites)
– Table IVb. absolute data by gender, age class and COR (pleura)

– Table Va. crude and standardised incidence rates by gender and COR (all sites)
– Table Vb. crude and standardised incidence rates by gender and COR (pleura)
– Table VIa. specific incidence rates by gender, age class and COR (all sites)
– Table VIb. specific incidence rates by gender, age class and COR (pleura)

– Table VII. exposure data: distribution by anamnestic code (AAMR)
– Table VIII. exposure data: distribution by economic sector

N.B.: For the COR of Liguria records began in 1994 for the municipality of Genoa only, in 1995 they were extended to the province of Genoa and in 1996 to the entire Liguria region. For the period 1994-1996 Liguria collected information only on pleural mesothelioma cases. The data of the COR in Emilia-Romagna for the period 1993-1995 refer almost exclusively to the province of Reggio Emilia, whereas for 1996 incidence is to be considered complete and referring to the entire Region. See Part four of this report for the specific survey characteristics of other regions.

DISTRIBUTION OF REGIONAL OPERATIVE CENTERS



THE DISTRIBUTION OF CASES

Statistical methods

For the years of incidence from 1993 to 1996, 991 cases of malignant mesothelioma were reported by CORs, 792 of which confirmed by histological diagnosis.

Table I shows the distribution of absolute values by diagnosis type and COR, Table II the distribution of cases with histological diagnosis by site and morphology (CIM code), Table III the distribution by year of incidence and COR for cases confirmed by histological diagnosis, indicating the year of reference. Table IVa shows the number of cases with histological diagnosis by age class, gender and COR. Age classes are ten-yearly apart from the first (0-44) and the final (74+); age is always defined as the age at the time of histological diagnosis. The number of cases for the entire period was 789, since in three cases the age of the patient at the time of the diagnosis was not available. Table Va shows the crude and standardised annual incidence rate (per 100,000 inhabitants) by gender and COR. The reference population is the Italian census in 1991; a direct standardisation method is adopted.

For the COR of the Liguria region, and consequently for all CORs, it should be noted that data elaboration began in 1994 only for the municipality of Genoa, being extended in 1995 to the province of Genoa and to the Liguria region in 1996. For the period 1994-1996 Liguria collected data on pleural mesothelioma cases only. It should also be noted that data collected by the COR of Emilia-Romagna for the period 1993-1995 referred almost exclusively to the province of Reggio Emilia, whereas since 1996 incidence should be considered as complete and referring to the entire Region. Specific rates by gender and age (Table VIa) are also obtained with reference to the resident population. Crude, specific and standardised rates were calculated separately for cases of pleural mesothelioma only (Tables Vb and VIb).

Expressed in symbols:

Crude rate = $T_{gr} = \frac{\sum_i n_i}{\sum_i p_i} \bullet 100.000$

Where n_i = number of cases in the age class period
p_i = resident population by age class
i = index of age class

Age specific rates = $T_i = \frac{n_i}{p_i} \bullet 100.000$

Standardised rates = $T_{st} = \frac{\sum_i (T_i \bullet \text{pop stand}_i)}{\sum_i \text{pop stand}_i}$

Where pop stand_i = reference population (Italian census 1991) by age class

Standard errors of standardised rates are calculated according to recommendations contained in *Cancer incidence in Five Continents* :

$$\text{S.E.} = \frac{\sqrt{\sum_i \left(\frac{n_i \bullet \text{pop stand}_i^2}{p_i^2} \right)}}{\sum_i \text{pop stand}_i}$$

Tables pertaining to the reconstruction of exposure refer to the set of data with histological diagnosis (792 cases). Table VII gives the distribution of cases by anamnestic code – as defined in ISPESL Guidelines – and by COR and the relative column percentages are related to the global number of cases and only to the number of cases where exposure has been defined.
For cases in which occupational exposure has been defined (ascertained, probable, possible), studies were conducted to ascertain the economic sector believed to be the source of exposure. Table VIII gives these sectors of economic activity in decreasing order. The exposure number does not coincide with the case number, since each case may be attributed to more than one type of occupational exposure.

Statistical Tables

Table I. Distribution of mesothelioma cases by diagnosis (year of incidence 1993-1996; all sites)*

Diagnosis	COR Piedmont	COR Liguria	COR Emilia-Romagna	COR Tuscany	COR Puglia	Total CORs	%
Histological diagnosis	316	148	123	104	101	792	79.92
Cytological diagnosis	36	21	13	8	2	80	8.07
Other diagnosis	-	65	10	29	15	119	12.01
Total	352	234	146	141	118	991	100.00

Table II. Distribution of mesothelioma cases by site and morphology (year of incidence 1993-1996; cases with histological diagnosis)*

	Malignant mesothelioma	Malignant fibrous mesothelioma	Malignant epithelioid mesothelioma	Malignant biphasic mesothelioma	Total	%
Site	**M90503**	**M90513**	**M90523**	**M90533**		
Pleura	255	47	340	105	747	94.32
Peritoneum	19	1	15	7	42	5.30
Pericardium	-	-	-	-	-	0.00
Tunica vaginalis of testicle	3	-	-	-	3	0.38
Total	277	48	355	112	792	100

Table III. Distribution of mesothelioma cases by COR and year of incidence (year of incidence 1993-1996; all sites; cases with histological diagnosis)*

Year of incidence	COR Piedmont	COR Liguria	COR Emilia-Romagna	COR Tuscany	COR Puglia	Total CORs	%
1993	80	-	16	21	21	138	17.49
1994	73	31	21	19	24	168	21.29
1995	83	54	31	28	26	222	28.14
1996	79	63	55	34	30	261	33.08
Total	315	148	123	102	101	789	100.00

* See N.B. page 36

Table IVa. Distribution of mesothelioma cases by COR, gender and age class (year of incidence 1993-1996; all sites; cases with histological diagnosis)*

	COR Piedmont			COR Liguria			COR Emilia-Romagna			COR Tuscany			COR Puglia			Total CORs		
Age class	**m**	**f**	**m+f**	**m**	**f**	**m+f**	**m**	**f**	**m+f**	**m**	**f**	**m+f**	**m**	**f**	**m+f**	**m**	**f**	**m+f**
0-44	11	2	13	3	-	3	3	3	6	1	-	1	3	2	5	21	7	28
45-54	37	24	61	10	5	15	9	7	16	15	2	17	5	4	9	76	42	118
55-64	55	29	84	27	4	31	28	10	38	25	6	31	33	10	43	168	59	227
65-74	62	31	93	52	12	64	27	13	40	30	9	39	24	8	32	195	73	268
75+	43	21	64	29	6	35	15	8	23	11	3	14	10	2	12	108	40	148
Total	208	107	315	121	27	148	82	41	123	82	20	102	75	26	101	568	221	789

Table IVb. Distribution of pleural mesothelioma cases by COR, gender and age class (year of incidence 1993-1996; cases with histological diagnosis) *

	COR Piedmont			COR Liguria			COR Emilia-Romagna			COR Tuscany			COR Puglia			Total CORs		
Age class	**m**	**f**	**m+f**	**m**	**f**	**m+f**	**m**	**f**	**m+f**	**m**	**f**	**m+f**	**m**	**f**	**m+f**	**m**	**f**	**m+f**
0-44	11	2	13	3	-	3	1	2	3	1	-	1	3	2	5	19	6	25
45-54	36	21	57	10	5	15	9	6	15	15	2	17	4	4	8	74	38	112
55-64	49	27	76	27	4	31	24	8	32	25	4	29	31	10	41	156	53	209
65-74	57	26	83	52	12	64	25	13	38	30	9	39	24	8	32	188	68	256
75+	43	19	62	29	6	35	15	6	21	10	2	12	10	2	12	107	35	142
Total	196	95	291	121	27	148	74	35	109	81	17	98	72	26	98	544	200	744

* See N.B. page 36

Table Va. Crude and standardised annual incidence rate (x 100,000) (cases with histological diagnosis; year of incidence 1993-1996; all sites; direct standardisation method; reference population: Italy 1991 and world WHO)*

	COR Piedmont				COR Liguria				COR Emilia-Romagna				COR Tuscany				COR Puglia				Total CORs			
	m	**f**	**m+f**	**SE**	**m**	**f**	**m+f**	**SE**	**m**	**F**	**m+f**	**SE**	**m**	**f**	**m+f**	**SE**	**m**	**f**	**m+f**	**SE**	**m**	**f**	**m+f**	**SE**
Crude annual incidence rate	2.50	1.21	1.83	*0.10*	7.75	1.55	4.48	*0.37*	1.08	0.51	0.79	*0.07*	1.20	0.27	0.72	*0.07*	0.95	0.31	0.63	*0.06*	1.77	0.64	1.19	*0.04*
Standardised annual incidence rate (Italy 1991)	2.25	1.08	1.64	*0.09*	5.99	1.19	3.44	*0.14*	0.90	0.44	0.67	*0.06*	1.01	0.23	0.62	*0.06*	1.11	0.37	0.73	*0.07*	1.61	0.60	1.09	*0.04*
Standardised annual incidence rate (world)	1.53	0.67	1.06	*0.06*	3.86	0.69	2.07	*0.09*	0.61	0.29	0.43	*0.04*	0.69	0.13	0.40	*0.04*	0.74	0.24	0.47	*0.05*	1.08	0.37	0.69	*0.02*

Table VIa. Age specific annual incidence rate (x 100,000) (cases with histological diagnosis; year of incidence 1993-1996; all sites)*

	COR Piedmont			COR Liguria			COR Emilia-Romagna			COR Tuscany			COR Puglia			Total CORs		
Age class	**m**	**f**	**m+f**	**m**	**f**	**m+f**	**m**	**f**	**m+f**	**m**	**f**	**m+f**	**m**	**f**	**m+f**	**m**	**f**	**m+f**
0-44	0.23	0.04	0.14	0.36	0.00	0.18	0.07	0.07	0.07	0.03	0.00	0.01	0.06	0.04	0.05	0.11	0.04	0.07
45-54	3.14	2.01	2.57	4.50	2.09	3.25	0.86	0.65	0.75	1.61	0.21	0.89	0.58	0.44	0.50	1.79	0.96	1.37
55-64	5.02	2.46	3.69	12.20	1.59	6.55	2.80	0.93	1.83	2.85	0.63	1.70	4.29	1.15	2.63	4.24	1.36	2.74
65-74	8.90	3.43	5.81	32.09	5.47	16.78	3.62	1.39	2.38	4.46	1.08	2.59	4.58	1.25	2.76	6.96	2.07	4.23
75+	8.73	2.32	4.57	25.89	2.77	10.64	2.95	0.92	1.67	2.38	0.38	1.12	2.99	0.40	1.44	5.66	1.22	2.85
Total	2.50	1.21	1.83	7.75	1.55	4.48	1.08	0.51	0.79	1.20	0.27	0.72	0.95	0.31	0.63	1.77	0.64	1.19

* See N.B. page 36

Table Vb. Crude and standardised annual incidence rate for cases of pleural mesothelioma (x 100,000) (cases with histological diagnosis; year of incidence 1993-1996; direct standardisation method; reference population: Italy 1991 and world WHO)*

	COR Piedmont				COR Liguria				COR Emilia-Romagna				COR Tuscany				COR Puglia				Total CORs			
	m	f	m+f	SE	m	f	m+f	SE	m	f	m+f	SE	m	f	m+f	SE	M	f	m+f	SE	m	f	m+f	SE
Crude annual incidence rate	2.35	1.07	1.69	*0.10*	7.75	1.55	4.48	*0.37*	0.98	0.43	0.70	*0.07*	1.19	0.23	0.69	*0.07*	0.92	0.31	0.61	*0.06*	1.69	0.58	1.12	*0.04*
Standardised annual incidence rate (Italy 1991)	2.12	0.96	1.52	*0.09*	5.99	1.19	3.44	*0.14*	0.81	0.37	0.59	*0.06*	1.00	0.20	0.59	*0.06*	1.06	0.37	0.71	*0.07*	1.54	0.54	1.03	*0.04*
Standardised annual incidence rate (world)	1.44	0.59	0.98	*0.06*	3.86	0.69	2.07	*0.09*	0.53	0.24	0.37	*0.04*	0.69	0.12	0.38	*0.04*	0.7	0.24	0.45	*0.05*	1.03	0.33	0.65	*0.02*

Table VIb. Age specific annual incidence rate for cases of pleural mesothelioma (x 100,000) (cases with histological diagnosis; year of incidence 1993-1996)*

	COR Piedmont			COR Liguria			COR Emilia-Romagna			COR Tuscany			COR Puglia			Total CORs		
Age class	m	f	m+f	m	f	m+f	m	f	m+f	m	f	m+f	m	f	m+f	m	f	m+f
0-44	0.23	0.04	0.14	0.36	0.00	0.18	0.02	0.05	0.04	0.03	0.00	0.01	0.06	0.04	0.05	0.10	0.03	0.07
45-54	3.06	1.76	2.40	4.50	2.09	3.25	0.86	0.56	0.71	1.61	0.21	0.89	0.46	0.44	0.45	1.74	0.86	1.30
55-64	4.47	2.29	3.34	12.20	1.59	6.55	2.40	0.74	1.54	2.85	0.42	1.59	4.03	1.15	2.50	3.93	1.23	2.52
65-74	8.18	2.88	5.18	32.09	5.47	16.78	3.35	1.39	2.26	4.46	1.08	2.59	4.58	1.25	2.76	6.71	1.93	4.04
75+	8.73	2.10	4.43	25.89	2.77	10.64	2.95	0.69	1.52	2.16	0.25	0.96	2.99	0.40	1.44	5.61	1.07	2.74
Total	2.35	1.07	1.69	7.75	1.55	4.48	0.98	0.43	0.70	1.19	0.23	0.69	0.92	0.31	0.61	1.69	0.58	1.12

* See N.B. page 36

Table VII. Distribution of mesothelioma cases by COR and anamnestic code (AAMR) (year of incidence 1993-1996; all sites; cases with histological diagnosis)

		COR Piedmont			**COR Liguria**			**COR Emilia-Romagna**			**COR Tuscany**			**COR Puglia**			**Total CORs**		
AAMR Code	*Exposure*	*cases*	*%*	*% of defined cases only*	*cases*	*%*	*% of defined cases only*	*cases*	*%*	*% of defined cases only*	*cases*	*%*	*% of defined cases only*	*cases*	*%*	*% of defined cases only*	*cases*	*%*	*% of defined cases only*
1	**Ascertained occupational exposure**	26	8.2	32.1	55	37.2	49.1	24	19.5	38.1	40	38.5	46.0	25	24.7	26.3	170	21.5	38.8
2	**Probable occupational exposure**	5	1.6	6.2	17	11.5	15.2	10	8.1	15.9	7	6.7	8.0	16	15.8	16.8	55	6.9	12.6
3	**Possible occupational exposure**	12	3.8	14.8	17	11.5	15.2	2	1.6	3.2	16	15.4	18.4	19	18.8	20.00	66	8.3	15.1
4	**Domestic exposure**	12	3.8	14.8	-	-	-	3	2.4	4.8	-	-	-	2	2.0	2.1	17	2.1	3.9
5	**Environmental exposure**	22	7.0	27.2	8	5.4	7.1	1	0.8	1.6	-	-	-	9	8.9	9.5	40	5.0	9.1
6	**Hobby-related exposure**	4	1.3	4.9	-	-	-	-	-	-	1	1.0	1.1	2	2.0	2.1	7	0.9	1.6
7	**Unlikely exposure**	-	-	-	-	-	-	16	13.0	25.4	1	1.0	1.1	15	14.8	15.8	32	4.0	7.3
8	**Unknown exposure**	-	-	-	15	10.1	13.4	7	5.7	11.1	22	21.1	25.3	7	6.9	7.4	51	6.4	11.6
9	**Exposure to be defined**	235	74.4	-	36	24.3	-	60	48.8	-	17	16.3	-	6	5.9	-	354	44.7	-
	Total	316	100	100	148	100	100	123	100	100	104	100	100	101	100	100	792	100	100

Table VIII. Distribution of exposures by economic sector (year of incidence 1993-1996; all sites; cases with histological diagnosis and occupational exposure)

Economic sector	Exposures	%
Shipyard building	80	20.57
Construction and lagging work	40	10.28
Metal and mechanical engineering	32	8.23
Navy and shipping companies	32	8.23
Iron and steel industry	28	7.20
Asbestos cement industry	24	6.17
Railways and rolling stocks	19	4.88
Cargo handling and dockyard hands	18	4.63
Oil refineries and petrochemical industry	11	2.83
Rag sorting, recovery and repair of jute sacks	11	2.83
Sugar-refineries and other food industries	10	2.57
Rubber industry	10	2.57
Chemical industry	9	2.31
Hydraulic, thermohydraulic and heating systems	8	2.06
Handicrafts	8	2.06
Production and distribution of electricity and gas	8	2.06
Manufacture and repairing of transport equipment	7	1.80
Electric materials production and electricians	6	1.54
Transport	5	1.29
Manufacture of tiles and other construction products	4	1.03
Textile industry	3	0.77
Mining and Quarrying	3	0.77
Agriculture	2	0.51
Manufacture of glass	2	0.51
Other economic sectors	10	2.56
Total	390	100.00

Epidemiological data

Incidence

The data contained in the statistical tables give rise to many starting-points for discussion on the spread of mesothelioma cases in regions where active surveillance and registration systems are operative.

The first indicator that emerges from the tables is the proportion of cases confirmed by histological or cytological diagnosis. This indicator serves to validate the completeness and quality of data [1] for all types of tumours, and especially for diseases such as mesothelioma, which is difficult to diagnose. For all data in the national registry, 88% of cases were histologically or cytologically verified (80% if one considers only histological diagnosis) (table I). This percentage appears to be basically in line with that recorded for population-based cancer registries in Italy [1].

With reference to the morphology of 792 histologically confirmed cases, 355 cases were of the epithelioid type, while the number of biphasic (112) and fibrous (48) mesothelioma cases were considerably lower.

With regard to the site of the pathology, ReNaM data, after excluding Liguria data that limited its research in the period ’93-’96 to cases of pleural mesothelioma, show a high pleura/peritoneum ratio (14.3:1). In literature this ratio varies from 2.7:1 to 11:1 [2] [3]. In Hillerdal’s bibliographical review [4], on 4,710 published cases, a ratio of 9.89:1 was obtained.

The reference time period for the data given in this report (just four years) clearly prevents the formulation of exhaustive assessments of trends. Table III (referring to 789 cases for which the year of incidence was available) shows up the cases histologically diagnosed as malignant mesothelioma which amount in absolute terms to 138 cases in 1993 and 261 cases in 1996. As already mentioned in the statistical methods adopted, it should be remembered that the COR of Liguria commenced surveys in 1994 for the municipality of Genoa, extending them to the province in 1995 and to the entire region in 1996. Data for Emilia-Romagna are exhaustive for 1996, while for the period 1993-1995 information was chiefly concerned with the Province of Reggio Emilia (refer also to specific regional sections).

A significant aspect emerging from Tables IVa and IVb was the male-female ratio of cases, 2.57:1 for the entire set of histologically diagnosed malignant mesothelioma cases and 2.72:1 for pleural mesothelioma cases only. These results were close to the global data on incidence of population-based cancer registries (for which the ratio was 2.88:1) [1], but lower than mortality data due to malignant tumours of the pleura in the United States (3.13:1) [5].

The high number of female cases in the ReNaM appears to be evident if we compare it with the 1998/99 Health and Safety Statistics Report drafted in Great Britain by the Health and Safety Commission of the Government Statistical Service, which gives a male-female ratio for mesothelioma cases that grew from 3:1 in 1974 to 7:1 in 1997 [6]. The number of cases by age class is also of great interest. Mean age of the cases is 64.5 years (std dev. =11.0); 64.7 (std dev. =11.0) for the men and 64.1 (std dev. 11.1) for the women. Cases aging below 65 years constituted 47.3% (for all sites) and 46.6% (for pleural mesothelioma only). These figures were slightly higher than the figure of 43.3% recorded by population-based cancer registries but considerably lower than the percentage obtained from data contained in the 1999 Work-Related Lung Disease (WoRLD) Surveillance Report of the United States (74.2%) regarding deaths owing to tumours of the pleura [5]. The high percentage of non-elderly patients may in part be attributed to the fact that elderly patients do not frequently undergo histological tests.

The incidence rates showed in Tables Va, Vb, VIa and VIb must be evaluated in relation to case selection criteria. In particular, it must be recalled that only those cases confirmed by histological diagnosis have been considered for the calculation of rates. The standardised annual incidence rate for all CORs was 1.09 per 100,000 inhabitants (1.61 for men and 0.60 for women) for all sites and 1.03 for pleural mesothelioma (1.54 for men and 0.54 for women). The highest values for men were recorded in Liguria (5.99) and in Piedmont (2.25).

Exposure

Table VII reports, for each regional operating centre and for all centres taken together, the distribution of histologically diagnosed cases by the anamnestic code reported in accordance with ISPESL Guidelines [7]. This table shows that exposure is still being defined in a large number of cases (45% of the set of cases confirmed by histological diagnosis). In relation to the 438 cases in which exposure has been assessed, 291 (66.4%) were the result of occupational exposure (ascertained, probable or possible). For each COR this percentage varies from 53.1% to 79.5%. Domestic exposure is the main cause for the disease in 3.9% of defined cases (17 cases), while the percentage was higher for cases of environmental exposure (9.1%, 40 cases). Exposure due to "hobby-related" activities refers to 7 cases, 1.6% of those defined.

Table VIII shows, in decreasing order, the economic sectors where occupational exposure has been observed (ascertained, probable or possible) for those cases of mesothelioma, confirmed with the histological diagnosis. These sectors were identified locally by CORs as those in which exposure occurred. In some cases more than one instance of exposure to asbestos was identified and classified in different time periods.

With regard to the type of exposure detected and defined as occupational, it appears clear that a significant percentage of cases confirms what emerges from the existing literature on the activities most at risk. In a significant number of cases there are however productive sectors, such as the metal and mechanical engineering industry, iron and steel industry, rubber industry and the sector of hydraulic and thermohydraulic systems, that, even if documented in literature, they do not appear to be as badly affected as those of previous studies. In these cases, it will be necessary to carefully follow relative trends and values in future information flows. It will be even more important to follow the trends of a phenomenon currently confined and not well documented in the literature which pertains to persons exposed to asbestos during the performance of working activities believed generally to be not at risk.
In next section of this report, focusing on single regional operating centres, more specific evaluations are given as to the various sources of occupational exposure recorded in local territories.

The sector having the highest number of cases due to asbestos exposure was **shipyard building and repairing**. Cases of mesothelioma in this sector have been reported for the past 30 years [8] [9]. More recently, numerous cases of persons contracting malignant mesothelioma after prolonged occupational exposure in the shipyard building industry have been documented in Italy [10] [11] [12], Europe [13], United States [14] and Australia [15].
Reports of cases of mesothelioma among **dockyard hands**, the **Navy** and **shipping companies** have been published in Italy for the territory of Friuli-Venezia Giulia [22], Tuscany [23], Liguria [24] and Puglia [12]. The ReNaM exposure archives contain 50 reports for these sectors.

A large number of cases seems to be related to exposure in the **construction and building material trade**. Well known are the high risk levels for carpenters, tilers and laggers [16] [17], as well as for plumbers responsible for hydraulic insulation [18]. High risk levels for numerous jobs were reported in a study on the Latium area [19].
In heavy industries (**metal and mechanical engineering, iron and steel industry**) significant sources of contamination may be present. The professions described in literature with high risk level are foundry maintenance workers [20], welders and boiler engineers [21].
A wide spread level of exposure has been observed, as it might be expected, in the **asbestos cement production** sector. Many epidemiological studies have been conducted on this industrial activity. It is known the dramatic level of exposure present in the now abandoned plants of Broni [25], Reggio Emilia [26] [27] [28], Bari [12] and, above all, Casale Monferrato [29]. Different studies have recently reported statistically significant excess risks for workers in the asbestos cement industry in Poland for both men and women and similar risks are described for the lagging of factory roofs and for piping maintenance [30] [31].

The huge use of asbestos as an insulating material for **railway locomotives** from the 1950s to the early 1980s was responsible for the high frequency of mesothelioma cases among workers in the sector, employed by locomotive manufacturers, maintenance firms and the State Railways company, in particular for maintenance workers but also for engine crew [32] [33] [34] [35] [36].
Thermohydraulic workers also appear to be another category of workers professionally exposed to asbestos and at risk of mesothelioma. These workers have installed and serviced insulated heating systems and have used large amounts of gaskets. [37] [38].

The insulation of piping used to transport hot fluids in **sugar refineries** produced significant exposure to asbestos especially for plant maintenance workers [39] [40] [41] [42]. The ReNaM has recorded ten cases of mesothelioma from this sector.
In **oil refineries**, asbestos was used in heat exchangers for the heat insulation of boilers, in piping (in the form of "coppelle") and was mainly handled by maintenance, lagging, welding and boiler workers. Eleven exposures were recorded in the ReNaM from this sector. Several studies have proved significant levels of mesothelioma risk for workers in this sector [43] [44] [45], especially assigned to the plant maintenance workers. In petrochemical plants, too, sources of occupational exposure to asbestos may be present [46].
The first survey aimed to ascertain the presence of asbestos in **rag-sorting** activities, because of an epidemiological evidence, was conducted in the 1980s in the area of Prato (FI). This study highlighted in the raghouse of the zone, numerous recycled sacks that had held asbestos used as a raw material in asbestos cement production [47] [48]. It is still unclear the possible exposure to asbestos in the (non-asbestos) textile sector in Italy [49] [50] despite the significant number of cases in this sector. In the **chemical industry,** an intensive use of asbestos gaskets and lagging has been made [51], placing maintenance workers at risk [52]. Occupational exposure to asbestos in this sector was recently documented overseas in a study on the Bulgarian chemical industry [53].
The maintenance of **turbines and plants producing electricity**, often insulated with asbestos lagging, has caused a significant number of exposures, which led to numerous cases of mesothelioma of ascertained occupational origin.
With regard to the **rubber industry,** and in particular tyre makers, it is plausible and likely, that exposure to asbestos is associated with the use of industrial talc maybe contaminated by asbestos fibres [54] [55].

86% of cases with defined occupational exposure, present in the national mesothelioma registry, refer to the above-listed sectors which are widely confirmed by Italian and international literature. The ReNaM archives also contain cases refer to other working activities in which asbestos exposure has occurred.

In the **transport** sector haulage contractors (lorry drivers) transporting materials containing asbestos are indicated.
The release of asbestos fibres during the production, maintenance or removal of disk brake pads in the **motor vehicle repairing** sector and related activities is responsible for the cases of mesothelioma recorded among workers in this sector [56] [57] [58]. Similarly to the Australian mesothelioma registry [15], the ReNaM also contains cases of mesothelioma among workers in the car repairing sector.
Possible sources of contamination in the **agriculture** sector, worth to be investigated, are asbestos filters used for wine production and industrial talc used as a vehicle for pesticides and herbicides [23]. In the **manufacture of glass,** asbestos was used during shaping, finishing and painting operations [59] [60].
With regard to occupational exposure to asbestos in the **quarrying and mining sector**, despite the high exposure to asbestos during the mining of chrysotile from the Balangero mine, the number of mesothelioma cases among these miners was high but well below the one observed in the secondary asbestos industry. It is necessary to take into consideration the characteristics of fibres in dimensional and aerodynamic terms, as well as the use of amphibole asbestos together with chrysotile [61] [62] [63].
Worthy of note are the peculiar conditions of exposure in the town of Biancavilla (CT) at the foot of Mount Etna, where a quarry of inert materials for the building industry proved to be contaminated by amphibole asbestos. A number of cases significantly higher than expected was recorded in this zone [64] [65].
In the **handicrafts sector**, cases were recorded among carpenters, typographers, welders and electricians. In the United States a significant excess risk of mesothelioma was recorded for workers in the **electrical sector** in a mortality study on more than 31,000 workers dying between 1982 and 1987 [66].

There are also cases in the National Mesothelioma Registry to be attributed to occupational exposure (generally in relation to indirect contamination in the workplace) for non-classifiable situations in the sectors listed in table VIII. Such exposure will be studied in greater depth following the publication of this report.

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PART THREE - REGIONAL REGISTRIES

THE REGISTRY OF MALIGNANT MESOTHELIOMA CASES IN PIEDMONT

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Activities pertaining to the Malignant Mesothelioma Registry (MMR) of Piedmont started in 1990 and were later extended to the whole region.
The MMR, together with the other registries, constitutes the national ReNaM. The database of the registry is and has been used for etiological epidemiology surveys and analytical studies on asbestos-related pleural diseases.

Aims

Calculation of incidence

The Registry provides incidence rates of malignant mesothelioma of the pleura and peritoneum in Piedmont, with temporal and geographic analysis, with the aim of identifying excesses that can be used for analytical surveys. Registry data are also used for comparisons with the data of other national or international registries.

Identification of exposure

To discover situations that may have led to exposure to asbestos and the ways in which this may have happened, information regarding working and residential histories of subjects is collected through interviews with patients or next of kin.
When case histories show up occupational exposure to asbestos, the fact is reported to the Occupational Health and Prevention Services and to medical practitioners (hospital and family doctors) so that they can inform patients of the possibility to apply to the competent insurance institute (INAIL) for the acknowledgement of the occupational disease[1].
Reports of cases of residential exposure to asbestos are sent to the Public Hygiene Services.

Criteria for the inclusion of cases

The Registry includes all histologically diagnosed cases of mesothelioma among Piedmont residents from 1990 onwards. Cytologically diagnosed or clinically-radiologically diagnosed cases are kept separate in the analysis and in the calculation of incidence rates.

(1) this procedure is currently applied to cases identified in the hospitals of Turin and surrounding area, Alessandria, Biella and Casale. It requires an interview during hospitalisation and a very high frequency of direct assessments; the procedure is gradually being extended to other hospitals in Piedmont.

Methods to identify cases

Active detection of cases of malignant mesothelioma confirmed by histological diagnosis

The MMR includes histologically diagnosed cases among Piedmont residents. Cases are recorded by physicians trained in pathologic anatomy and collaborating with the MMR, working in all pathologic anatomy and histology departments of Piedmont hospitals, both public and private, and in some important centres outside the region. Cases are registered according to the diagnosis of the histopathological report. The following information is given in the report, supplemented by contacts with hospitals and municipalities of residence: personal data, detailed diagnosis, morphology, site of pathology and tests carried out, number and dates of examination, hospital and department, diagnosis service, immunohistochemical tests performed.

Comparison with existing data records

To verify the thoroughness of MMR studies and estimate the frequency of cases of possible m.m. not confirmed by histological diagnosis, a comparison is effected with Hospital Discharge Records (HDR). Hospital data are selected according to ICD code 9 of the discharge diagnosis defined as primary malignant tumour of the pleura (163) and peritoneum (158.8-158.9). This list is compared with that of malignant mesothelioma cases included in MMR archives. For HDR diagnoses not matching with the MMR, the relative hospital is asked for a photocopy of the front cover of the patient's clinical record and, if it is not a coding error, the clinical record itself.

Cases for which a histological examination is not available, but there is a likelihood of mesothelioma on the basis of clinical-anamnestic and radiological data, are included in the MMR but kept separate for the calculation of incidence rates.

Assessment of diagnosis quality

Diagnostic review of histological material

A panel of five pathologists has reviewed histopathological examinations to assess the quality of the diagnosis of malignant mesothelioma on a sample of 69 cases (residents in the former LHA 76 area - Casale Monferrato) in the period 1990-1993. Histological documentation was acquired for each case (slides coloured with haematoxylin-eosin and immunohistochemical dye), and reviewed independently by a pathologist.

Review of clinical records

Documentation is reviewed and assessed by MMR medical staff to verify whether the discharge diagnosis indicated on the HDR is confirmed, and the technical elements for the diagnosis.

Evaluation of exposure

All interviews[(2)] are examined by an industrial hygienist who, on the basis of available data, expresses an opinion on asbestos exposure - ascertained, probable or possible - and on its occupational or environmental origin.

Whenever it is deemed necessary for better defining exposure, further studies are conducted via new contacts with interviewed persons or requests for information from Occupational Safety and Prevention Services and Public Hygiene Services, to which a report on the examined case is sent.

Living status controls

For all cases included in the registry, controls were carried out on living status in 1999, acquiring this information from the registry offices of the municipalities of residence.

Filing of information

All information is recorded in an access-protected database using security procedures; paper-based materials are stored in archives kept under lock and key.

Results

In those cases in which an interview has been given, occupational exposures were prevalent.

In particular, a high percentage of cases was the result of working activities performed in the sectors of asbestos cement production and the rubber industry.

Asbestos cement industry

There were 8 cases in which at least one working period spent in the asbestos cement industry was recorded. Only one of these cases was female.

In the Casale Monferrato area of Piedmont, Italy's largest factory of asbestos cement products was operational from 1908 to 1985. This factory used both serpentine and crocidolite depending on the type of manufacture, leading to the onset of m.m. in both the cohort of exposed workers [1] and the general population [2]. For all eight cases included in this period of observation it was possible to reconstruct the working history in this industry and confirm it by controls on employment registration books. The period and duration of exposure vary from person to person: all cases had working periods between 1943 and 1961, while the mean duration of exposure was around 20 years.

The asbestos cement industry was thus confirmed as one of the main sectors of exposure and of risk for the population of Piedmont, especially for workers from the area of Casale Monferrato

(2) see note 1

The rubber industry

The eight cases, for which at least one working period in a rubber-manufacturing company was recorded, present some common characteristics that need to be discussed.

Four cases were concerned with maintenance work performed over long periods of time from the 1940s (one case), 1950s (one case) and 1960s (two cases), in one case in a company moulding industrial rubber parts, in the other three cases in tyre-making companies. None of the patients mentioned in the questionnaire the presence of asbestos-based materials in the company's heat-insulation equipment, yet it is certainly known that in the tyre firms in question the steam and hot water pipes were insulated with chalk/amosite (thick tubing) and with a braid of chrysotile (thinner tubing). Valve units and equipment (condensate collectors for instance) were moreover insulated with crocidolite mattresses. It is also well known that plant maintenance workers, electricians, mechanics and building workers were exposed: although they did not fit lagging, they removed or demolished it. In addition, two cases mention other circumstances of asbestos exposure: the use of covering during welding operations and, respectively, the demolition of extended areas of damaged asbestos cement.

In the other four cases, jobs were performed in various phases of the production cycle: one finisher and one storeman in tyre companies, and, two moulders using standing presses in two plants where sundry industrial parts were manufactured. Questionnaires do not provide sufficiently detailed information to permit direct interpretations. On the basis of more general information it is possible to assume a passive exposure to fibres released by insulating materials in a state of deterioration during maintenance/removal/re-fitting operations. These cases of exposure are known because they occurred in the tyre companies in question and in one of the two firms making industrial parts. It is also possible to assume an exposure to the contaminating tremolite of industrial talc. It is also known that in these plants talc was the main anti-adhesive agent up until the 1970s, being used in huge quantities and not subject to any control on the quality of talc entering the plant. What is more, there were small firms that separated the talc used for rubber waste and took it back to the factories that made use of it, but by doing so, they mixed the various lots of talc and added talc that was doubtless contaminated by serpentine. With regard to the fourth subject, who worked only for two years in an industrial parts maker, about which we have no direct information, the questionnaire refers to the use of very large amounts of talc, but also mentions a sure source of environmental exposure, with the patient's home situated close to a large-sized asbestos-using textile factory.

In addition to the two sectors in which the highest number of cases have been recorded, evaluations have also been made on cases from the carmaking and transport sectors.

Car building and repairing industry

In three cases, patients had spent at least one working period in the carmaking industry. One of them (a woman) has no apparent explanation from a professional or environmental viewpoint. The woman had been a social worker in an industrial group dealing with the construction of automobiles. In the other two cases, one patient had worked as a fitter of cylinder head valves, and had previously worked in a cast-iron foundry that produced bases; it is during that period that the patient was probably exposed to asbestos, in view of the extensive use made in foundries of materials containing asbestos to keep in heat. In the other case, the person in question worked as mechanic and was responsible for plant maintenance in an upholstery shop, but he was undoubtedly exposed to asbestos as a car mechanic and repairer (self-employed) from 1931 to 1936 and from 1940 to 1944. None of these cases thus appears attributable to the manufacturing activities involved in carmaking.

Transport

Two cases recorded at least one working period in the transport sector. The first patient had worked for a long time as self-employed haulage contractor. 95% of his activity was performed on behalf of the Eternit plant at Casale Monferrato. This offers ample opportunity for considerable exposure to asbestos. The second patient worked as coordinator of mechanical and fitting repairs on carriages and locomotives in a large-sized railway repair shop. In this case therefore it would be more appropriate to change the economic sector to 35.20 (ISTAT classification), even though the "repairing of rolling stock" does not actually appear in the list of relative works.

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THE REGISTRY OF MESOTHELIOMA CASES IN LIGURIA

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The Mesothelioma Registry of Liguria (REM) is a population-based cancer registry specialising in the study of the *incidence* and *etiology* of malignant mesothelioma of the pleura (MP). The REM collaborates with Liguria's health services, with the cancer registries of neighbouring regions and with the National Mesothelioma Registry (ReNaM). In order to identify the environmental and occupational settings most at risk of asbestos-related diseases and to assess occupational (direct and indirect), environmental, domestic and family exposure to asbestos, the REM submits a standard questionnaire to patients or next of kin. As from 1999 clinical and etiological information regarding mesothelioma of the peritoneum, pericardium and tunica vaginalis of the testicle is gathered and analysed.

Aims

The REM sets out to: 1) describe and study the incidence of mesothelioma in Liguria; 2) assess the etiology; 3) transmit specific information to the Liguria Region, LHAs and the ReNaM, operating through ISPESL (DL 277/91); 4) make national and international comparisons with similar cancer registries; 5) conduct ad hoc studies; 6) disseminate and publish results; 7) promote the primary prevention of asbestos-related diseases and pathologies caused by other carcinogenic agents present in the general and working environments.

Cases of interest

The REM collects and analyses demographic, clinical and etiological information about cases of MP diagnosed for residents in the Liguria Region. The entire regional population has gradually been covered by the registry, starting in 1994 with the Municipality of Genoa (estimated population at December 1995: 310,385 men and 348,731 women). In 1995 activity was extended to the entire province of Genoa, then in January 1996 to all inhabitants of the Liguria Region (estimated population at December 1995: 772,613 men and 856,989 women).

Methods to identify cases

The REM follows the procedures of data collection, evaluation, registration and verification as adopted by population-based cancer registries. Active research on cases is carried out by directly contacting diagnosis and treatment centres in the Liguria region. As from 1996 Hospital Discharge Records (HDR) are used to check the quality of activity performed and the completeness of collected data (passive research).

Methods to define exposure to asbestos

In addition to the personal and clinical data acquired from traditional population cancer registries, each patient (or next of kin if unavailable) that has been diagnosed with an ascertained or suspect MP is given a specific standard questionnaire in order to provide an accurate *etiological evaluation* of possible occupational, environmental, family and domestic exposures to asbestos to define exposure levels. When the interview was not possible, other sources of information were used (clinical records, INAIL, UOPSAL data, etc.).

Quality controls

Collected data are entered in three databases (DBIII) that separate personal data from clinical and etiological data to respect the privacy of patients (as per law 675/96). The three databases are periodically linked up, thanks to a specific statistical programme in order to carry out quality and completeness controls such as detecting possible input errors and validating the correctness of personal, clinical-diagnostic and etiological data. Finally, the correctness of codes used is checked.

Results

Incidence

Compared with previous periods (1986-1987 and 1988-1992: data from Genoa Cancer registry - RTG) the age-specific incidence rates, for MP in the Municipality of Genoa in the period 1994-1996, rose considerably for men aged over 70 considering both possible degrees of certainty and only ascertained or probable diagnosed cases. The situation among women is less serious and is correlated to the age of the patient at the time of diagnosis, but does not indicate a precise temporal trend. Geographically the highest number of cases was recorded in the province of Genoa, but the province of La Spezia had the highest incidence. In the period 1996-2000 approximately 120 new cases of pleural tumours per year were recorded in Liguria.

Demographic and clinical analysis

Of the 247 cases diagnosed in the period 1994-1996, 78% involved men, and the mean age at the time of diagnosis was 70 years. The diagnosis of mesothelioma was ascertained in 53% of cases, probable in 30% and suspect in 15%. 61% of diagnoses were histologically confirmed, with the epithelioid type being the most frequent morphology.

Etiological analysis

To define the possible role of occupational exposure, the professional histories of two groups of patients suffering from mesothelioma were compared. Members of the first group had *declared* a direct exposure to asbestos, while those of the second group had not. The *first*

working area, in order of time, in which occupational exposure to asbestos was *reported directly* by patients (or relatives) and confirmed by an ascertained or probable diagnosis of MP in the period 1994-1996, was *shipyards*, where 37% of MP patients worked, while 10% of MP cases worked in *cargo handling* at the Port of Genoa. Other working areas in which exposure to asbestos has been reported, with at least two patients per area, were maritime transport, oil refineries, the cement and brick industry, electricity, gas and water production and, with one patient per area, national defence, carmaking, the textile industry, the manufacturing industry, the chemical industry and others. Finally, roughly 8% of MP cases were recorded for both *metalworking* and *construction*. The time elapsing from the start of working activity and the diagnosis of pleural mesothelioma - induction and latency times – was around 40 years on average. This same period was used to identify the working area having the greatest etiological probability in the group of mesothelioma subjects who had *not* declared themselves to be *exposed* to asbestos or had claimed to be *non-exposed to* asbestos. This preliminary analysis led to the surprise finding that about 40 years prior to the diagnosis of MP the first three working areas having the greatest frequency of cases were the same for both groups of patients (exposed vs non-exposed). This appears to suggest the direct, indirect and unknowing role of occupational exposure to asbestos for a relevant percentage of patients.

Conclusions

Incidence

In Liguria, as in other European areas, incidence is more dramatic among men and grows steadily with age and over time. This appears to be attributable to the constant rise in the number of persons professionally exposed to asbestos in the 1960s. Our studies have confirmed that the mean latency period for the development of pleural mesothelioma is 30-40 years.

Exposure and latency

It has been observed that although there is an almost complete absence of areas having a high frequency of workers, the main working areas frequented by MP patients who did not expressly declare themselves to have been “exposed” were practically the same as those frequented by patients who did declare themselves to have been exposed to asbestos, both directly and indirectly. This fact leads us to believe that many patients had not been informed about the possible presence of asbestos in the places where they worked, and that potential exposure had been underestimated or forgotten, since it had occurred many years earlier. At the same time, it was clear that declaring oneself to have been exposed to asbestos was not an essential qualification for obtaining possible compensation.

Future studies, based on a larger number of cases, will give us the possibility of studying in greater depth specific sub-groups, such as persons below the age of 50 or women, of assessing

the effects of other variables such as socioeconomic level, different working activities, duration of employment, induction-latency time depending on the intensity of exposure, and also of defining the emergence of other asbestos-related pathologies in working and general environments in relation to the high incidence of mesothelioma cases.

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REGIONAL ARCHIVE OF MALIGNANT MESOTHELIOMA CASES - TUSCANY

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The Archive was established in 1988 and, methods for the identification of cases and the ways of collecting and analysing information on past exposure to risk factors have been changed over time. Modifications are the result of efforts made to gradually improve activities, but criteria and working methods have also been affected by some legislative decisions (regional and national) on national and Tuscan asbestos-related legislation.

The Archive is the result of coordinated work performed by the Epidemiology Unit of the CSPO and some Pathologic Anatomy centres in Tuscany (Pathologic Anatomy department of Ospedale Careggi, Florence, Policlinico Le Scotte, Siena, and University of Pisa) with the aim of setting up an epidemiological surveillance of this disease owing to its importance in the occupational sphere. It was decided that pathologic anatomy structures would report each new diagnosed case to the Epidemiology Unit. Each new diagnosis should be checked by a Panel of Pathologists; for each new case, information should be acquired on past exposure to risk factors typical of mesothelioma cases through interviews with the patient or next of kin, to be performed by staff of the Epidemiology Unit or of the Occupational Prevention Services of the local health authorities of Tuscany. An evaluation should be effected on the likelihood of asbestos exposure, in order to activate a medical-insurance procedures for the recognition of occupational diseases in confirmed cases of ascertained occupational exposure. Ever since its creation, the Archive has set out to provide the occupational prevention units of Tuscan health authorities with information on single identified cases in order to encourage workplace controls. It should be recalled that the Archive was created before that the law on the banning of asbestos had been promulgated.

Pathologic Anatomy centres, initially involved, encouraged the participation of other Pathologic Anatomy structures in identifying new cases and, in some structures, in undertaking controls on past diagnoses of secondary pleural tumours in order to identify possible false negative cases. Furthermore, some pathologic anatomy centres decided to make a systematic use of immuno-histochemical techniques for each new diagnosis of suspected mesothelioma and to undertake retrospective research on diagnosed mesothelioma cases (e.g. Pathologic Anatomy unit of Ospedale Careggi from 1970 onwards).

In 1994 a new classification of occupational diseases was approved (Presidential Decree 336 of 13 April 1994, published in Official Journal of 7 June), classifying mesothelioma (all sites) and lung tumours as professional disease if sufferers were exposed to asbestos in the workplace.

With Decision n° 102 of 8 April 1997 the Regional Council of Tuscany (Official Bulletin no. 51, 4 June 1997) set out an "environmental protection, decontamination, disposal and clean-up plan to protect against asbestos-related dangers", implementing art. 10 of law 257 of 27 March 1992 and the Presidential Decree of 8 August 1994. The text established that the aims of the Archive were: "to describe the magnitude of this pathology in the Tuscany Region; to develop a surveillance system in order to promote prevention activity, especially in those sectors still at risk of asbestos exposure; to pinpoint possible unknown types of exposure; to promote medical-insurance procedures in favour of persons suffering from mesothelioma; to contribute towards epidemiological research…".
Finally, on the basis of the 1997 Decision and art. 36 of Legislative Decree 277/91, prescribing the establishment within ISPESL of a registry of confirmed cases of asbestosis and asbestos-related mesothelioma to which the National Health Service offices were to transmit a copy of clinical data regarding each case of asbestosis or asbestos-related mesothelioma, the Tuscany Region chose the Epidemiology Unit of the CSPO as the reference regional structure for the collecting and registration of cases of ascertained or suspect mesothelioma and for the periodical sending of such data to ISPESL.
It was only from 1998, in conclusion, that the regional Archive of Tuscany commenced procedures for the systematic search, in conjunction with diagnosis and treatment centres of the Tuscany Region, for new cases of ascertained or suspect mesothelioma and for the use of information sources previously unavailable (in particular through the study of hospital discharge records, centralised and made available in the Tuscany Region only from 1998).

Completeness of cases 1993-1996

The new procedures set up in 1997 have indeed led to an increase in the number of mesothelioma cases and to the recovery of cases from previous years. Cases for the period 1993-1996 for instance, initially numbering 103 ascertained or suspected cases of mesothelioma (mostly based on histologically diagnosed cases), went up to 141 ascertained or suspected cases of mesothelioma through the recovery process (again most cases were histologically diagnosed). Controls on retrospective cases are ongoing.

Methods to identify cases

The activities of the archive consists in periodically contacting all pathologic anatomy centres operating in the Tuscany Region, asking them to send a report form for every new diagnosis of ascertained or suspected mesothelioma. Structures that store ICD-O diagnoses are requested to carry out controls every year; report forms are periodically sent to diagnosis and treatment centres (Thoracic Surgery and Pneumology hospital departments) for every new case of ascertained or suspected mesothelioma treated in hospital; all new diagnoses of ascertained or suspected mesothelioma from the Cancer registry of the province of Florence

are identified; hospital discharge records of residents in the Tuscany Region for pleural mesothelioma cases (code 163) and possible peritoneal mesothelioma (code 158) are examined every year; all deaths caused by pleural and peritoneal primary tumours for residents in the Tuscany Region are identified in the centralised Regional Death Registry.
Although for each new hospitalisation due to mesothelioma, the Health Management is asked for a copy of the clinical record, the clinical history of patients dying of pleural and peritoneal primary tumours is not studied in depth in the case of deaths not previously known, and deaths not backed up by clinical records are not included in the Archive.
In recent years moreover, it has not been possible to continue with the systematic support of a regional Panel of pathologists, and each new patient diagnosed with mesothelioma or a compatible disease is treated as a new case.

Methods to collect information and define exposure to asbestos

The Tuscany Archive, for all cases of identified mesothelioma, seeks to reconstruct possible past exposure to risk factors, obtaining replies to a specific questionnaire to be submitted to the patient or, if deceased, to any next of kin, by suitably trained interviewers.
Additional information may be obtained from other sources. In Tuscany, the structures, that mostly collaborate with the collection of additional data, are the Occupational Prevention Services of Tuscan health authorities.
The Italian Institute for Insurance of Occupational Accidents (INAIL) carries out studies on work risks for mesothelioma cases in which applications have been made for the recognition of an occupational disease. However, it has not been possible to ascertain from INAIL's regional structure in Tuscany which cases have to be reported, which cases have been investigated, whether cases, not known to the Archive, have been identified or whether investigation studies have produced a better definition of past exposure to asbestos.
With regard to anamnestic studies performed by Tuscany Registry, the periodical recovery (and not the systematic reporting) of new diagnoses by Pathologic Anatomy centres has the meaning, for past cases, that reports were received only when a large number of patients could no longer be interviewed owing to the death or serious illness of the patient.
The collection of information from relatives rather than from the patient himself can effect the quality of information collected, and for this reason, attempts are made to receive reports and timely interview patients suffering from ascertained or suspected mesothelioma.
Interviews are usually submitted by Archive staff, but in some areas of Tuscany by staff of PISLL Services. When the interview is conducted at the patient's home, the family doctor is informed and asked for his consent (naturally in addition to the patient's consent) to the interview.
If the identified person is deceased, a lapse of time is left (about 6 months) before contacting relatives, who are identified through local registry offices.

Archive staff have drafted several versions of the questionnaire, gradually producing the current version, which is the same proposed by ReNaM on the basis of the experience in Tuscany.
It should also be mentioned that in 1998 it was decided to review all interviews conducted and to proceed with a homogeneous reclassification of evidence of asbestos exposure. Reclassification activity and classification for each new case are performed by an industrial hygienist.
A copy of each new dossier (consisting of clinical data, the interview and the opinion on exposure) is sent to the PISLL Service where the patient resided, together with the request, if deemed necessary, to carry out studies in the workplaces where the patient had worked or to seek information on the firms where the person had worked. This working circuit may provide useful information for reconsidering the presence of past occupational exposure to asbestos and thus for reclassifying exposure.

Results

Identification of mesothelioma cases: methods and limits

Cases refer to the period 1993-96, during which time cases of mesothelioma were reported through a special contact with some Pathologic Anatomy centres in the Tuscany Region. As a result, even though checks had been carried out on the completeness of data for some areas of Tuscany for cases diagnosed by Pathologic Anatomy centres and some Thoracic Surgery departments, the cases collected for the years in question could have been underestimated, failing to identify all new diagnosed cases, especially in some areas of the region. Identification is facilitated by the existence of stored diagnoses in the various Pathologic Anatomy centres (when coded by site of the pathology and morphology). These were absent for the period in question in the Pathologic Anatomy centres of two areas having high mortality rates, Massa Carrara and Leghorn. The recovery process for diagnosed cases is still ongoing. Finally, for those years there were no stored hospital discharge records for Tuscan residents.
Patients contracting forms of mesothelioma other than pleural (i.e. peritoneal, pericardial or of the tunica vaginalis for men) probably resort to diagnosis and treatment centres other than Thoracic Surgery or Pneumology departments, and it is more difficult for the Archive to obtain reports of new diagnoses. Identification of such cases, in the absence of studies on hospitalisation records, has in the past been based on reports from Pathologic Anatomy centres. It is thus possible that the Tuscan Archive underestimates new cases of mesothelioma in general and of non-pleural cases in particular. Cases for the period 1993-1996 indicate the relative rarity of cases of peritoneal mesothelioma and suggest that, during the period in question, cases of mesothelioma of the pericardium or of the tunica vaginalis were not

diagnosed. In conclusion, incidence estimates for Tuscany given in this publication must be considered as purely indicative.
Presented incidence estimates refer only to cases of mesothelioma confirmed up by histological diagnosis (105 cases). As a consequence, the analysis does not include 36 cases of mesothelioma identified in the same period given a definition based on a cytological diagnosis or instrumental examinations (CAT and radiographs) or on death certification only. Not all histological diagnoses of mesothelioma have been checked by pathologists. Only one patient underwent a post-mortem examination. The percentage of histological tests supplemented by immuno-histochemical tests was 59% (for 43 patients the histological diagnosis was not confirmed by immuno-histochemical examinations). In Tuscany analyses of the fibre content of lung tissue for cases of deaths due to mesothelioma are few and unsystematic.
Interviews were conducted with patients or next of kin to assess exposure to risk factors (26 to patients, 60 to next of kin). The percentage of patients interviewed directly was not high (30%), suggesting that most reports of new cases are received when the patient can no longer be interviewed or is already deceased.

Anamnestic reconstruction of exposure to risk factors: methods and limits
In 22% of cases it was not possible to conduct an interview with the patient or any next of kin due to refusal to the interview or the absence of living relatives.
The interview scheme has changed over time, with the original questionnaire being replaced by a questionnaire deemed more appropriate for making evaluations on past occupational or non-occupational exposure to asbestos. This new questionnaire is based on the one drafted by the technical group set up within ISPESL for the establishment of the ReNaM. In the same period, a questionnaire drafted as part of a European multicentric case-control study on mesothelioma was adopted in two areas (Florence and Leghorn).
The objective of the national registry is to identify asbestos-related mesothelioma cases and thus assess whether asbestos exposure is present in case histories. In a certain number of patients (9 cases, 10%) interviews did not produce information deemed adequate for evaluating possible past exposure to asbestos (classified exposure cases: 9).
In conclusion, it was not possible to conduct an interview in 32% of the cases in question (28 patients), and in 36% of cases the interview was still missing or the information gathered was considered to be incomplete and insufficient to assign an exposure category (exposure code: 9 and 8). The percentage of cases with incomplete and insufficient information for the assignment of an exposure category was considerably higher for women (60% of interviews) than for men (9%).

Past exposure to asbestos and to other risk factors in (histologically confirmed) mesothelioma cases under review

All Archive cases have been classified in relation to past exposure to asbestos using standard criteria, on the basis of an opinion expressed by an industrial hygienist, supplemented, when possible, by the results of interviews and additional information, requested for each single case, from the local Occupational Prevention services of Tuscan health authorities. The exchange of information on single cases has brought up the need to effect a reconstruction of past working conditions and for studies of risk frequency among the workers of some firms.

In Tuscany three censuses have been undertaken over the past decade on the use (Silvestri E, Merler E, 1995) and consumption of asbestos in productive activities before and after its banning, and information has been collected on past uses, partly with the use of annual reports as per art. 9 of Law 257/1992.

Estimates of exposure for the cases under review have been summarised by identifying the most likely exposure to asbestos. There are thus no temporal records of all information on the possible duration of other exposures to asbestos, characterised by lower probabilities.

It appears from collected data that no cases of mesothelioma were recorded for the period 1993-1996 in which patients had undergone radiation treatment of the chest or abdomen. There were no cases of exposure to artificial mineral fibres alone.

Percentage of exposed persons by gender for the cases under review

The examined cases show different situations by gender with regard to the identification of asbestos exposure. Percentages were considerably higher for men (62 male patients out of a total of 85, 73%) than for women (3 women patients out of a total of 20, 15%) for cases with histologically diagnosis of mesothelioma in which the anamnestic reconstruction suggests the presence of a past occupational exposure to asbestos (anamnestic code from 1 to 3). These percentages rose for women only (to 20%), if possible past domestic or environmental or non-occupational exposure are considered (anamnestic code 4, 5, 6). The percentage was very high for men.

This judgement is of course conditioned by the results of interviews and by our knowledge of the use of asbestos in various production cycles. For example, among women we have recorded a significant number of mesothelioma cases in subjects that had worked solely as tailors for long periods, but we do not have for that subject or for the activity performed in that specific situation the information that exposure has occurred due to the occupational use of asbestos or of products containing asbestos.

Cases of mesothelioma in women and occupational exposure to asbestos

Of the cases of histologically confirmed mesothelioma in women, no case has been classified as ascertained or probable occupational exposure (anamnestic code 1 or 2). There are however

3 cases in women with possible exposure (anamnestic code 3) for having worked in the textile cycle in the rag-sorting trade in the Prato zone.

Cases of mesothelioma in males and occupational exposure to asbestos: analysis of occupational exposure

Among men a wide variety of occupational exposures to asbestos emerged as well as several clusters of cases from single productive sectors and firms. Although in most cases exposure to asbestos was from mixed fibres, in a number of working activities a prevalent use was made of specific commercial fibres.

In the period in question the highest number of mesothelioma cases among men (17 cases) was for dockers, in particular, workers in merchant and navy shipyards, merchant and navy cargo handlers, ship fitting construction workers. These persons were residents in coastal areas of Tuscany, with the exception of mesothelioma cases from a firm located inland, at Massa, where ship fittings were built (with the use of amosite). Occupational exposure was high in the shipyards of Leghorn and La Spezia (place where the presence of a navy shipyard attracted Tuscan labourers). The highest number of mesothelioma cases caused by occupational exposure in the shipbuilding industry was recorded in the L. Orlando yard in Leghorn. Large quantities of crocidolite were used in shipyards. Dockyard activity was the cause of some cases of mesothelioma contracted by cargo handlers. Finally, for some subjects occupational exposure was due to their working activity on merchant and navy ships. It should be recalled that the province of Leghorn has the highest mortality rates in Tuscany in relation to primary tumours of the pleura.

The occupational group with the second highest number of mesothelioma cases among men (8 cases) was the rag-sorting workers employed in the Prato area, confirming a trend that has already emerged and been documented, indicating the continuation of cases among persons that have usually performed this activity for a long time. Studies and possible explanations for this cluster, which particularly affects Tuscany, have already been presented (e.g. Seniori Costantini et al, 1995). With regard to the difficulty in identifying occupational exposure to asbestos, these cases are classified with anamnestic code 3 (possible exposure). In order to obtain an adequate number of cases of mesothelioma among rag-sorting workers, 3 female cases (mentioned previously) need to be added.

In Tuscany a number of firms built and repaired rolling stock and there was also the presence of *Officine Grandi Riparazioni* or *Depositi Locomotive e Squadre Rialzo* of the Italian Railways. From the mid-1950s railway vehicles were spray-insulated using crocidolite, triggering off the subsequent exposure of repair or demolition workers as well as Italian Railways employees working on the trains and along railway lines. In Tuscany in the period 1993-1996 there were 5 identified cases of mesothelioma, with 1 case at the Breda plant of Pistoia, 2 cases at SACFEM in Arezzo: in these firms locomotives and carriages were built,

repaired and demolished; 2 cases of mesothelioma among Italian Railways workers, one at the *Officine Grandi Riparazioni* of Florence, the other at the *Depositi Locomotive*. An estimate of the risk of mortality due to primary pleural tumours and lung tumours was published for Breda workers (Seniori Costantini et al., 2000) and for SACFEM workers (Battista G et al., 1999).

For several cases of mesothelioma among men there had been occupational exposure in the civil or industrial building industry (7 cases). Building workers generally are employed in many firms during their working lifetime and it is usually difficult to reconstruct the occasions and periods of exposure to asbestos-containing or surface-insulating materials. For this reason attributed exposure was code 3 (possible) in some cases. Largely overlapping exposure was diagnosed for 2 cases of mesothelioma contracted by plumbers.

The use of asbestos products in the building industry is a cause for concern, both for their wide presence on the territory and for the difficulty to persuade the industry to adopt adequate safety measures in the workplace to keep risk under control. The high number of cases among building workers (and plumbers) in Tuscany is an indicator of possible new cases that might emerge in the future in this sector.

There also emerged a wide range of other working sectors.

Three cases of mesothelioma were identified among sugar-refineries workers, 2 of which in a sugar-refineries of Cecina and one in Mugello (to the north of Florence).

Two cases of mesothelioma were detected among asbestos lagging workers. One case involved the worker of an important manufacture of glass firm in Pisa, where asbestos was used to build and repair smelting furnaces.

There were two cases in the chemical industry, in chemical companies operating in Leghorn and Rosignano.

There were 2 cases of mesothelioma in the energy production sector. One was a worker in a thermoelectric plant, while the other worked in the geothermal sector. In thermoelectric plants crocidolite was used for the insulation of turbines. An evaluation of the risk of mortality caused by primary pleural tumours was conducted for thermal plants (Crosignani P et al., 1995). In a small area of Tuscany over a hundred kilometres of large-diameter steam pipes were insulated using amosite to transfer high-temperature water steam, emerging naturally, to plants that convert it into electrical energy. This type of production, the only one of its kind in Italy, is a cause for concern owing to the spread of amosite contamination affecting the workers of ENEL and contractor firms, and to the resulting emergence of environmental pollution (Pira E et al, 1999; Merler E. et al., forwarded).

Two cases of mesothelioma were the result of exposure to asbestos in the engineering industry.

One case of histologically documented mesothelioma was found in a firm still in business in the province of Arezzo that produced asbestos cement products.

Exposure to asbestos was ascertained in two cases of mesothelioma among the armed forces. Information on the magnitude of past risk in this working area is more fragmented than in other sectors. The significance of this sector may be seen if one considers the global number of mesothelioma cases in Tuscany among civilians and military personnel that have worked for the armed forces, including workers of the military Arsenal of La Spezia.
It would be easier to interpret past occupational exposure to asbestos in Tuscan firms if, instead of assessing occupational exposure only for histologically confirmed cases, all cases for the period under review were considered. There are indeed numerous documented cases of workers in the productive sectors already mentioned, and these would point up clusters of cases in single firms.

Conclusions

In conclusion, activities performed by the Archive of Tuscany are not yet sufficient to make reliable estimates of incidence, being based on the voluntary reporting of new cases of mesothelioma and on a partial retrospective recovery of cases. Despite this limitation, activities have pointed up a significant number of mesothelioma cases and permitted a reconstruction of past exposure to asbestos.
The limits of the Archive's retrospective activity derive from problems connected with the definition of cases and identification of exposure. With regard to definition aspects it should be said that, in the period 1993-1996, the use of immuno-histochemical techniques to confirm morphological diagnoses is not yet optimal in Tuscany.
In regard to the identification of exposure, the percentage of cases late reported or identified was high in the period considered. These delays resulted in a large percentage of subjects not being interviewed, thus making it more difficult to assess the presence of past exposure to risk factors for mesothelioma cases.
It has been difficult in Tuscany to pinpoint the reasons for the frequency of mesothelioma cases among women, of which only a small percentage are attributable to occupational exposure, showing up the limits of an instrument based solely on anamnestic reconstruction.
The cases of mesothelioma, in which occupational exposure to asbestos has not been detected or occurred in younger age classes, should be studied in greater depth, not necessarily with the study of single cases but rather through case-control studies and an evaluation of fibre content in lung tissues.
The overall picture emerging for male mesothelioma cases is the frequent occupational exposure to asbestos. Despite the above-mentioned limitations, it was found that 73% of male cases were due to ascertained, probable or possible occupational exposure to asbestos. For men a significant proportion of mesothelioma cases were the effect of past conditions of asbestos exposure, involving numerous productive sectors in Tuscany or clusters of single

firms, sometimes validated by analytical studies and by nominative identification of those subjects exposed to asbestos.

There has been an improvement in the Archive's efficiency for periods after 1996: a positive influence has come from the inclusion of mesothelioma in the list of occupational diseases and from the legislative decision to establish a national registry.

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EMILIA-ROMAGNA MESOTHELIOMA REGISTRY

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The Emilia-Romagna Mesothelioma Registry (ReM) has been set up since 1993. Initially it covered the province of Reggio Emilia only. Interest in this disease is due to a study on mortality for a cohort of workers in 10 firms of Emilia-Romagna in the asbestos cement sector, which at the beginning of the 1990s had detected an excess mortality rate for malignant tumours of the respiratory apparatus and of the pleura in particular.
Eight of these firms had operated in the province of Reggio Emilia, thus in 1993 a provincial pathology registry was created with the aim of studying the incidence of the neoplasia and exposure to asbestos.
In 1996 the Registry's coverage was extended to the entire region, and it was designated as a COR (Regional Operating Centre) of the National Mesothelioma Registry. The Emilia-Romagna Region extends over a surface area of 22,125 km^2; the territory is divided into nine Provinces, and the average population in the period under review (1993-1996) was 3,927,834 inhabitants (2,027,880 women and 1,899,954 men).
This publication describes the experience of the Emilia-Romagna COR: results for the period 1993-1995 refer almost exclusively to the province of Reggio Emilia, while from 1996 onwards incidence should be taken as complete for the entire region.

Aims

Incidence

The main aim of the Registry is to systematically and actively collect data on all cases of malignant mesothelioma (m.m.) of the pleura, peritoneum, pericardium and testicle occurring in Emilia-Romagna: the completeness of data and accuracy of collected information have been the two targets characterising this registry ever since its creation.

Exposure

Information about occupational and non-occupational exposure to asbestos is collected by means of a standard questionnaire that acquires very detailed information about the working and residential history and life habits of single subjects.

ReM cases of interest

The ReM records cases of m.m. occurring throughout the region, for patients residing there at the time of diagnosis. *Benign* mesothelioma cases, initially suspected before proving to be *non-mesothelioma cases* upon subsequent study, and cases involving *non-residents* are filed but excluded from the calculation of incidence. The ReM has exhaustive information on

persons suffering from malignant mesothelioma and relative exposure to asbestos from 1993 onwards only for the province of Reggio Emilia. The creation of a regional network from 1 January 1996 has enabled the acquisition of sporadic cases from the period 1993-1995 in some provinces of the Region, but data on exposure are incomplete.

Sources of information

The Regional Information Network includes all Pathologic Anatomy Services, both public and private, operating in the region, a number of hospital departments where patients suffering from mesothelioma are treated and all Public Health Departments. 20 reporting members from Pathologic Anatomy centres and 20 from Public Health departments have been designated.

Cases are recorded in part *actively*, through periodical requests for information, and in part through *prearranged* reports from reporting members of the Regional Information Network. Each reported case requires the acquisition of documentation pertaining to pathological examinations carried out and of significant hospitalisations clinical records from both public and private health centres inside and outside the region. This medical documentation is examined by ReM medical staff to determine the diagnostic classification of the case and record most of the information given. Cases are coded in accordance with IARC rules adopted by Population Cancer registries and records are filed on paper (backed up by all clinical-anamnestic documentation) and on magnetic storage media using methods that ensure the confidentiality of data.

Definition of exposure

The adopted definition of exposure is the one proposed by the ReNaM (cf. Guidelines: *Fogli d'Informazione ISPESL*, year IX, no. 1/96). Exposure is defined according to information obtained from a standard questionnaire, proposed by the ReNaM, submitted to the patient or any next of kin and processed by the reporting occupational physicians of Public Health Departments. The information network tends to acquire in real time the reports of newly diagnosed cases in order to acquire first-hand information from the patient.

Exposure is defined by a group of experts, consisting of one occupational physician and two industrial hygienists during regular meetings. The opinion is expressed by the group without knowing the opinion of the reporting member. In case of disagreement a discussion is held between ReM operators and the reporting occupational physician who gave the interview.

Quality controls

Special care is taken over data quality controls in terms of completeness and accuracy of acquired information.

Completeness is meant to collect thoroughly all cases of m.m. occurring in the region. This aim has been pursued by means of crosschecks carried out for 1996 with regional mortality registries and hospital discharge records of the region (HDR) and through the collaboration of population-based cancer registries, of which there are four in Emilia-Romagna covering over 50% of the entire territory. Work was long and complex (for all deaths due to suspected mesothelioma it was necessary to obtain death certificates and then, thanks to HDRs, clinical records in the event of hospitalisations). This linkage enabled us to acquire 5 new cases in 1996 and, since this was the first year in which regional incidence was recorded, we believe that the information network worked well.
Accuracy on the other hand is concerned with the reliability of information gathered and filed, with regard to both diagnosis of the neoplasia and the level of asbestos exposure. All cases are confirmed, if possible, by the histological report and the report on immunohistochemical tests and relevant instrumental tests.
If data do not tally, more than one clinical record is compared and the general practitioner or, more frequently, the specialist treating the patient, is consulted.

Results
In the period 1993-1996, 156 cases were recorded, of which 148 results of interest to the ReM, 6 cases being ruled out in subsequent studies and classified as non-mesothelioma cases, and 2 cases concerning residents of other regions. Of the 148 cases recorded (103 men and 45 women), 133 concerned the pleura, 12 the peritoneum and 3 the testicle. 83% of cases were confirmed histologically (with immunohistochemical confirmation in 82% of cases), 15% were substantiated by cytological and instrumental tests (CAT, Rx) and only 2% were confirmed by Death Certificate only. The histological diagnosis of ascertained cases was performed through biopsies, effected via surgical intervention in 47 cases (38%), endoscopies in 47 cases (38%), transparietal biopsy in 12 cases (10%). In 17 cases (14%) the biopsy method was not disclosed.
In the period 1993-1995, incidence should be considered as practically complete only for the province of Reggio Emilia, while for other provinces the cases reported are “sporadic”, received only occasionally by the registry and not through active searches.
In 1996 however incidence may be deemed to be complete for the entire Emilia-Romagna region. The number of cases of m.m. recorded in the province of Reggio Emilia remained high, and has risen over the years (*5* cases in 1993, 9 cases in 1994, 8 cases in 1995 and 13 cases in 1996). This fact is confirmed by mortality and incidence studies in our region in more recent years, since Reggio Emilia regularly shows higher rates than other provinces for both sexes. A high number of cases were recorded in Forlì (19 cases), Modena (17 cases), Parma (14 cases) and Bologna (14 cases).

To assess exposure to asbestos, 64 interviews have so far been conducted: for 27 cases (42.2%) the interview was held directly with the patient, important for the accuracy in reconstructing occupational and personal histories, especially for elderly patients.
Exposure to asbestos (occupational, domestic or environmental) was detected and documented in 40 cases: in 36 cases (56%) exposure was occupational, in 24 cases (37%) it was not possible to identify or suspect any type of asbestos exposure. The distribution of exposure to asbestos differs according to the gender: among men it is present in 70% of cases, among women in 35%.
The 64 questionnaires referred to residents in all nine provinces of Emilia-Romagna, although distribution was very uneven, going from 35 cases (55%) of residents in the province of Reggio Emilia to only one case interviewed in the province of Rimini. In other provinces the situation was more balanced: 2 cases in Piacenza, Parma and Forlì, 4 cases in Modena, 5 cases in Ferrara, 6 cases in Ravenna and 7 in Bologna. This is due to the fact that for the period 1993-1995 information on exposure was available only for the province of Reggio Emilia (88% of cases).

With regard to occupational exposure to asbestos, the sectors most affected for men were rolling stocks (25%), asbestos cement products (23%) and construction (16%). For women, 4 cases of occupational exposure were recorded, all in subjects residing in the province of Reggio Emilia. Two women were employed in the manufacture of asbestos cement products, one in the recycling of jute sacks coming from asbestos cement firms and one involving a junior school teacher who for professional reasons had frequented for over 10 years a swimming pool insulated with asbestos plaster.

Conclusions

New cases of mesothelioma should be examined in greater depth, since they constitute an excellent indicator of exposure, especially occupational exposure, to asbestos among the general population. It may be useful to observe the disease's trends over time in clinical-epidemiological terms but also from an insurance and legal viewpoint.
The sending of information to a central structure, the ReNaM, may contribute towards the acquisition of useful information on environmental or occupational exposures that have so far been undetected, as well as fostering the undoubted advantages deriving from the standardisation of procedures for the identification, filing, diagnostic and exposure-related definition of cases.
With reference to the Emilia-Romagna region, the results given in this report offer some encouraging indications on the methodology adopted by the registry: the Regional Information Network appears to have worked rather well, and the good quality of data is validated by the high percentage of histological confirmations and by a low number of DCOs.

This has been possible partly because of the widespread use of video-thoracoscopies throughout the region's pneumology and thoracic surgery departments, guaranteeing the availability of good-quality biopsies for the pathologist through low-level invasive methods.
The collection of work history information was also positive. Of special significance was the gathering of information directly from the patient in 42% of cases. We believe this percentage can be raised further, since the information network, based on the widespread presence of Prevention Services, is designed to facilitate such interviews.
In Emilia-Romagna, occupational exposure to asbestos was particularly evident in the asbestos cement sector, in the rolling stock building/repairing sector and in the construction. Activities connected with the manufacture of asbestos cement products (9 cases), the use of asbestos in building trade material (5 cases), and one case relating to the recycling of used sacks, are undoubtedly the most common for the occurrence of m.m. (15 cases out of 35, 42.9%). Also significant is the fact that the data acquired point up exposure in these economic sectors almost exclusively in the province of Reggio Emilia. This may be explained by the wide presence of industrial firms that have worked in the area from the 1950s until the early 1990s. Other sectors most affected by the phenomenon were food production and fertilisers/plastic materials.

Acknowledgements
The collecting, filing and diagnostic definition of cases of malignant mesothelioma from the Emilia-Romagna Region has been possible only through the precious and valid collaboration of reporting members of the Regional Information Network.
The network, made up of 20 officially designated Pathologic Anatomy reporters from all over the region and numerous specialists from other branches, firstly from the Pneumology and Thoracic Surgery departments of the ASMN of Reggio Emilia, significantly contributed to the acquisition of new ascertained cases of malignant mesothelioma.
An important contribution has also been made by local Industrial Medicine services (SPSAL) and by Public Hygiene services (SIP). The completeness of information has enabled to provide with the presence of computerised regional mortality records and HDRs. Occupational and personal history information was collected in a thorough manner thanks to the contribution of 13 SPSAL industrial physicians designated by all regional AUSL Prevention Departments.
Our warm thanks go to everybody concerned for the results achieved, certain that the collaboration till now established can only go to improve our knowledge and familiarity with this disease.

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COR OF NATIONAL MESOTHELIOMA REGISTRY - PUGLIA

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In the Puglia Region, where one of Italy's most important shipbuilding areas is located (Taranto), and where asbestos cement products are also produced (Bari), asbestos exposure has been intense and prolonged especially from the 40s to the 80s.
Owing to the presence of this sort of production, since 1988 a feasibility study for a regional registry of mesothelioma cases (see references) has been promoted in collaboration with the Higher Institute for Health as part of the project "Surveillance of Pleural Mesothelioma in Italy". The registry was established in 1989 in regional collaboration with the Institute of Pathologic Anatomy and the faculty of Thoracic Surgery of the University of Bari, the Thoracic Surgery Division of the Ospedale "Cotugno" of Bari and the Pathologic Anatomy department of the Ospedale "SS. Annunziata" of Taranto. Registry staff consisted of a technician from the University of Bari and an Industrial Medicine postgraduate. Resources were supplied through University research funds (60% of total).
With the coming into force of D.L. 277/91, article 36 providing for the establishment of a National Mesothelioma Registry (ReNaM), existing regional registries were designated as Regional Operating Centres (CORs).
In 1996 the Puglia Region, through Decision n° 366 of 26/02/96 ref. no. SAN-DEL 196/00104, named the faculty of Occupational Preventive Medicine of the Industrial Medicine Section, DIMIMP, of the University of Bari, as seat of the Regional Mesothelioma Registry and Regional Operating Centre of the National Mesothelioma Registry. This recognition did not entail extra costs by the Regional Health Department.
The current COR staff consists of a coordinator and a technician from the University of Bari, an industrial medicine postgraduate and a research assistant.
The Regional Information Network involves physicians or medical staff of the departments and services of Industrial Medicine, Pathologic Anatomy and Histology, Thoracic Surgery, Pneumology, Respiratory Physiopathology and Oncology, as well as all other public and private subjects of the NHS that come to know about cases of mesothelioma of the pleura, pericardium or peritoneum in view of the legal obligations (Presidential Decree n° 336 of 13 April 1994) of reporting cases of mesothelioma, even suspected cases, to INAIL and to judicial authorities.
The Regional Information Network is now being expanded to cover the entire region. For this purpose, in November and December 1997 the COR of Puglia organised an Advanced Training Course for Employed Medical Staff (FAPSO). This course was funded by the Puglia Region, as part of the Vocational Training Plan, and was cofinanced by the European Social

Fund. It was attended by 83 persons, mostly physicians of various specialisation, from all five provinces of Puglia.

The 83 course participants automatically became COR reporting members for Puglia in their respective workplaces by virtue of the skills acquired during the Course. A request was made for them to be officially recognised as "COR reporters for Puglia" by the Regional Health Department. At this point in time, therefore, the COR of Puglia has an information network formed by 56 Centres (figure 1).

COR Puglia Network

56 operative centers

Figure 1

Coverage of the entire region through local reporters signalling cases that reach their observation points is a necessary precondition for obtaining a complete picture of the incidence of this pathology in our Region and for pinpointing the sources of exposure that may still be present, in order to perform relative clean-up activities.

Collaboration with the COR entails the possibility for local reporters to gain access to statistics on regional cases and bibliographical updates, use data for scientific publications, and receive advice from pathologists to support diagnoses.

Aims

- Registration of all cases of mesothelioma diagnosed for residents in Puglia to assess the spread of the disease (incidence, prevalence) (estimated resident population 1994 = 4,038,759, source: BURP - Bollettino Ufficiale Regione Puglia)
- Retrospective reconstruction of each case of exposure to asbestos (military, occupational, family, environmental, hobby-related)

- Fulfilment of existing legislative obligations (D.L. 277/91, Presidential Decree n° 336 of 13/04/94)
- Epidemiological research and surveillance: to detect unexpected sources of exposure, plan preventive and health surveillance measures, study the relationship between environmental exposure to asbestos and the occurrence of mesothelioma, in favour of the Regional Reference Centre, which draws up guidelines for the training and regional coordination of family doctors, SPESAL physicians (Prevention Departments), competent physicians, hospital physicians, specialists and the physicians of other NHS structures involved in the health management of workers exposed/previously exposed to asbestos.

COR Puglia - Tasks

- Acquisition, processing and filing of information on each single case
- Diagnostic definition of each single case
- Definition of exposure submitting a standard questionnaire to the patient, if possible, or to next of kin
- Creation of an archive, either on paper or computer-based storage medium, allowing data access to each element of the regional information network
- Operational support with medical-legal aspects for compensation in mesothelioma cases as an occupational disease, when applicable.
- Reporting single cases forms to National Mesothelioma Registry.

The regional flow of information for the case reporting

The case-reporting system entails firstly a passive phase of collecting new cases from reporting members of the information network. Collected information are passed to the regional COR of mesothelioma cases, supplying an ad hoc case reporting form containing all the personal data needed to identify the sufferer and clinical data relative to the diagnosis. This first phase is periodically carried out by COR through an active search at diagnosis and treatment centres.

Once reports have been received from local reporters, the COR proceeds with an active survey, consisting in the acquisition of all diagnostic elements able to raise the degree of certainty of the diagnosis. It also reviews, if necessary, the histological diagnosis effected by referent pathologists in suspected cases. Once the clinical diagnosis has been defined, the COR proceeds with the reconstruction of exposure through an interview with the patient, if still alive, or with next of kin, using the standard questionnaire approved at a national level. Interviews are submitted in a direct meeting whenever possible, or by telephone when subjects (patients or their families) are unwilling to meet or indisposed. This often happens for cases reported very late and those with diagnoses effected more than two/three years prior to

the report. There are also frequent cases of next of kin interested in medical/legal/insurance aspects that are willing to collect documentation on the case in question and to give a direct interview after the initial telephone-based interview.

Completeness and thoroughness of data collection

As already mentioned, in November 1997 the COR of Puglia commenced procedures for the completion of the regional information network and the systematic collection of ascertained or suspected cases of mesothelioma throughout the region. For some information sources that have not previously been available, activities are being performed for the acquisition of data in order to integrate and verify the completeness of reported cases. In particular, both HDRs and ISTAT death records have been available in our region since the creation of the Regional Epidemiological Observatory and the Jonico-Salentino Cancer registry (for the provinces of Brindisi, Taranto and Lecce) in 1998, comprising HDRs available from 1997 onwards and ISTAT death records from 1998. The same data acquisition procedure is ongoing for the start-up of regional collaboration between the COR and INAIL.

The acquisition of information on cases of mesothelioma contracted by residents in Puglia diagnosed outside the region has been regularly commenced for cases diagnosed in regions where other CORs are operational (Piedmont, Liguria, Tuscany, Emilia-Romagna), with the mesothelioma Registry of Brescia/Bergamo and with the newly formed CORs of Sicily and Basilicata.

With regard to the above, we wish to stress that the registration of cases is an ongoing process with the retrospective checking of outstanding cases and the time needed to complete and produce incidence data is more than 36 months on average.

Data transmission to national level

Cases entered in the regional registry are forwarded to the National Registry, indicating: personal data of subject, cancer site, date and type of diagnosis, occupational history, information on relatives with ascertained or probable exposure, information on plants for production and/or manufacture of asbestos products located close to the house, information sources. These data are encrypted using software supplied by ISPESL to guarantee confidentiality and sent via computer-based media.

Results

With regard to the completeness and thoroughness of data presented, refer to the previous chapter of this report. It should be remembered that the recovery of cases is an ongoing process, since for example HDR data are unavailable for the years under review (1993/1996).

The exposure is still to be defined in 13% of cases. On this point it should be borne in mind a peculiar feature of our region: although the COR was officially recognised in 1996, the

Regional Asbestos Plan has not yet been approved, nor has the census on the use and consumption of asbestos been undertaken.
The cases of mesothelioma currently registered by the COR of Puglia for the years 1993/1996 amount to 118, of which 101 (86%) confirmed by histological diagnosis, of the latter 37% with immunohistochemical testing. Of the 101 cases, here presented, 95 have been defined/reconstructed (94%). With regard to distribution by gender, 74% of cases were men and 26% women, while if the distribution by gender of reconstructed/defined cases is considered, 75% were men and 25% women. For defined/reconstructed cases, information was acquired directly from the patient in 26% of cases, from spouses or children in 64% and in the remaining 9% by other relatives (parents, brothers/sisters, son/daughter-in-law, brother/sister-in-law).
Looking at the distribution of the 101 cases by anamnestic code and by gender, there was a clear prevalence of occupational exposure among men (58 cases, 97%) as compared with women (2 cases, 3%), giving a total of 60 cases of occupational exposure.
For female cases (11 out of 24 reconstructed cases), 46% of them were classified as unlike exposure, because the use of asbestos could not be detected, while for men this percentage is only 5% of reconstructed cases (4 out of 71).
With regard to productive sectors where occupational exposure was recorded, 39% of cases were associated with activities performed in the navy or merchant shipping and in shipbuilding, 9% were connected with activities performed in the iron and steel industry. Thus a total of 48% of cases of occupational exposure concerned the two main industrial poles of our region, especially in the province of Taranto (shipbuilding and iron and steel).

The occurrence of mesothelioma as a result of non-occupational exposure to asbestos has been the subject of a number of studies, case-reports in particular, of which Gardner and Saracci (1989) have published an exhaustive review.
Numerous scientific papers have reported the health effects caused by exposure to asbestos to those living near mines and industrial plants where asbestos was manufactured (the main papers are given below).
Since there were 9 cases of environmental exposure recorded in the COR of Puglia, relative to the period 1993-1996, which represent 8.9% of all reported cases (101) and 9.4% of all defined/reconstructed cases (95), we believe that a specific comment should be made for such cases.
Of the 9 cases under review, 5 were for women and 2 for men, 7 (77%) were for residents in Bari and 2 (22%) in Taranto. Distribution of these cases by municipality of residence confirms the role of the asbestos cement industry in the environmental pollution of neighbouring areas, as reported recently in literature. The residence of sufferers in the cases reported for Bari was within a 1 Km radius of the plant producing asbestos cement.

The mean age at the time of diagnosis was 57.6 (interval 38/75), 65.2 for men (interval 58/74) and 51.6 for women (interval 38/75).
Distribution by histotype for the 9 cases was as follows: Epithelioid, 4 (44.4%), Biphasic, 4 (44.4%), Fibrous, 1 (11.1%). As regard as the distribution of histotype by gender, all 4 biphasic cases involved women, with latency above 30 years.
The mean duration of reconstructed exposure was 21.5 years (interval 4/49), with the start of exposure between 1947 and 1972 for all 9 cases. The mean latency was 37.3 years (interval 22/49 years). The mean age at the start of exposure was 20.3 years, with an age from zero (from birth) to 48 years. It is interesting to observe that for 4 cases aging at diagnosis from 38 to 55 years, all women and all resident in Bari, the age at the start of exposure was between zero (from birth) and 23 years. It should be stressed that in the case of the 38-year-old woman whose exposure started at birth, her family lived from 1958 to 1964 inside the asbestos cement product plant in Bari, thus the patient had been subjected from birth to the age of 6 to "occupational" amounts of exposure.

Conclusions

With reference to scientific literature on the causal association between tumours and exposure to asbestos in areas close to production units (factories, shipyards, etc.) where asbestos was manufactured and/or handled, these data confirm that:

- residents in areas close to asbestos cement factories, within a 1 Km radius, are exposed to the inhalation of low doses of asbestos fibres;
- exposure to "low doses" in not professionally exposed persons, brings about the risk of pleural mesothelioma, which is higher among residents living close to factories using asbestos.

In conclusion, this "environmental" type of exposure is an important "sentinel event" highlighting the presence of undetected sources of contamination that the general population may be exposed to, now and in the past, as well as the need to clean up these areas and assist with compensation procedures for cases caused by environmental exposure.
We should however recall the difficulties tied up with a more accurate attribution of exposure, in terms of the underestimating of risk pertaining to exposure occurring several decades ago and/or during childhood, and of the impossibility of assessing exposure in quantitative terms, given the absence in most cases of data measuring environmental exposure for the years 1940/1970.

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PART FOUR - A PROVINCIAL REGISTRY

THE REGISTRY OF MALIGNANT MESOTHELIOMA CASES - PROVINCE OF BRESCIA

PG Barbieri, A Candela, S Lombardi

The Registry of Mesothelioma cases of Brescia took form as a result of the experience of "actively" collecting information on the neoplasia from 1989 onwards by Industrial Medicine units in a highly industrialised province where this sort of tumour was practically unknown with reference to its possible "occupational" origin.

In the province of Brescia, firms worked with asbestos for several decades. Asbestos was used as a raw material in the production of asbestos cement roofing and friction and sealing materials. It was also present in many products used in a number of productive sectors, including iron and steel and metalworking, which are particularly important locally.

The retrospective study of Malignant Mesothelioma (MM) cases has enabled to identify tens of cases that were previously unknown to Prevention Services. Of these, a significant percentage of workers were exposed to asbestos [1], suggesting the need to carry on with epidemiological surveillance in a more structured manner.

Thus after one year of experimentation, and having verified the feasibility of the initiative, the local Registry of Mesothelioma cases was established in 1994, handled by three local Industrial Medicine services of the local health authorities and supported by the Brescia section of the Anti Tumour League.

The population-based Registry covers a population totalling 1,017,093 residents according to the ISTAT 1981 census.

With Decision n° 36754 of the Lombardy Region of 12 June 1998 the Regional Mesothelioma Registry was created in January 2000. It should be noted that in Brescia a Registry of Mesothelioma cases has been set up since 1994, managed by the Occupational Health and Safety Service. The Registry of Brescia actively collaborates with the COR of Lombardy.

This report contains a summary of the way the Registry is organised and a description of cases observed in the period 1993-1996.

Aims of Brescia Mesothelioma Registry

The Brescia Mesothelioma Registry sets out to achieve the *aims* described below.

- Epidemiological surveillance of all diagnosed cases involving residents of the province of Brescia, and estimate of incidence, mortality and survival of the neoplasia.
- Systematic collection of information on the working and environmental history of individual cases regarding possible exposure to asbestos and to other known or suspected risk factors causing the occurrence of the neoplasia.

- Evaluation of the significance of asbestos exposure in the recorded cases, encouraging the use of clinical tests useful for achieving this purpose.
- Preparation of information useful for cognitive and preventive purposes and for medical-legal and insurance aims.
- Reporting of cases to the National Mesothelioma Registry pursuant to art. 36 of D.L. 277/91, as from January 2000 through the Mesothelioma Registry of Lombardy.

Organisation of Registry and cases of interest

The Registry of Malignant Mesothelioma cases of the Province of Brescia is managed by some operators of the Occupational Health and Safety Service (SPSAL) of the local health authority of the province of Brescia.
Up until December 1999 no ad hoc funding or personnel have been set aside for the Registry.
The Registry is kept at the PSAL Service, LHA of Brescia, v. Pericoli 4, 25058 Sulzano.

Registry activities are guaranteed by a collaboration network supported by public and private health service workers.
Active collaboration with the *reporting* of cases is provided by:
- the Pathologic Anatomy units of the hospitals of Esine, Chiari, Leno, Desenzano, Brescia;
- the Industrial Medicine unit of the Public Hospitals of Brescia;
- the pneumology units of the hospitals of Brescia, Desenzano, Esine;
- the Hygiene services of the LHA of Brescia.

Active collaboration with the *collection of information* is provided by:
- the PSAL Service of the LHA of Brescia, in its local centres;
- the Industrial Medicine service of the Public Hospitals Brescia;

Active collaboration with *controls on the completeness of data* is provided by:
- the Epidemiology Service of the regional Health Department and the IST of Milan;
- the Data Processing Centres and Health Management of hospitals in the province.

An industrial hygienist collaborates to assess exposure to asbestos in reported cases.
Pathologists from hospital units have helped with the histological review of cases.
The Mesothelioma Registry of Brescia records *all cases of malignant neoplasia of a mesothelial nature clinically defined as ascertained, probable, possible or suspect*, diagnosed among residents only of the province of Brescia.
As soon as they are reported, cases diagnosed as ascertained or suspect mesothelioma are considered as potential cases of occupational or environmental origin deriving from exposure

to asbestos, unless otherwise proved; the standard procedures described below are applied to all cases.

Sources, identification methods and flow of cases

The *primary sources* for the collection of case data are the following health structures of the province of Brescia:

- Pathologic Anatomy services of public hospitals;
- Pneumology units;
- Surgery unit;
- Radiotherapy service;
- Industrial Medicine service of the public hospital of Brescia;
- Health management of private clinics in the province.

Additional sources for the collection of data are as follows:

- Hospital Discharge records (HDR) available from hospitals' EDP centres;
- ISTAT death certificates available from LHA;
- INAIL databases.

Cooperation with the reporting of cases is also sought from the following structures identified "a priori", given the possibility that cases in the province of Brescia can be diagnosed:

- Registry of Mesothelioma cases of the province of Bergamo;
- Milan Cancer Institute.

Cases diagnosed in the above centres are reported to PSAL Services of the competent LHA. These services send to the Registry the individual clinical records gathered by diagnosis units and anamnestic information obtained through the standard questionnaire, as well as any other information deemed to be useful in defining possible exposure to asbestos.

These Services promote their own *active research*, mainly through Pathologic Anatomy services and the units where cases are usually diagnosed.

In view of the brief mean survival rate of patients suffering from mesothelioma and treated in the province of Brescia, *cases are actively studied every six months.*

Cases that have been diagnosed by health centres of Lombardy outside the province of Brescia are studied, again every six months, by the Registry, partly by verifying Hospital Discharge Records supplied by the Epidemiological Service of the Lombardy Region for codes ICD IX 158 and 163.

The Registry also receives ISTAT death certificates stating as cause of death *mesothelioma or tumour of the pleura, pericardium and peritoneum*, from the PSAL services of the Province of

Brescia, which carry out active research through medical examiners of the LHA Hygiene Service.

Finally, it is suggested that the Registry should also receive reports of cases among non-residents in the province of Brescia so that they can be systematically forwarded to the competent LHA.
As from January 2000, according to indications provided by the Regional Mesothelioma Registry, the Directors of Medicine, Pneumology, Thoracic Surgery, Radiotherapy and Pathologic Anatomy units are invited to send to the Reporting member of the Registry of Mesothelioma cases of Brescia the ad hoc “case report form”.

Documentation acquired and processed
For each case diagnosed and/or treated in a hospital structure the following data should be gathered:

- front cover of the clinical record and anamnestic information contained therein;
- cytological, histological and post-mortem reports;
- thoracoscopic, surgical, CAT, RMN reports.

The above documentation is similarly acquired for cases reported by means of:

- ISTAT certificates stating the cause of death;
- Hospital Discharge Records of the Region Lombardy;
- the reporting of hospitalisations outside the Province.

For each patient suffering from mesothelioma, the professional history of the patient is acquired through the submission of a standard questionnaire to the patient or next of kin, handled by industrial medicine specialists.
For each case, basic information common to Cancer registries is coded [2] and supplemented by specific information of interest to the Registry.
The Registry of Malignant Mesothelioma cases is made up of individual cases containing the data entered in the computerised Archive, sorted in alphabetical order and by year starting from 1999.
The clinical data and anamnestic information of each case are included in individual files.
The local seats of the PSAL Service receive, for the cases under their jurisdiction, reports on ascertained or suspected occupational diseases drafted in accordance with art. 365 of Italian Criminal Code and art. 334 of Italian Code of Criminal Procedure, accompanied for statistical purposes by a copy of the first INAIL certificate, if available.

The collection of anamnestic data for patients not easily found because currently hospitalised, requires a preliminary contact with the attending practitioner and subsequently the sending of a written communication to the patient or to any next of kin to arrange a meeting.
When studies are complete, communications are sent to the patient or next of kin, to the physician that reported the case, to the family doctor and, for their information, to medical examiners in accordance with specific *Operating procedures for the handling of cases*.
Finally, a copy of the final assessment effected by the Registry is sent to colleagues of the PSAL Service that have territorial jurisdiction over the case.

Criteria for the diagnostic definition of cases
In line with indications provided by ISPESL [3] the Registry of mesothelioma cases of Brescia requires the collection and coding of all diagnosed cases, including those believed to be suspect or doubtful.
The criteria used to define the diagnostic certainty of cases reported through December 1999 are described below.

Malignant mesothelioma *ascertained*	clinical situation compatible with M.M., with at least one positive histological (or cytological with immunohistochemical test) examination
Malignant mesothelioma *probable*	clinical situation compatible with M.M. with doubtful or suspect histological or cytological examination
Malignant mesothelioma *possible*	clinical situation compatible with M.M. in the absence of positive histological or cytological documentation
Non Malignant mesothelioma	case which following a review of relative clinical documentation cannot be considered as malignant mesothelioma

Diagnostic reliability is assessed by reporting physicians of the Registry, with the possible collaboration of hospital physicians, in particular pathologists.

Evaluation of exposure to asbestos and relative actions
Information on residential history, professional history and life habits of the subject is contained in the standard questionnaire used systematically since 1994, with some modifications. The questionnaire is the one proposed by ISPESL in 1996 [3], with subsequent updates.
In additional to the general questionnaire, and when interview conditions allow, specific forms are used to collect information on professional histories for certain working sectors. These forms serve for the *BIOMED* multicentric case-control study on mesothelioma [4].

To define asbestos exposure, the criteria provided by ISPESL are used [3]. Also, to obtain a more uniform evaluation of exposure to asbestos, the same criteria have been retrospectively applied to all cases.
Exposure to known or suspected risk factors is assessed by 3 expert occupational physicians and by an industrial hygienist.

For cases showing *occupational and environmental exposure to asbestos*, all documentation is sent to the local seats of the PSAL service for possible actions under its jurisdiction, e.g. certification to INAIL of occupational disease, notice of offence to Italian Judicial Authority, possible indications pertaining to a post-mortem findings in accordance with *Operating procedures for the handling of cases*.
Cases of MM involving occupational exposure to asbestos received directly by the Registry are sent to the locally competent reporting member of the PSAL Service for the management of medical-legal aspects.

Quality controls

The Registry has set up quality controls ranging from the gathering of information on the case to filing activities; controls are concerned with both the *completeness* of information and the *accuracy* of acquired data.
With regard to the *completeness* of data, annual checks are carried out on:

- single cases concerned to acquired data;
- the reporting of all cases diagnosed through the collection of ISTAT death certificates, Hospital Discharge Records of the Region, checking the Registries of Pathologic Anatomy services. The percentage of cases not reported in the year of diagnosis is checked.

As regard as the *accuracy,* annual checks are carried out on:

- single cases with reference to personal data;
- aggregate cases, relative to the prevalence of the histological diagnosis and the prevalence of complete information useful to define exposure to asbestos.

The *accuracy and completeness* of the Registry is also checked, in the same way as for other Cancer registries, through the following indicators:

- percentage of cases confirmed by cyto-histological evidence;
- percentage of cases known only on the basis of the death certificate (DCO);
- mortality/incidence ratio.

Results

In the period 1993-1996 there were 51 diagnosed cases of malignant mesothelioma among residents in the province of Brescia. Below are data on incidence for the period, clinical and diagnostic aspects and the results of anamnestic studies designed to single out types of risk exposure.

Incidence and clinical-diagnostic aspects

Distribution of the 51 cases by site of the pathology, gender and age class is given in table A. 46 pleural mesothelioma cases and 5 peritoneal mesothelioma cases were diagnosed.

Table A. Distribution by gender, age class and site of 51 cases of Mesothelioma diagnosed for residents in the province of Brescia from 1993 to 1996

MEN			*Cases by age class*					
ICD IX	*Site*	*Cases*	*0-34*	*35-44*	*45-54*	*55-64*	*65-74*	*+75*
163	*Pleura*	31	0	1	4	7	13	6
158	*Peritoneum*	1	0	0	0	0	0	1
WOMEN			*Cases by age class*					
ICD IX	*Site*	*Cases*	*0-34*	*35-44*	*45-54*	*55-64*	*65-74*	*+75*
163	*Pleura*	15	0	1	2	2	6	4
158	*Peritoneum*	4	0	0	0	1	2	1

In the period in question active epidemiological surveillance of the neoplasia was already in place, handled by the local Mesothelioma Registry. Data acquired using the aforementioned methods, enabled to consider the completeness of the collection of cases as being adequate and to calculate annual incidence rates for the neoplasia in the province of Brescia for a time period close to 1993-1996 and follows.

As can be seen in table B, in the subsequent four-year period (1996-1999) there was a significant rise in incidence rates for both genders and sites. Mean annual incidence rates were 2.95 for men and 1.35 for women for pleural mesothelioma, and 0.17 for men and 0.37 for women for peritoneal mesothelioma. Incidence rates were calculated for all cases known to the Registry and were coded according to different levels of diagnostic evidence.

Table B. Incidence of Malignant pleural and peritoneal mesothelioma by gender and period in the province of Brescia

MEN			Total			Age specific rates					
period	ICD-IX	*site*	no. cases	crude	stand.	0-34	35-44	45-54	55-64	65-74	+ 75
92-95	163	*pleura*	25	1.3	1.4	0.0	0.7	1.0	1.5	7.9	13.7
	158	*peritoneum*	1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	1.7
96-99	163	*pleura*	50	2.5	2.9	0.0	0.3	2.1	7.7	18.5	13.7
	158	*peritoneum*	3	0.2	0.1	0.0	0.0	0.0	0.5	1.8	0.0

WOMEN			Total			Age specific rates					
period	ICD-IX	*site*	no. cases	crude	stand.	0-34	35-44	45-54	55-64	65-74	+ 75
92-95	163	*pleura*	14	0.7	0.7	0.0	0.4	0.8	0.9	2.5	3.9
	158	*peritoneum*	3	0.1	0.1	0.0	0.0	0.0	0.0	1.2	0.8
96-99	163	*pleura*	26	1.2	1.3	0.0	0.4	1.2	0.9	6.8	7.1
	158	*peritoneum*	7	0.3	0.3	0.0	0.0	0.8	0.9	1.8	0.0

With reference to the level of diagnostic certainty, coded according to the criterion suggested by ISPESL, 47 cases (92%) were classified as ascertained mesothelioma cases, confirmed by histological evidence; for 38 of these (81%) the diagnosis was supported by immunohistochemical techniques.

In 3 cases (6%) the diagnosis was of a possible mesothelioma, while one case was detected only by virtue of the death certificate (DCO).

The most common histotype was the epithelioid variety, accounting for 29 cases (56.8%), followed by fibrous mesothelioma with 3 cases (5.8%) and biphasic mesothelioma with 2 cases (3.9%); in 13 cases (25.4%) the histotype could not be determined.

Exposure

For 51 cases observed in the period 1993-1996 the exposure to asbestos and to other known risk factors was assessed by 45 interviews (88.2%). The professional history was acquired directly from patients in only 28 cases (62.2%); from the spouse in 12 cases (26.6%) and from children in 3 cases (6.6%).

Of the 51 mesothelioma cases observed there was only one case of radiation treatment to the chest region due to a mammary neoplasia. There were also 8 cases of isolated pleural asbestosis (pleural growths) and only 2 cases of parenchymatic asbestosis, contracted by workers in the asbestos cement industry.

With regard to asbestos exposure for the 51 cases, distribution by gender is given in table C. Exposure to asbestos was ascertained in about 44% of cases.

It is interesting to observe the clear difference in exposure between men and women, with around 60% of men and just 15% of women exposed to asbestos. Of the latter group, there were no cases of ascertained exposure, but only 3 cases of probable or possible exposure.

Table C. Distribution by gender of asbestos exposure in 51 mesothelioma cases diagnosed in Brescia from 1993 to 1996.

Asbestos exposure	Men		Women		*Total*	
	no. cases	%	no. cases	%	*no. cases*	*%*
1. Ascertained	14	43.8	0	0.0	*14*	*27.4*
2. Probable	1	3.2	2	10.5	*3*	*5.9*
3. Possible	4	12.5	1	5.3	*5*	*9.8*
4. Domestic	0	0.0	0	0.0	*0*	*0.0*
5. Environmental	0	0.0	0	0.0	*0*	*0.0*
6. Hobby-related	0	0.0	2	10.5	*2*	*3.9*
7. Unlikely	2	6.2	0	0.0	*2*	*3.9*
8. Unknown	9	28.1	10	52.6	*19*	*37.3*
9. Unclassifiable	2	6.2	4	21.1	*6*	*11.8*
TOTAL	32	100.0	19	100.0	*51*	*100.0*

With reference to working sectors where occupational exposure to asbestos has been assessed, only 3 out of 14 cases were related to productive sectors in which asbestos was traditionally used as a raw material: production of asbestos cement roofing and production of asbestos gaskets. Most mesothelioma cases occurred to workers in the construction industry, with 5 cases. There were also 3 cases among plumbers, including 2 craftsmen, and 3 cases among mechanical and electrical maintenance workers in metalworking industries.

There was one “probable” exposure among men, e.g. a carpenter in the construction industry, and four cases of “possible” exposure, in the building and electrical repairing sectors. As far as women are concerned, there were two cases of probable exposure, in the filature sector and at a junior school, and one case of possible exposure in the textile industry.

Finally, there were no reported cases of mesothelioma due to environmental or para-occupational exposure to asbestos. The 2 cases classified as “hobby-related” exposure were

concerned with two women who had used ironing boards probably made of asbestos for a long period of time.

Final considerations

Five years after the establishment of the Registry of Mesothelioma cases in Brescia, some of the aims initially set may be said to have been achieved.

- The level of completeness and accuracy of the Registry may currently be said to be satisfactory.
- Initial estimates of Mesothelioma incidence and survival rates for the province of Brescia have been obtained [5]; although these rates do not appear to be particularly high compared with those of other provinces where Cancer registries are in place, a progressive and significant increase in incidence for both sexes has been confirmed, particularly for pleural tumours.
- The data acquired through the Registry's activities provided additional knowledge about exposure to asbestos in the local context, indicating that most mesothelioma cases of occupational origin are associated with exposure to risks connected with the use of the mineral not as a raw material but as a component of a large number of products of differing uses. Informational initiatives were also promoted, culminating in the organisation of the Exhibition and Seminar "*Bastamianto*", held in June 1994.
- Occupational exposure to asbestos was confirmed in a relevant percentage of cases. This facilitated the process of certifying numerous occupational diseases with the Insurance Institute, in some cases paving the way for compensation and the initiation of criminal proceedings.
- In some cases lung tissues were made available to determine the qualitative and quantitative properties of mineral fibres through the use of electron microscopy, and the foundations were laid for resorting if possible to post-mortem examinations in special cases.
- Finally, the Registry made a contribution to a European multicentric case-control epidemiological study on mesothelioma [3] and to a study of incidence in malignant mesothelioma cases in an area near Lake Iseo [6].

Some limits that hampered activities have in part not been overcome.

In the past, regional guidelines to steer the Registry's activities were unavailable and the Registry also encountered difficulties due to officialdom delays.

Active studies of the neoplasia are still required because of the partial notification of cases. This has required a considerable investment in resources, something that could have been avoided if attending practitioners had complied with reporting obligations.

Only in some cases was it possible to directly interview patients with due haste, partly due to organisational obstacles that should not be present. The result of this was the acquisition of partial information on possible exposure to risk.
In most cases, especially those of women and those classified as having an *unknown* exposure to asbestos, conditions did not permit the development of studies to gain a better knowledge of the general and working environments in which subjects have lived for a long time.
Finally, systematic and significant opportunities for using the data acquired by the Registry have not yet been grasped by health diagnosis and treatment centres for the assessment of clinical and therapeutic aspects. Cases collected through 1999 have not yet been acquired by ISPESL.

Acknowledgements
The activity of the Registry of Mesothelioma cases of Brescia has been possible thanks to the valuable cooperation of physicians operating in hospital diagnosis services and units and the health workers of Occupational Health and Safety Services. We also wish to thank the numerous workers that helped to facilitate the work performed.

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CONCLUSIONS

The main purpose of this report is to provide the first results of epidemiological surveillance activity for malignant mesothelioma performed thanks to the collaboration between ISPESL and five Italian regions, Piedmont, Liguria, Emilia-Romagna, Tuscany and Puglia, which over the past few years have set up systems to registry the cases in question and represent, in terms of resident population, 30.7% (17,450,190 residents) of the Italian population and, in terms of mortality, around 45% of national primary tumours of the pleura.
The reference legislation for this initiative is article 36 of Legislative Decree 277/91, which sets out the establishment within ISPESL of the National Registry of Malignant mesothelioma cases.
The need to put off no longer the creation of a national system of epidemiological surveillance of this tumoural pathology, even in the absence of a Prime Minister's Decree implementing the foregoing law provision, derives from the widely-held belief that an epidemic of Mesothelioma cases is ongoing in our country and in other European nations.
Such a belief is borne out by data on mortality and incidence taken from a number of statistical-epidemiological sources and from numerous national and international studies reported in literature and mentioned in the present publication.
The main factors that have had a bearing on the significant levels of exposure to asbestos in Italy have been the growing and widespread consumption of this material up to early 1980s, the relevant shortcomings in terms of hygiene characterising numerous productive sectors for a long time and delays in the banning of asbestos in various technological processes (Law 257/92). These conditions have left unaltered the possible growth in incidence and mortality for mesothelioma cases in Italy.
The epidemiological surveillance of the neoplasia in question, performed in a coordinated, standardised manner in several areas of the country at the same time is thus fundamental in assessing the frequency, evolution and reasons for the emergence of mesothelioma in Italy, identifying and eliminating or "defusing" undervalued or undetected sources of contamination, still present on the ground, and supplying elements of use in drawing up effective public health policies and optimising resource allocation.
It has been observed on this point that regardless of particular exposure scenarios, cases of mesothelioma regularly occur, and in quantities beyond all expectations, in those areas where cases are studied actively, systematically and in a structured manner. This leads us to believe that the frequency of mesothelioma cases correlated to asbestos exposure is currently underestimated. What has also been observed is the spread of mesothelioma among younger age groups, with tumoural pathologies affecting a higher number of worker categories and a significant number of cases caused by non-occupational exposure.
But the key question is: for how long must we continue to suffer the effects of undiscerning evaluations regarding the widespread use of materials containing asbestos?

Since the latency of mesothelioma is 30 years on average, we are currently recording the neoplastic effects of exposure, practically all of occupational origin, in the 1960s. But because in Italy the consumption of asbestos grew steadily until the 1980s the likely number of cases is at best destined to remain at current levels for at least another 10-15 years, as confirmed by national and international studies already mentioned in this report.

It should also be noted that these forecasts are based on the extrapolation of case series deriving from past occupational exposure caused by the direct use of asbestos. All projections based on mortality data do not take into account the emerging risk associated with the presence of asbestos as an environmental pollutant both in the workplace and in the environment.

The scenario, as it now appears, prompts two considerations:

- the first relates to past occupational exposure. The effects of workers' direct use of materials containing asbestos before its banning (1992) will probably be felt for another 10-15 years;
- the second relates to the intensive and wide use of materials containing asbestos, also outside production facilities, which has contributed to spread exposure also to unaware subjects, with the result of a difficult *a posteriori* identification. In Italy this has led to the creation of numerous sources of contamination, many of which undetected, a fact borne out by the cases of unknown exposure recorded in the Registry. The banning of asbestos has not resolved this serious problem which, as presented in this report, is starting to produce a large number of cases. At this point in time we cannot say whether the current trend will in the future assume greater proportions. There is no doubt, however, that this sort of exposure is particularly dangerous, as it affects persons totally unaware of the risk they are running.

The banning of asbestos has stopped the importing and mining of asbestos and the manufacture of new asbestos-based products, with a progressive casting off of existing asbestos. It is now necessary to enact all the technical provisions required by existing laws on this matter to ensure that the forced coexistence with asbestos, still used indirectly, does not cause exposure that could further raise the number of mesothelioma cases.

The above considerations reinforce the belief that the epidemiological surveillance of malignant mesothelioma should be continued and extended throughout the country. This aim is helped by ongoing expansion and improvement of collaboration with the CORs of Piedmont, Liguria, Emilia-Romagna, Tuscany and Puglia. These Centres constitute an invaluable point of reference for the epidemiological appraisal of the pathology in question as well as a pilot experience that can be extended to all regions.

New initiatives are now being developed in Sicily, Lombardy, Venetia, Marche, Campania, Sardinia, Basilicata and Friuli-Venezia Giulia, some more advanced than others, that herald

interesting practical developments, for which the Institute and CORs are providing their assistance and encouragement.

The desirable creation of a national flow of information on cases of malignant mesothelioma, characterised by active and exhaustive reports of cases and significant in-depth analyses, would indeed constitute a major contribution to the identification of strategies and priorities to clean up the environment and, in terms of the number of preventable cases, to an evaluation of the potential impact of prevention measures (Comba P, Magnani C, Botti C. L'individuazione delle priorità per il risanamento ambientale dall'amianto: aspetti etici. Epid Prev 2000; 24: 85-86).

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The National Mesothelioma Registry (ReNaM) is the result of the commitment, helpfulness and cooperation of all those who, at different levels, have helped with the recording of all cases of Malignant mesothelioma, in terms of both diagnosis and exposure, presented in this publication.

Special thanks go to the colleagues of the Operating Centres of Piedmont, Liguria, Emilia-Romagna, Tuscany and Puglia and to everyone that has collaborated with them, since without their help the ReNaM would never have started up and would not have been able to carry out its mission of awareness-creation and motivation, efforts that are now giving results with the start-up of a number of new regional initiatives.

Staff of the Laboratory of Occupational Epidemiology and Health Statistics wish to thank everyone involved, auguring that collaboration may continue as profitably as it has begun, and that the epidemiological surveillance of Malignant mesothelioma cases may continue and spread nationwide.

Massimo Nesti