Health surveillance for subjects with past exposure to asbestos: from international experience and Italian regional practices to a proposed operational model

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Summary. The authors have examined Italian and international approaches to the health surveillance of subjects with past occupational exposure to asbestos, with special emphasis on the practices adopted by some Italian regional governments. The principal theoretic features of a surveillance programme, such as its usefulness in terms of oncological prevention, have been described and an operational proposal has been put forward for the consideration of interested health operators.

Key words: asbestos, asbestosis, health surveys, occupational exposure, pleural diseases.

Riassunto (La sorveglianza sanitaria degli ex-esposti ad amianto: dalle esperienze internazionali e le attività regionali italiane alla proposta di un modello operativo). Gli autori hanno descritto alcune esperienze nazionali ed internazionali in tema di sorveglianza sanitaria dei soggetti con pregressa esposizione professionale ad amianto. Un'attenzione particolare è stata rivolta a quanto predisposto da alcune Regioni italiane. Vengono evidenziati i punti teorici rilevanti di un processo di sorveglianza, ad esempio l'utilità in termini di prevenzione oncologica, e viene avanzata una proposta operativa, per fornire elementi di riflessione agli operatori sanitari interessati.

Parole chiave: asbesto, asbestosi, indagini sanitarie, esposizione professionale, malattie della pleura.

PROFESSIONAL EXPOSURE TO ASBESTOS IN ITALY

According to the international database, Carcinogen Exposure (CAREX), there are an estimated 300 000 subjects in Italy with past exposure to asbestos [1]. Projections for some European countries envisage a trend of increasing numbers of deaths from mesothelioma until 2018, followed by a decrease [2]. A recent Italian study [3] forecast approximately 800 deaths per year from mesothelioma between 2012 and 2024.

The present paper, while not exhaustive, offers a review of the available scientific literature and identifies some interesting experiences of health surveillance of subjects with past occupational exposure to asbestos: it includes a summary of practices adopted by Italian regional governments that have formulated or are in the process of formulating an approach to the management of the problems posed by asbestos.

The study concludes with an operational proposal that is intended to offer Local Health Unit operators some points to consider when contemplating the establishment of a health surveillance programme.

THE EFFECTS OF ASBESTOS ON HEALTH

Specific aetiology:

- asbestosis: diffuse interstitial pulmonary fibrosis

caused by inhaling asbestos fibres;

- pleural plaques: circumscribed thickening of the parietal pleura, with or without calcification;
- diffuse pleural thickening: non-circumscribed fibrous thickening of the visceral pleura with areas of adherence to the parietal pleura and obliteration of the pleural space, with or without calcification, including obliteration of the costophrenic angle;
- benign asbestos pleural effusions: small unilateral effusions, usually asymptomatic, often occurring as blood-stained exudates with various types of blood cells and mesothelial cells. They are among the earliest manifestations of asbestos exposure. These effusions typically last for months, and may occasionally recur. Their presence can precede the occurrence of diffuse pleural thickening;
- malignant mesothelioma: tumour arising from the thin serosal membrane of the body cavities, occurring in the pleura, peritoneum, pericardium, tunica vaginalis testis. There are three histological types of malignant mesothelioma: epithelial, mixed and sarcomatous.

Pathologies of the respiratory apparatus of multifactor origin:

- lung tumour: malignant neoplasm of lung tissues, generally starting from cells lining the res-

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piratory tract. Exposure to asbestos is associated with all major histological types of lung carcinoma (adenocarcinoma, squamous cell carcinoma and oat-cell carcinoma);

- chronic bronchitis: mucus-producing cough on most days, for at least three months in two successive years;
- pulmonary emphysema: anatomical changes in lung marked by abnormal enlargement of air spaces distal to the terminal bronchioles, accompanied by destruction of the alveolar walls;
- chronic obstructive pulmonary disease (COPD): chronic condition marked by a not fully reversible chronic obstruction of the airways.

DIAGNOSTIC TOOLS

Respiratory function

Respiratory function tests in subjects with past exposure to asbestos should include measurement of static and dynamic lung volumes and carbon monoxide lung diffusion (Dl,co). The classic pattern of asbestosis is a restrictive ventilatory defect, but a combination of restrictive and obstructive respiratory impairment is not unusual, though an exclusively obstructive defect is rare. The differential diagnosis should consider the possible presence of COPD, restrictive defects due to obesity, or pleural alterations. Dl,co is usually reduced as a result of changes in the ventilation-perfusion ratio and reduced diffusion of gas in the alveoli and capillaries: this reduction is an early sign of asbestosis, but is not very specific [4]. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) have published a series of joint statements for lung function tests, specifically: a) general considerations for the correct performance of lung function tests [5]; b) comments on the standardisation of spirometry [6]; c) information on standardising the measurement of lung volumes using plethysmography, nitrogen wash-out and helium dilution [7]; d) criteria for the correct performance of Dl,co measurement [8]; and e) interpretative strategies for lung function tests (LFT) [9].

RADIOLOGY

Chest X-rays (CXR) are of major importance in the diagnosis of asbestos-related disorders. The International Labour Organisation (ILO) has elaborated a standardised system for the performance and classification of CXR used in the study of pneumoconiosis, which has recently been updated [10]. In mild cases of asbestosis traditional CXR are limited in sensitivity and specificity; subjects with histologically confirmed asbestosis have been positively diagnosed in 80-85% of cases [11]. Low dose computed tomography (LDCT) is more sensitive for detecting parenchymal lesions and pleural plaques. High-dose computed tomography (HRCT) is useful in ambiguous cases, such as when a normal CXR is accompanied by compromised respiratory function, or pleural involvement makes it difficult to assess the pulmonary parenchyma. An international system for the classification of pleural and parenchymal findings when CT is used in subjects with past exposure to asbestos would be helpful [12]. The use of computed tomography (CT) in screening programmes can identify non-calcified nodules in up to 50% of subjects at first check-up and up to 75% of those given yearly check-ups for 5 consecutive years; most of these nodules are benign [13, 14]. Computed tomography can be used as a supplementary diagnostic tool in individual cases, but the scientific usefulness of screening programmes for lung tumours in terms of reduced mortality [15, 16] and the risk of, paradoxically, causing lung neoplasms as a result of repeating tomography over long periods of time [17] advise against the generalised and routine use of this tool.

TUMOUR MARKERS AND PLEURAL MESOTHELIOMA

Recent studies have described the results of measuring the serum concentration of certain markers of malignant mesothelioma. Osteopontine, a bonederived glycoprotein, is present at higher levels in patients with some malignant neoplasms, including those of the lungs, breast, gastro-intestinal tract and ovaries. However, it is not tumour-specific, as it is expressed by several tissues in both normal and pathological conditions. Serum osteopontine levels have been compared in: a) subjects with no exposure to asbestos; b) patients exposed to asbestos and suffering from non-malignant asbestos-related disorders; and c) patients with malignant mesothelioma: the highest values were found in the latter group. Raised levels of osteopontine were also found in the second group, but they were not as high as in subjects with mesothelioma [18]. Serum osteopontine levels are not reliable for distinguishing mesothelioma from metastatic pleural carcinomas or benign pleural pathologies: further studies to investigate the usefulness of this protein in assessing tumour progression will be useful [19].

Mesotheline is an antigen found in mesothelial cells of the pleura, pericardium and peritoneum. It may be present in a number of tumours, including malignant ovarian neoplasms, pulmonary adenocarcinoma, endometrial carcinoma and carcinomas of the gastro-intestinal tract. Because it is also present in tumours other than mesothelioma, mesotheline is of limited use as a diagnostic tool. Soluble mesotheline-related proteins (SMRPs) have been found in the serum of patients with various types of neoplasm. In one study serum levels of SMRPs were measured in: a) subjects with malignant mesothelioma; b) patients with pulmonary fibrosis, benign pleural pathologies and neoplasms other than mesothelioma; c) healthy subjects with past exposure to asbestos: raised levels were found in the first group, in a few cases from the second group and in some subjects from the third. Few subjects with raised mesotheline levels from the third group subsequently developed malignant mesothelioma [20]. A prospective study confirmed the presence of higher levels of SMRPs in cases of malignant mesothelioma than in cases of other malignant pathologies involving the pleura or of benign asbestos-related pleural pathologies [21].

While in purely theoretical terms an early diagnosis of malignant mesothelioma can be an advantage from the prognostic point of view by identifying patients who might benefit from radical surgery, it should also be borne in mind that some healthy subjects (false positives) would inevitably endure anxiety without developing the disease. Before large-scale screening based on tumour markers can be recommended, we need to know the findings of prospective studies in terms of the sensitivity and specificity of tests, the history of individuals with high levels of a marker, and the impact of such screening programmes in reducing mortality [4, 22].

THERAPEUTIC TOOLS FOR TUMOUR PATHOLOGIES

Treatment regimes for lung tumours have been tried and tested and do not depend on the cause of the neoplasm (smoking, asbestos, etc.) [23, 24].

Surgery, chemotherapy and radiotherapy are the three tools for the therapeutic or palliative management of malignant pleural mesothelioma: one or more of these may be adopted, according to the particular circumstances of each clinical case [4, 25].

Surgery may be more or less radical, according to whether extrapleural pneumectomy or cytoreductive surgery is chosen, depending on the tumour stage and the patient's general health condition.

The aim of extrapleural pneumectomy is to remove as much of the tumour mass as possible, together with surrounding structures (lung, homolateral diaphragm, pericardium) and it carries a mortality rate of between 4 and 9%, while post-operative complications occur in 60% of patients. Surgery is followed by chemo- and radiotherapy, and average survival is 19 months. The absence of randomised clinical trials makes it impossible to define the role of this type of treatment in mesothelioma.

Cytoreductive surgery, while aiming to remove the tumour mass, does not involve the lung; survival would appear to be longer, but the absence of randomised clinical trials again makes it impossible to define its usefulness.

Pleurectomy and decortication are palliative treatments for effusion and for pain deriving from the tumour mass; recurrent effusions can be treated by inducing pleurodesis with sclerosants.

Brief radiation protocols directed to small portions of the pathology may be used in palliative pain treatment. In a multimodal approach, pneumectomy followed by intensity-modulated radiotherapy seems to be more effective locally than other more traditional treatment regimes, though without any improvement in survival.

Significant differences in survival rates have been found between patients receiving different chemotherapy protocols, although there would not appear to be any improvement in the quality of life. The US Food and Drug Administration (FDA) has approved the use of pemetrexed, an antifolate, in the treatment of mesothelioma, based on a randomised stage III trial that showed an average increase in survival of about 3 months in patients treated with pemetrexed and cisplatin [26]. The European Medicines Agency (EMA) has given similar authorisation [27]. The combination of carboplatin and pemetrexed has been shown to cause fewer side effects (nausea and vomiting) than the combination of cisplatin and pemetrexed [28].

The prognosis for peritoneal mesothelioma is worse and no treatments able to improve it are currently available.

LUNG CANCER SCREENING

The search for a method of screening for lung tumours began in the second half of the last century [29]: CXR and cytological sputum analysis were used to evaluate the efficacy of an approach based on the early diagnosis of this widespread type of tumour. No measurable benefits to the populations examined were found in terms of a reduction in the lung tumour mortality rate. It is thought that this can be achieved only through randomised studies in which subjects are randomly assigned to the screening or control groups. The greater sensitivity of CT compared with CXR has led various research groups to assess the efficacy of experimental screening programmes using LDCT for high-risk subjects, usually heavy smokers. No data on mortality have yet emerged from the studies under way [30]. The US National Cancer Institute (NCI) has enrolled more than 50 000 heavy smokers aged between 55 and 74 and assigned them randomly to be given either one annual LDCT or one annual CXR for three years. The results are expected to be published in 2011 [31]. To date it is believed that lung cancer screening programmes cannot be proposed because the data from both studies that used traditional CXR and those that used CT scanning present a high number of false positives, leading to invasive diagnostic procedures and unnecessary treatment [32].

EXPERIENCES OF HEALTH SURVEILLANCE International activities

A review by Merler covering the years 1969-1996 reviewed the national health surveillance programmes adopted in certain countries [33]. Two in150

teresting initiatives were launched in Finland and in Norway. In Finland [34] the protocol included collecting data on employment histories and an assessment of CXR. The participants were below 70 years of age and had worked for at least 10 years in construction, or one year in a shipyard or in the manufacture of asbestos products. Where a CXR revealed parenchymal lung or asbestos-related pleural lesions it was followed by a medical visit and LFT. Each subject was given information on the effects of exposure to asbestos and of smoking. The programme in the heavily industrialised Norwegian county of Telemark, where routine CXR had led to the diagnosis of several cases of asbestosis or pleural plaques, followed male subjects aged over 40 years in a cross-sectional survey to evaluate the incidence of exposure to asbestos and smoking habits [35, 36]. The respondents to a self-administered questionnaire were given primary CXR screening and those with past occupational exposure to asbestos were identified. Information on smoking habits was also collected. Subjects with fibrotic parenchymal lesions or pleural alterations at CXR were given further clinical and radiographic tests. The requisite criteria for a diagnosis of asbestos-related lung disease were past exposure, a radiographic lesion compatible with an asbestos-related pathology and the absence of past diseases that could have caused the observed CXR finding. This study differed in its approach from others in that the subjects with past exposure to asbestos are generally identified *a priori*. In South Africa a female population with previous occupational exposure to asbestos fibres (in mining) was examined as part of a protocol that included clinical examination with special attention to the chest, a questionnaire, postero-anterior (PA) CXR and sputum collection for the presence of asbestos fibres and ferruginous bodies [37]. Almost half the participants were born into families in which one or more adult relatives were employed in mining asbestos. Rohs et al. performed a followup study, 25 years after a primary CXR performed in 1980, of a group of former employees of a US company mining vermiculite in Libby, Montana, in a mine contaminated with tremolite [38]. The study aimed to quantify pleural and interstitial lesions and accumulated exposure to amphibole fibres. Vermiculite had been used in processing plants in Minneapolis, Minnesota, and had contaminated parts of the city, inducing the Minnesota Health Department (MDH) to conduct a survey to characterize of exposure of the community, in workers and in their families (members cohabiting at the time of their employment in the plant), and to make recommendations for future health studies [39]. The Port Allegany Asbestos Health Program (PAAHP), a non-profit organisation founded in 1981, responded in an original manner to concerns expressed in the local community (Port Allegany, PA, USA) about the temporary use (1964-72) of amosite by a local glass-making company [40]. During the 1980s the

PAAHP offered to those who had been employed by the company during the relevant period and their families a programme of health surveillance, health education (possible symptoms of neoplasms, early treatment for respiratory infections) and support for quitting smoking. The workers' doctors were given additional information on asbestos-related disorders.

ITALIAN EXPERIENCES OF HEALTH SURVEILLANCE

The health department of a metal-working company in Lombardy launched a programme of health surveillance for former employees who had been exposed to asbestos [41] aimed at investigating the risks, evaluating the possibility of preventive strategies against asbestos-related tumours, and taking steps to grant legal-medical recognition of possible occupational pathologies. A study conducted in Puglia [42] recovered the health records of subjects currently or formerly exposed to asbestos from the Italian Workers' Compensation Authority (INAIL) and of those who presented spontaneously at the Labour Medicine Unit of the Bari General Hospital between 1994 and 2005. It was thus possible over the years to report suspected occupational diseases in the subjects involved, including several cases of asbestosis, pleural plaques and pleural mesothelioma. This initiative had not been planned in advance, but re-examined the records of institutional activities performed over the years. A Local Health Unit in Livorno conducted a survey into the health of males formerly employed in an industrial glassworks [43] and exposed to asbestos, silica, polycyclic aromatic hydrocarbons (PHAs) and glass fibres. Subjects who had worked for at least one year for the company and whose employment there had terminated between 1942 and 1992 were contacted by post using the company's personnel records. Occupational histories and exposure levels were collected for each participating subject (about 50% of those contacted) and they were given a medical examination, spirometry and CXR. Several cases of diseases of suspected occupational origin (lung and bladder cancers, silicosis) were reported to INAIL. Pleural plaques were found, but no cases of asbestosis were identified. The reasons for the failure of the remaining subjects to respond were not investigated. The study mentions four cases of pleural mesothelioma. As part of a study to investigate a cluster of pleural mesotheliomas identified through the Regional Mesothelioma Archive, a in Tuscany launched a programme of health surveillance for former employees of a small metal-working company [44]. The subjects to be contacted were identified through the company's personnel records and each was notified of the initiative after their family doctors had also been informed. The protocol comprised the collection of employment histories, LFT (including Dl,co), PA chest radiography with left anterior (LAO) and right anterior (RAO) oblique projections and LDCT where deemed necessary.

ITALY – LOCAL UNPUBLISHED STUDIES AND REGIONAL BYE-LAWS ON PUBLIC HEALTH

In Italy the health surveillance of subjects with past exposure to asbestos is regulated by Legislative Decree n. 257 of 25 July 2006 which, among other things, demands that surveillance should continue even after exposure to asbestos has ceased [45]. This section describes the procedures that have been adopted at different times by some Italian regional administrations to address the needs of subjects with past exposure to asbestos: *Table 1* provides a comparison among the different initiatives.

Tuscany

The regional government of Tuscany has issued guidelines [46, 47] for dealing with persons with current or past occupational exposure to carcinogenic agents, including asbestos.

The role of the regional government is to provide general indications and information about reference centres; the public occupational health services (SPP) are responsible for coordinating, organising and implementing the activities; general practitioners (GPs) monitor their patients' general health and provide counselling on how to give up smoking and reduce other risk factors. The latter function can also be performed on an *ad hoc* basis through the Local Health Units or other specialised centres. In these cases the Services for Accident Prevention, Hygiene and Safety in the Workplace (SPISLL) should act as consultants and provide general guidance. Subjects still in employment refer to their GPs.

When requested to do so by individuals or groups of workers, the SPISLL are responsible for offering a two-tiered health monitoring service. The first tier is of a general nature and is available for all; the second and more specialist level is for those with high exposure and is aimed at diagnosing asbestosis at regional specialist facilities.

First level:

- a) information concerning health risks related to exposure to asbestos and preventive measures (giving up smoking and avoiding exposure to dusts and respiratory tract irritants);
- b) collection of occupational and medical histories through special questionnaires, examination of health records, information on subsequent health surveillance services;
- c) medical examination, with further tests where necessary.

Second level:

- a) LFT, including Dl,co (if not already performed or where available but performed more than 2-3 years previously);
- b) PA chest radiography where necessary, with LAO and RAO projections according to MacKenzie's

protocol [48] (if not already performed or where available but performed more than 2-3 years previously);

c) HRCT where necessary.

An CXR is in any case considered necessary for staging asbestosis.

The results of all tests will be reported to the SPISLL so that potential occupational diseases can be notified. Structured counselling programmes with specially trained staff are to be organised to help those wishing to quit smoking and to reduce possible additional risks. The regional guidelines also include the testing and validating of protocols for health surveillance in situations of particular interest.

Emilia Romagna

In 1998 the Regional Oncological Committee for "Health surveillance of subjects with past exposure to asbestos" issued regional guidelines [49]. No active surveillance is envisaged, in light of the lack of evidence of the efficacy of screening for lung tumours, mesothelioma and asbestosis. Regional facilities able to offer radiological services (CXR, CT) and LFT with specially trained staff will be indicated.

The guidelines envisage:

- a) occupational history, with a standard questionnaire to permit a semi-quantitative estimate of exposure;
- b) medical history, with a standard questionnaire to identify which type of counselling is required and which further tests. For respiratory tract symptoms the questionnaire of the American Thoracic Society – Division of Lung Disease (ATS-DLD-78) [50] is used;
- c) counselling: physicians supply information on asbestos-related diseases, on the importance of giving up smoking, and of suspending exposure to respiratory tract irritants. The possibility of medico-legal recognition of occupational diseases is illustrated and asymptomatic subjects are informed of the need for check-ups if respiratory symptoms appear. Only these three services are available to asymptomatic subjects with low past exposure.

Subjects with respiratory symptoms and low exposure are invited for further tests and treatment where necessary through the local GP or another physician of their choice. Subjects with high exposure and symptoms are referred to centres previously selected by the SPISLL or, if asymptomatic and more than 15 years have elapsed since first exposure and no recent (last 2-3 years) CXR is available, they follow the diagnostic procedures for asbestosis. Subjects with no previous CXR follow the same procedures even if less than 15 years have elapsed since first exposure.

Tests for asbestos-related diseases comprise:

pneumological examination and medical history (European Community for Coal and Steel

 ECSC [51] or ATS-DLD-78 [50] questionnaire);

152

Table 1 Italian Regions: comparison of health surveillance programmes						
Region	Friuli Venezia Giulia	Emilia Romagna	Campania	Veneto	Tuscany	Lombardy
Surveillance	Active	Passive	Active	Passive	Active	Active
Identification of ex-esposed	Register of ex- exposed subjects. Regional standards. GPs, SPISLL, Trieste University Labour Medicine Clinical Units inform interested persons. Ex-exposed apply for inclusion in the list	Information campaign	Active search through Campania Mesothelioma Register	Application to companies for names of ex-exposed (INPS, Local Health Units)	SPISLL act at the request of individuals or groups	Register of current and ex-exposed. Active search by Local Health Units
Procedures Occupational history	Regional standard	Semiquantitative estimate of exposure. If low and symptoms absent, only counselling; if low with symptoms, referral to GP or hospital. If exposure high, referral to specialist centres for asbestosis diagnosis	Standard questionnaire	Standard questionnaire, to be replaced by simplified version	Specific questionnaires; information on health surveillance and risks of exposure, and possible preventive measures	Identification of exposure level. Inclusion in Register of ex-exposed and referral to nearest hospital Labour Medicine Centre
Medical history	Information on smoking habits	Yes	Yes	Yes (standard questionnaire)	Special questionnaire. Examination of medical records	Yes. Assessment as per <i>Table 2</i> . Exposed may apply for inclusion in list of current and past exposed, and be included in surveillance programme
Medical examination	Pneumological	Pneumological and ECSC or ATS questionnaire	Pneumological	General	General	General
LFT	Static and dynamic lung volumes, Dl,co	Flow/volume curve and static lung volumes	Flow/volume curve and static lung volumes, Dl.co. Residual volume if needed	Spirometry	Flow/volume curve and Dl,co if needed (if not available or more than 2-3 years old)	Static and dinamic lung volumes, Dl,co
CXR	Yes	Yes (PA projection), ILO interpretation criteria	Yes, ILO interpretation criteria	Only if clinical problems are present	Yes (PA projection), ILO interpretation criteria (if not available or more than 2-3 years old)	Yes (PA, LAO, RAO projections), ILO interpretation criteria
СТ	HRCT on basis of definite criteria	LDCT or HRCT if CXR positive or borderline	LDCT, criteria being defined	Only if clinical problems are present	HRCT if deemed necessary	Doctor's discretion
Medico-legal procedure	SPISLL	SPISLL	Unspecified	Unspecified	SPISLL	Unspecified
Further diagnostic tests	Yes, based on definite criteria	Yes, based on overall assessment	Unspecified	Only if clinical problems are present	Unspecified	Yes, if any test is positive
Counselling	Anti-smoking, psychological	Anti-smoking, information on early diagnosis if requested. Medico- legal assistance	Anti-smoking	Limited anti-smoking, free anti-smoking course	Anti-smoking, and risk reduction	Appropriate lifestyle, possible diseases
Frequency	If tests negative, exposure <10 years, no follow-up Tests negative, or pleural plaques, exposure >10 years, follow-up after 5 years Asbestosis at age <75, follow-up after 3-4 years. No follow- up if age >75 Variations in procedures for special cases	No	To be defined	After three years on request	Unspecified	If tests negative, follow-up after 5 years (3 years for smokers >1 pack/day) If tests positive, frequency to be defined

Table 1 (Continued)							
Region	Friuli Venezia Giulia	Emilia Romagna	Campania	Veneto	Tuscany	Lombardy	
Regional level (standardisation)	Regional database. Examinations and tests by SPISLL	Regional guidelines. Examinations and tests at easily reached predefined centres. Requisite criteria, instruments and training of personnel	Regional coordination. Six regional operating units. Scientific committee coordinates for first two years: frequency and other measures to be defined			Regional procedures for definition and grading of exposure. Local Healt Units manage register of exposed subjects and surveillance	
Research	No	Epidemiological surveillance (study of cohorts independently of health surveillance)	Mesotheline, osteopontine, genetic markers	Comparison of CXR and TC in 1.165 subjects (sensitivity and false positives). Validation of simplified questionnaire	Possible health surveillance protocol trials	No	
Training and information	Information on asbestos-related risks, and on tests' results	Health operators. Users. Information on asbestos-related risks	Information on asbestos-related risks	Free anti-smoking course.	Coordinated information regional campaign together with preventive medicine departments	Information on asbestos-related risks	
Prescription charge	No	No	Unspecified	No	Unspecified	No	

- 2) LFT, following ATS guidelines [5], flow/volume curve and static lung volume measurement;
- PA chest radiography, in accordance with ILO guidelines [10]. Borderline cases and subjects with positive CXR are given CT or HRCT.

Where applicable, the SPISLL initiates the procedure for recognising an occupational disease. Cases of mesothelioma must be notified to the Regional Mesothelioma Register. All the healthcare services offered to subjects with occupational exposure are exempt from the prescription charge. An information campaign is to be launched at regional level addressed to all workers involved and to all subjects with past occupational exposure to asbestos. Finally, the Committee has proposed conducting a study involving approximately 3000 subjects employed in the asbestos cement sector and already enrolled in an epidemiological surveillance programme in order to quantify the efficacy of giving up smoking on the risk of developing lung tumours.

Lombardy

The regional government of Lombardy has established a Register of workers with current or past exposure to asbestos and adopted an operational protocol for their health surveillance [52, 53].

In order to classify individuals as currently or previously exposed to asbestos and to assign them to a high or a low exposure category, the following criteria must be taken into consideration.

Level of exposure is rated as high, medium, or low in accordance with existing criteria for measuring past exposure. Where such information is lacking, direct exposure to asbestos or asbestos products through specific tasks described in a special list is rated high; indirect exposure in places where such tasks are performed is rated moderate; exposure due to working in areas where insulating using asbestoscontaining materials has been performed is rated low (generic exposure).

Direct or indirect exposure for at least 10 years in the performance of tasks involving the continuous processing of asbestos, or generic exposure for at least 20 years is defined "long continuous"; direct or indirect exposure for more than 3 years or generic exposure for more than 10 years is defined as "short continuous"; infrequent exposure in places where asbestos-containing products or materials are processed or where caulking or casing with asbestos-containing materials is performed, for up to a maximum of 20 days/year is defined as "occasional".

Table 2 shows how the combinations of parameters are used to define the two classes of exposure, high (A) or low (B).

Local Health Units will be required to seek out subjects with past exposure during employment in

Table 2 Lombardy: classes of exposure to asbestos								
Exposure class	A (h	igh)	B (low)					
Intensity	High	Medium	Low					
Frequency/Time Type/Cause	Long continuous Occupational	Short continuous	Infrequent Familiar/Occupational					

specific types of company or in the performance of specific tasks (such as insulating, asbestos removal), including by retrieving data from the Mesothelioma Register, available for certain sectors of production.

Subjects considered as potentially exposed will be asked to attend a detailed assessment of their exposure and be given information concerning appropriate lifestyles, possible diseases and tests requested by the surveillance protocol. Consenting exposed subjects will be added to the Register of subjects with past exposure and advised to contact the nearest Occupational Medicine Operating Unit so that the surveillance programme can be initiated. Current or former employees in the listed types of employment or who believe they have been occupationally exposed may apply to the Preventive Medicine Department of their Local Health Unit for inclusion in the Register of former exposed persons and in the health surveillance protocol. The Local Health Units will provide information setting out the procedures to be followed.

The following procedures are planned for subjects assigned to Class A:

- a) record of occupational and relevant medical histories;
- b) clinical examination, with particular emphasis on the chest;
- c) PA CXR with LAO and RAO projections, as indicated in ILO 2003 [10];
- d) LFT, including Dl,co.

Those testing positive will be given further diagnostic tests. The scheduling of these procedures will be defined on the basis of the results of the first series of tests: an interval of five years would seem reasonable for subjects who initially test negative. Class B subjects will be given counselling.

Friuli Venezia Giulia

This Region published regional guidelines for the surveillance of current and former asbestos-exposed subjects in 2007 [54]: surveillance is intended to be a means of detecting possible occupational diseases and of offering anti-smoking counselling and information on the risks related to past exposure to asbestos. The programme provides a standard regional approach to this issue to enable the setting up of a centralised archive to store the relevant data.

The protocol comprises:

- a) occupational history;
- b) record of smoking habits;
- c) medical check-up, the results of which are classified as: negative; positive for non-occupational disease; positive for suspected or unequivocal occupational disease;
- d) CXR, classified as: positive for pleural plaques; evidence of pulmonary parenchyma abnormalities of probable occupational origin (asbestos); other occupational lung disease; neoplasm; other abnormalities not classifiable as of occupational origin;
- e) LFT, including Dl,co. The result is classified as:

normal; obstructive; restrictive; or mixed damage, with three degrees for each type;

- f) anti-smoking counselling for smokers, based on a standard regional programme;
- g) information about risks related to past exposure to asbestos;
- h) psychological counselling where SPISLL operators deem it necessary.

HRTC is provided on a one-off basis for subjects with continuous exposure for more than 10 years in the following cases: 1) finding of thickening/pleural plaque at CXR that cannot be explained by other non-occupational diseases; 2) positive or doubtful CXR for interstitial lung disease; 3) moderate or serious restrictive respiratory function, or altered lung diffusion. Where CXR or HRCT reveals suspect alterations (*e.g.* suspected neoplasm), subjects are referred to a lung or oncological specialist for further diagnosis. The results are stored on computer.

Where no symptoms or significant alterations are found, no further examinations will be performed. The SPISLL are responsible for notifying suspected cases of occupational disease.

In addition:

- a) no further check-ups are planned for subjects with negative finding at first clinical check-up and with past exposure to asbestos of less than 10 years;
- b) subjects testing negative but with past exposure to asbestos of more than 10 years may be advised to have another check-up after 5 years;
- c) subjects with pleural plaques will be advised to have a further check-up after 5 years;
- d) subjects with asbestosis who are under 75 years old will be advised to have a check-up after 3 years;
- e) no further check-ups are envisaged for subjects with asbestosis who are over 75 years old.

The SPISLL physicians may vary the above intervals when variations are justified. On conclusion of the tests, the subjects concerned and their GPs will receive a written report. Regional agreements are envisaged for subjects with past non-occupational exposure to asbestos to be followed by general medicine departments. These protocols will be reviewed after three years and additional periodic reassessments may be made to take account of new scientific evidence.

Campania

This regional government [55] has drawn up a health surveillance programme for workers and individuals with past exposure to asbestos: the programme is managed through six operational units in cooperation with the Campania Mesothelioma Register, which also manages a regional Register for asbestos-exposed subjects.

An active surveillance programme is available to subjects with high cumulative exposure (annual checkups) and passive surveillance is offered to subjects with low cumulative exposure (specific tests at the subject's request). Testing for carcinoma of the larynx is also included.

Each operational unit must be able to offer the services of a physician specialised in labour medicine, a social worker trained in counselling, an IT expert and appropriate instruments (computed spirometer to measure static and dynamic lung volume, Dl,co, electrocardiograph, blood collection unit and blood storage facilities). Special procedures are to be implemented to link these operational units to centres offering CXR and LDCT, to a Chest Surgery Unit, to a centre for Pathologic Anatomy and Histology able to perform differential immunohistochemical tests, and to a SPISLL for the notification of occupational diseases and the identification of possible previously unknown sources of exposure.

The Campania Mesothelioma Register will be required to guarantee homogeneous health surveillance protocols for subjects with past exposure to asbestos, to coordinate the biostatistical data produced by each operational unit and to ensure that the processed data are transmitted to the Regional Epidemiological Observatory. At the end of its first two years in operation, the Regional Mesothelioma Register will produce a report that will serve as the basis for the continuation of the health surveillance programme.

Regardless of the level of exposure, the initial check-up will comprise the following:

- a) occupational history and classification in the moderate- or high-exposure group;
- b) medical history;
- c) record of smoking habits;
- d) acquisition of existing medical records;
- e) medical examination;
- f) counselling with regard to tumour risks;
- g) LFT (flow/volume curve, Dl,co), performed at the operational unit;
- h) radiological exams (CXR, LDCT) performed by the network of units linked to the operational unit;
- i) assays of serum lung carcinoma and pleural mesothelioma biomarkers (osteopontine, SMRP) at the operational unit, coordinated by the Department of Experimental Medicine of Naples II University;
- j) entering of the biological monitoring data in a specific database.

The surveillance data will be comunicated to the Mesothelioma Register.

Subjects diagnosed with an occupational disease are to be given special assistance; those with neoplastic diseases are to be offered a fast track procedure for therapy and provisions for home care may be set in place.

Veneto

In a resolution of 28/12/2998 [56] the Veneto regional government approved the implementation of a research programme: "Testing of a model for surveillance and care of workers with past occupational exposure to carcinogenic substances: vinyl chloride monomer (VCM) and asbestos" involving a sample of subjects taken from those with past exposure (socalled ex-exposed) to asbestos and VCM [57]. At the end of 2005 the administration approved the 2005-2007 three-year plan for health surveillance, leaving approval of the guidelines on prevention and early diagnosis of damage from exposure to asbestos and the setting up of a programme of health education [58, 59] to be addressed in a later provision. The programme included among its objectives the definition and identification of risk levels for various groups of ex-exposed in different working conditions, and the drawing up of protocols or guidelines for appropriate and timely early diagnosis and health care according to risk levels. The criteria for access to screening (level of exposure, years since first exposure, age of subject), for assessment of the efficacy of screening, the care available and the timing of controls were to be defined. The aim of the project was to build a model based on exposure and effect variables on the basis of which to draw up a plan of action for subjects with past exposure to asbestos.

Companies were identified by examining applications submitted to the National Social Security Institute (INPS) in compliance with Law 254/92 and documents held by the SPISLL. The companies thus identified were then asked to submit a list of past employees who had been exposed to asbestos and ceased employment after 1970. Workers from companies in the building and railway rolling-stock maintenance sectors were included, as were those in the asbestos cement, insulating and asbestos removal business, and other groups of exposed workers previously identified by the Local Health Units involved in the project.

Information was gathered using the questionnaire drawn up by Magnani [60]. Of about 2000 subjects contacted, 1165 were given radiological screening (58%), PA CXR and LDCT. Lung nodular lesions were managed in accordance with the protocol elaborated by Henschke *et al.* [61].

In July 2005 the trial had identified 5 cases of lung tumour and 3 of malignant mesothelioma; a further 12 cases of primitive lung tumour had come to the notice of the SPISLL physicians in the course of their medico-legal work. During the trial project a comparison was made between the estimated exposure attributed by the interviewer and the estimate derived from multiple regression analysis, with a view to identifying and validating a model that would give a more streamlined and faster method of grading exposure levels. The model was considered acceptable for groups of at least 50-70 subjects with similar levels of exposure. The researchers believe that because of the low incidence of lung tumours in the subjects examined there may be an unacceptable number of false positives and a risk-biased risk/benefit ratio (exposure of healthy subjects to ionising radiation). Initially, because the incidence of lung tumours appeared greater in smokers who had been exposed to higher cumulative doses of asbestos, it was thought prudent to limit radiological screening to smokers and former smokers with cumulative exposure in excess of 200 fibres-year/ml. However, on the basis of recent studies [16, 62] that appear to demonstrate that LDCT screening does not reduce either the number of deaths due to lung cancer or the number of advanced cases diagnosed, the researchers deemed it reasonable to cease radiological screening as of December 2007.

In preparation for the surveillance programme the population of ex-exposed subjects was identified and software was created to trace them through the use of regional death records and data on discharges from hospitals. Surveillance aimed at diagnosing non-neoplastic disorders traceable to exposure to asbestos is guaranteed for all subjects with past exposure who request it.

The programme comprises: estimate of exposure, using a simplified version of the questionnaire drawn up for the trial stage; medical history and examination, including respiratory function tests; radiological exams (CXR, LDCT) only where indicated by clinical parameters; other tests (specialist visit if clinical parameters suggest it); brief anti-smoking interview and free access to an anti-smoking course. Check-ups are provided after three years, if requested by the subject.

Sicily

In 2004 the Messina Local Health Unit n. 5 (Villari C., personal communication, 12/07/07) initiated a health surveillance programme for former employees of a local company that had manufactured asbestos-cement products between 1958 and 1993. The programme also includes periodic medical check-ups for members of the workers' families who were living with them during the relevant period. Enrolment in the programme was voluntary. Participants were given information concerning the health risks associated with past exposure to asbestos, the diagnostic possibilities, preventive measures (giving up smoking, suspending exposure to respiratory system irritants). Where occupational diseases are suspected the appropriate procedures are set in place. The protocol includes collecting data on the medical and occupational histories of participants (the latter only for ex-employees), LFT, O2 saturation test, walking test, laboratory tests, PA CXR with LAO and RAO projections. Where necessary, CT without contrast medium or Positron Emission Tomography (PET) is performed and surgical and oncological consultations are available for further diagnosis or treatment. Subsequent check-ups are carried out at varying intervals.

COMMENTS

Other regional governments are currently in different stages of preparing health surveillance programmes. Liguria, for example, has published online information about controlling exposure to asbestos in the region's building sector [63] and a 2006 regional proposal is available online [64]. In July 2008 the government of Piedmont [65] opened a Regional Centre for Research, Surveillance and Prevention of Risks, and gave approval for its operating programme, which includes, among other provisions: health surveillance for subjects with past exposure and employees of companies involved in reclamation, the registering of mesothelioma, a list of exposed subjects and workers in the reclamation business, treatment protocols for mesothelioma and lung cancer patients.

A comparison between regional procedures reveals significant differences. While some regions favour the provision of health surveillance at the request of interested subjects, others aim actively to seek out subjects with past exposure as soon as their names are entered in a register.

Another aspect on which regional approaches differ is the level of centralisation and standardisation of procedures: Tuscany, for instance, while issuing generic guidelines, leaves decisions regarding actual procedures largely to the operators, while in Friuli Venezia Giulia a standardised procedure for classifying and managing health surveillance is in operation, so that data and findings can be compared at the regional level.

There is a more homogeneous approach to the careful recording of occupational histories (in more or less codified form), to the indications for certain clinical examinations (specialist consultation, LFT, CXR), albeit with some variations, particularly in regard to the type of projection used in chest radiography, the parameters for identifying subjects for CT, the frequency of medical check-ups and the classes of subjects for whom they are indicated. The facilities assigned to follow up the medico-legal aspects when occupational diseases are identified and to perform further diagnostic tests, as well as the centres for treatment, where necessary, are generally indicated.

Almost all the regions indicate anti-smoking counselling as paramount, though the procedures for implementing it are not set out in detail. Another frequent measure is the exemption from subscription charges for the relevant tests and examinations.

AN OPERATIONAL PROPOSAL Foreword

A health surveillance programme is not a research project, and the presentation of new scientific knowledge is not one of its objectives; nor is the adoption of experimental techniques or procedures whose usefulness has not already been documented in the literature as complying with its aims. A programme managed in accordance with available scientific evidence and international standards may provide a model that can be exported for use in other, similar circumstances. Those responsible for managing a health surveillance programme will need to identify, clarify and rationalise the programme's objectives and ensure that its contents effectively comply with the declared aims, which should be presented and discussed with those directly interested.

The following need to be defined: the criteria for inclusion in the programme, the diseases to be covered, the timetable for implementing the programme, the frequency and type of tests to be performed, the procedures for advanced diagnosis, the medical facilities involved, the procedures for communicating contents and findings, the role of general practitioners. The obligation to notify INAIL of possible cases of occupational diseases must also be borne in mind.

A thorough assessment of the programme's feasibility will be needed, together with a precise specification of the necessary resources, in terms of personnel, skills, instruments and appropriate work organisation.

Decisions must be taken regarding the persons responsible for the programme, tasks need to be assigned to specific individuals and, naturally, the amount of time and the premises available for implementing the programme need to be identified.

As well as being very knowledgeable regarding the medical issues involved in exposure to asbestos, the personnel involved in the programme will need to possess the appropriate skills to perform and interpret the medical tests and to answer all the questions posed by participants. As an example, specialists such as pneumologists, radiologists, pathological anatomists, surgeons, oncologists and the technical personnel experienced in performing the specific tests will be essential. Liaison with specialised centres for the treatment of neoplasms, and in particular mesothelioma, will be very important.

Aims

The specification of a programme's aims is fundamental, as they determine and influence the procedures for its implementation.

It needs to be made clear to participating subjects that the programme does not aim to prevent tumours or to provide an early diagnosis of neoplasms, given that to date there is no evidence that this is possible in the case of lung tumours or of mesothelioma.

Defining the categories involved in order to classify subjects for assignment to different procedures

Once the diseases to be addressed have been defined, the criteria for inclusion in the programme and for assigning participants to different classes need to be clearly stated, in terms of both medical history (*e.g.* duration and level of exposure, time since first exposure) and the clinical situation that emerges from the initial contact with the programme.

Computer storage

All the data collected will need to be held on computer, including test results, which should be stored in a standard format that does not preclude the possibility of reproducing the text of a report *in toto*. It would be helpful to request the persons who actually perform the tests and report the results to do so in summary form so as to facilitate the input of data and their subsequent processing. A rational selection of the findings to be held on computer would be appropriate.

General practitioners

One important element of the programme is the general practitioner, whose involvement is highly useful, whose possible responsibilities and field of action need defining and who needs to be provided with all the necessary information. General practitioners are constantly in touch with the programme's participants, including during the intervals between check-ups, and are thus in a position to detect and assess particular symptoms that may be relevant to the programme in advance of other physicians, as well as to exclude the need for subjects with symptoms or diseases not related to asbestos to be referred to the health structure managing the programme. As well as providing GPs with information and training, the possibility of periodic contacts (by post, email or meetings) to update them regarding the health of their patients could be considered; this would serve also to highlight the usefulness of their contribution to the programme.

Contents and timing of the programme

The minimum components of the health surveillance programme can be summed up as follows:

- 1. medical examination;
- 2. LFT (flow/volume curve, Dl,co);
- 3. CXR (performed and interpreted in accordance with ILO indications);
- 4. smoking cessation;
- 5. planned procedures for handling cases requiring further diagnosis;
- 6. pneumococcal disease and influenza vaccinations [66].

Points 1, 2 and 3 should be repeated at five-yearly intervals.

The findings of the initial check-up will form the basis of the decision as to whether a subject should be given subsequent tests. Workers who test negative for asbestos-related diseases and whose first exposure to asbestos is remote should not have to undergo further check-ups. These subjects should be informed that if specific symptoms, defined by the programme manager, should occur they should consult their GPs who will, if necessary, refer them back to the health centre managing the programme. Health and case history data collected during the initial phase of surveillance and during potential subsequent tests (even if the results are negative) should remain in a specially created database. Subjects who test negative and whose first exposure was less remote should repeat the check-ups five years after joining the programme. In these cases, too, the GP will be responsible for evaluating whether any respiratory symptoms are relevant and warrant a referral to the health centre managing the programme regardless of the specified time lapses.

Workers who test positive for asbestosis should be vaccinated yearly against influenza and pneumococcal disease in order to prevent any deterioration in respiratory function due to infection, and be given five-yearly check-ups in accordance with the programme [66]. Medical examinations, LFT and CXR should in any case be suspended on reaching an appropriate age. If relevant symptoms occur subjects should refer to their GPs, regardless of the timetable of the surveillance programme; the GP will have been appropriately informed and will be able, in specific circumstances, to refer the subject back to the health centre managing the programme.

Reference health structures for advanced diagnostic tests

The tests provided for in the programme, and in particular the CXR, may identify clinical situations, such as pulmonary nodules, that need further investigation. The surveillance programme should therefore specify the facilities equipped to carry out further tests and the steps to be taken by the interested subject from the moment a problem is identified until a clear diagnosis is reached and treatment decided. It is to be hoped that at the same time that these structures are identified, diagnostic protocols may also be planned and that these can be included in the document describing the health surveillance programme. Where the diagnosis and treatment of pleural mesothelioma are concerned, appropriate liaison will have to be arranged with structures and personnel having the necessary experience in this field [4].

All the services included in the programme and potential "second level" tests should be exempted from the prescription charge.

Cigarette smoking

In order to reduce the risk of individual lung neoplasms and to slow the deterioration of lung function, smokers should be encouraged to give up smoking. Counselling on how to cut down smoking effectively is usually offered by specially trained staff. The facilities implementing the programme should either identify centres that offer this type of counselling (www.iss.it/ofad/?lang=1.) or evaluate the possibility of training their own personnel to offer this service to smokers participating in the programme.

Quality

All personnel working on the programme, in whatever capacity, should meet constant and predefined standards: the collection, management and storage of data should follow well defined procedures. The performance of tests and the interpretation of their results should always follow codified and validated guidelines. This approach will enable the comparison of health data over the years, ensure that different operators provide homogeneous results, and minimise variations in findings between operators and in time. Every procedure should be recorded and the relative data (including decisions on what to do, what not to do, and why) stored so that, if necessary, each case history can be retrieved and each procedure fully understood by third parties.

All the instruments used must always be kept in optimum condition and should conform to requirements that, in the case of LFT and CXR for occupational lung diseases, already exist [5-10].

Reports of tests should be filed in terms that will enable subsequent comparisons to be made both for each individual and between individuals. The use of predetermined and validated procedures for test reports not only contributes to a proper evaluation over the years of the evolution of the relevant diseases, but also enables the data thus collected to be used for scientific publications, one of the means of publicising the working of the programme.

Communication

A considerable number of people will receive communications of differing kinds. The subjects participating in the surveillance programme should be given clear and comprehensible information regarding its aims and contents; this will enable them to rationalise their expectations, reduce the possibility of misunderstandings and help to foster confidence in the institutions and staff responsible for the controls. The role of GPs vis-à-vis their patients and their involvement in the protocol mean that they are unquestionably an important pillar of the programme: both on account of their existing acquaintance with the subjects and the possibility of being the first to detect relevant health problems and to take the proper measures, and on account of their role as "educators" in helping subjects to adopt healthy life styles and behaviour. Periodic reports on the programme should be forwarded to leading figures in the Local Health Units to promote full awareness of the field of operation of the health structure and of the possible need for human or other resources to ensure the smooth running of this public health initiative. The scientific community could be kept informed by means of publications.

Review

At intervals to be defined, the contents and calendar of the programme should be reviewed in the light of the characteristics of the participants and of scientific knowledge. All those interested should be properly notified of relevant variations in the content or aims of the programme.

CONCLUSIONS

The problems involved in health surveillance have been addressed in a more or less similar man-

159

ner against differing backgrounds. The differences may be attributed both to dissimilarities in local situations and to variations in aims and approaches. This review of research and experiences shows that some issues relating to neoplastic diseases remain open in terms of both an early diagnosis and, equally, of a satisfactory treatment schedule. This does not exempt physicians from offering patients with either neoplastic or non-neoplastic diseases assistance in the form of adequate care, medico-legal help in obtaining possible damages, and initiatives aimed at reducing individual risks. The review of studies, experiences and projects presented here is intended to provide food for thought to all those

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designated by the institutions to address these issues. The proposal put forward is intended both as a cue for debate and as a blueprint for the drawing up of guidelines for the management of health surveillance programmes for subjects with past exposure to asbestos, so that they can be as homogeneous as different local contexts allow. To this end the authors believe it could be helpful for the regional governments to meet to compare their experiences, to discuss technical and organisational aspects and to share their findings.

Received on 15 January 2009. *Accepted on* 24 March 2009.

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