

Asbestos and Cancer: An Overview of Current Trends in Europe

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This review assesses the contribution of occupational asbestos exposure to the occurrence of mesothelioma and lung cancer in Europe. Available information on national asbestos consumption, proportions of the population exposed, and exposure levels is summarized. Population-based studies from various European regions on occupational asbestos exposure, mesothelioma, and lung cancer are reviewed. Asbestos consumption in 1994 ranged, per capita, between 0.004 kg in northern Europe and 2.4 kg in the former Soviet Union. Population surveys from northern Europe indicate that 15 to 30% of the male (and a few percent of the female) population has ever had occupational exposure to asbestos, mainly in construction (75% in Finland) or in shipyards. Studies on mesothelioma combining occupational history with biologic exposure indices indicate occupational asbestos exposure in 62 to 85% of the cases. Population attributable risks for lung cancer among males range between 2 and 50% for definite asbestos exposure. After exclusion of the most extreme values because of methodologic aspects, most of the remaining estimates are within the range of 10 to 20%. Estimates of women are lower. Extrapolation of the results to national figures would decrease the estimates. Norwegian estimates indicate that one-third of expected asbestos-related lung cancers might be avoided if former asbestos workers quit smoking. The combination of a current high asbestos consumption per capita, high exposure levels, and high underlying lung cancer rates in Central Europe and the former Soviet Union suggests that the lung cancers will arise from the smoking-asbestos interaction should be a major concern. - *Environ Health Perspect* 107(Suppl 2):289-298 (1999). <http://ehpnet1.niehs.nih.gov/docs/1999/Suppl-2/289-298albin/abstract.html>

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Asbestos exposure can induce malignant and nonmalignant diseases. This article only addresses the former, and it is further restricted to those diseases unequivocally associated with asbestos, that is, mesothelioma and lung cancer. These diseases are induced by all commercial asbestos qualities (chrysotile, amosite, crocidolite, and anthophyllite) and by tremolite, with exposure-response patterns determined by fiber size and fiber type (1).

This article reviews the contribution of occupational asbestos exposure to the

occurrence of mesothelioma and lung cancer in Europe through a summary of available information on national asbestos consumption, proportion of the population exposed, and exposure levels. Population-based studies from various European regions on occupational asbestos exposure, mesothelioma, and lung cancer are reviewed to present information on population-attributable risk.

Asbestos Exposure in Europe

Asbestos Mining

Europe has long been an important producer of asbestos. Major chrysotile mines are or have been active in the USSR and in Italy, Greece, Cyprus, and Yugoslavia; Finland has been the only commercial producer of anthophyllite. In 1986 significant production took place in Italy, Greece, Cyprus, and Yugoslavia, for a total output of 2,688,000 tons, corresponding to 63% of world production. Asbestos mining in the world has sharply declined since 1990. The European share declined even further, from 63% of world production in 1986, to 58% in 1990, and 35% in 1996 (Table 1).

Some of the European asbestos producers have stopped the mining activity, such as Finland in 1975 (2), Cyprus in 1988 (3), and Italy in 1990 (4). Presently, Russia is the only significant producer of asbestos in Europe and the most important producer in the world (Table 1).

Trends in Asbestos Consumption

Industrial use of asbestos started 100 years ago, but became widespread during and after the Second World War. World asbestos consumption peaked in the mid-1970s and has since been decreasing. The latest available statistics for Europe refer to 1996: The world output was then approximately 2.2 million tons, most being chrysotile and only a few percent amphibole asbestos. Available sources refer to chrysotile as the only asbestos type mined in Europe. The main part of the asbestos output is used in the manufacturing of asbestos cement products [85% of the output globally (3); 85-90% within the European Union (5)].

Domestic consumption of asbestos decreased from 1986 to 1994 by 94% in Northern Europe, 76% in Western Europe, 82% in Mediterranean Europe, 69% in Central Europe, and 69% in the former Soviet Union. However, time trends in asbestos consumption are heterogeneous throughout Europe. The decrease started in northern and Western Europe, followed by the Mediterranean region and, after 1990, also by Central Europe and the former Soviet Union. The consumption of asbestos per capita in 1990 ranged from 0.07 kg in Northern Europe to 7.0 kg in the former Soviet Union. In 1994 the rank of the European regions was unchanged, but the range was between 0.004 and 2.4 kg (Table 2).

Proportion Exposed in the Population

Direct information on the proportion of workers exposed to asbestos is available from some of the European countries only and is provided by ad hoc surveys, which have been conducted mostly in the Nordic countries, and from case-control studies.

Occupational asbestos exposure in the general population was studied in a stratified

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Presently with Orestadshalsen, Malmö, Sweden. Abbreviations used: cc mix, case-control study with a mixed design; CI, confidence interval; corr, correlation study; f/ml, fibers per ml air; f-y/ml, intensity (f/ml) × duration of exposure (years); hosp cc, hospital-based case-control study; NA, not assessed/not applicable; OR, odds ratio; PAH, polycyclic aromatic hydrocarbons; PAR, population attributable risk; p(e), proportion of exposed cases/controls; POP cc, population-based case-control study; RR, relative risk.

Table 1. Asbestos mining in Europe. Output in tons.

Country	1986	1990	1996
Bulgaria	300	3003	500
Czechoslovakia	247	?	?
Cyprus	13,011	-	-
Greece	51,355	65,993	78,000
Italy	115,208	20,0003	-
Former Soviet Union	2,500,000	2,300,0003	720,0003
Yugoslavia	8,596	6,578	1,179
Europe total	2,688,717	2,392,871	799,679
World total	4,300,000	4,100,000	2,290,000

Symbols: ?, unknown; -, no production. *Estimated production. Information from British Geological Survey (71). Also, some asbestos has been mined in Romania with an estimated output of 4,600 tons in 1989 (71).

Table 2 Domestic asbestos consumption in tons from 1986 to 1994 by European region."

Region (population x 10 ⁶)	1986		1990		1994	
	Total, tons	Per capita, kg	Total, tons	Per capita, kg	Total, tons	Per capita, kg
Northern (18.6)	13,503	0.7	1,395	0.07	785	0.004
Western (234.8)	266,882	1.1	139,208	0.6	63,373	0.3
Mediterranean (143.9)	276,754	1.9	177,010	1.2	49,277	0.3
Central (87.7)	160,500	1.8	119,393	1.4	49,956	0.6
Former Soviet Union* (285.9)	2,231,500	7.8	2,096,300	7.3	687,100	2.4

*Northern - Denmark, Finland, Sweden; Western - Ireland, U.K., Germany (FR and OR), France, Austria, Switzerland, Netherlands, Belgium, Luxembourg; Mediterranean-Portugal, Spain, Italy, Greece, Yugoslavia, Albania; Central - Poland, Czechoslovakia, Hungary, Romania, Bulgaria. bData from British Geological Surveys (71). *Estimated production.

sample of 1275 subjects 18 to 73 years of age in Hordaland county, Norway (which is 10% of the Norwegian population). The lifetime prevalence of asbestos exposure reported at interview was 36% among men and 1% among women. It was associated with age, and was most prevalent (42%) among men 55 to 73 years of age (6).

A survey of men 40 years of age and over in nine municipalities in the county of Telemark estimated from self-administered questionnaires that 18% of the subjects had former asbestos exposure. Current and former smokers were more prevalent among those exposed to asbestos. On the basis of an interview with a subset of the subjects, the authors concluded that the questionnaire had a low sensitivity (but a high specificity) for asbestos exposure and that the real proportion of exposed men was probably 28 to 37% (7).

Malmberg and Hillerdal (8) found in a general health survey of men in the county of Uppsala, Sweden, which has a low proportion of its population employed in industry, that 7% of the men reported exposure to asbestos (self-administered questionnaire).

A national survey in Finland estimated from the occupational title that 14% of men 35 years of age or more had significant asbestos exposure (9). A similar estimate was obtained for the Helsinki area, based

on the lung tissue concentrations of asbestos fibers (10). The proportion of men with lung tissue concentrations indicating occupational exposure showed a clear age dependence (approximately 10% among men 40-49 years of age and 30% among men older than 60 years of age).

In another study conducted from 1978 to 1981 on a population sample (n=8000) representative of the Finnish population 30 years of age and over, 13% of the men and 0.8% of the women were classified according to the job title as probably exposed to asbestos (11). Virtually all had been exposed as construction or shipyard workers.

Thirty-six percent of male hospital referents in London reported ever having a job (held for at least 6 months) that was assessed from the occupational title to include definite or probable asbestos exposure, and 20% had had such exposure for at least 10 years. Only 3% of the women had a job with definite or probable asbestos exposure. The study was conducted in a London area where asbestos exposure, according to the authors, is "known to be high" (12). As in the study by Hilt et al. (7), sensitivity for self-reported asbestos exposure was probably poor. Only 45% of the patients classified as asbestos exposed based on their occupational title reported that they had worked with the material.

The specificity may have been better, as only 16% reported exposure, although their occupational title did not indicate it (12).

Information on the prevalence of asbestos exposure is also provided by population-based and hospital-based case-control studies (Tables 3, 4, respectively). The prevalence of definite exposure among the controls ranges from 2 to 15%.

Downstream Use

Most of the available information on exposure levels and effects are from asbestos mining and manufacturing processes, but in all countries, downstream use is also very important in terms of the number of workers exposed. For instance, in Poland it was estimated that in 1991 a total of 6000 workers were exposed in asbestos manufacturing and more than 12,000 in downstream use (13). In Finland 200,000 workers were estimated to have had an exposure to more than 2 fibers per milliliter air (f/ml) for at least 2 months during their working life. Seventy-five percent of these workers were exposed in the construction industry and only 5% in asbestos products manufacturing or in asbestos mining (9).

Current Exposure Levels

Asbestos exposure is limited in European Community (EC) countries. According to the European Directive of the EC 477/83 permissible limits are 1 f/ml for chrysotile and 0.5 f/ml for amphiboles. Several European countries have adopted lower limits or banned asbestos use, such as Denmark, Norway, Sweden, Finland, Holland, Germany, Switzerland, Italy, and France.

To our knowledge, no countries have introduced a ban on asbestos in Central and Eastern Europe. Comparison with current exposure in Western European countries is complex, as the occupational standard for asbestos is usually given as mass concentrations (2-8 mg/ml (1)), and fibers are not routinely counted.

As examples of current exposure, in Yugoslavia in 1987, mean fiber concentrations were 2 to 16 Until for textile manufacturing, 3 to 4 f/ml for friction materials production, and 1 to 4 f/ml for asbestos cement production (14). In Poland in 1994, exposure levels in the textile industry were estimated to be much greater than 2 f/ml air, approximately 2 f/ml in asbestos cement and friction products manufacturing, and greater than 0.5 f/ml, in downstream use (15). In Latvia in

1994, fiber concentrations in asbestos cement production ranged from 0.1 to 1.1 f/ml for the machine line to 1.1 to 5.2 f/ml for the milling and mixing areas (16).

Asbestos Exposure and Cancer Risk in Europe

We estimate the impact of asbestos exposure on European lung cancer and mesothelioma rates using population-based data. This approach has previously been used to estimate the proportion of lung cancer (17,18) and bladder cancer (18) attributable to occupational exposure. The population-based studies on asbestos and respiratory malignancies have rarely included individual dose estimates, but have the advantage of

contributing risk estimates for frequent exposures such as downstream use. These studies often use the occupational title as a proxy for the intensity of exposure and use the duration in a given activity to compute a proxy for the dose. Information about fiber type is rare. Dose-response models obtained from mining and manufacturing cohorts are also presented, but their use in predicting lung cancer and mesothelioma rates in the population is limited by the scarcity of information on intensity and frequency of exposure in downstream use.

Mesothelioma

Dose-Response Association. Mesothelioma risk is determined by time since first

exposure, asbestos type, and dose. The mesothelioma incidence (1) t years after starting exposure for a period of years has been estimated by the equation $I(t) = k \times c \times (tp - (t-d)p)$, where k is a constant possibly dependent on fiber type among other factors, c is the average fiber concentration level during exposure and p is a constant representing the power of time since exposure, to which incidence is proportional (1). k has been estimated to be on the order of 10^{-10} to 10^{-8} , with lower values for chrysotile than for amphibole exposure (19). The model fit to empirical data was reasonable. However, no measure of the uncertainty in the estimates was presented. From this model, combined with life table

Table 3. Population attributable risks for lung cancer from occupational asbestos exposure as estimated from population-based case-control, case-cohort, and correlation studies.

Reference	Study design	Cases/controls	Country	Sex	p(e)cases	p(e)controls	OR (95%CI)	PAR, % (95% CI)	Exposures
Pastorino et al., 1984 (49)	Pop cc	204/351	Italy	M	0.16	0.11	1.9 (1.1-3.5)	7.6b	Only asbestos
Pannett et al., 1985 (46)	Pop cc	312/312	U.K.	M	0.12	0.05	3.3 (1.6-7.4)	8.4b	Asbestos +PAHs
					0.07	NA	1.0 (0.5-1.9)	1.8	Moderate
					0.04		1.8 (0.7-4.4)		High
Oamber and Larsson, 1987 (57)	Pop cc	589/582 (dead) 456/453 (alive)	Sweden	M	0.17	0.08	2.6 (1.6-4.3)	1.0b	See text
Ronco et al., 1988 (47)	Pop cc	126/384	Italy	M	0.17	0.15	1.1 (0.7-1.7)	1.7b	
Parolari et al., 1992 (50)	Pop cc	19/255	Italy	M	0.05	0.02	2.4 (0.7-8.0)	2.8b	Asbestos production (see text)
De Vos Irvine et al., 1993 (28)	Corr		U.K.	M	NA	NA	NA	5.7 (2.3-9.1)	Exposure to amosite in manufacturing of insulation
Bovenzi et al., 1993 (54)	Pop cc	756/754	Italy	M	0.22	0.12	1.4 (1.0-1.9)	5.9	Possible
van loon et al., 1997 (48)	Case-cohort	524 cases Subcohort=1688	Netherlands	M	0.29	0.15	2.0 (1.4-2.8)	14.1	Definite
					NA	0.088	2.5 (1.3-4.8)	11.6	Ever vs never exposed
Martuzzi et al., 1998 (55)	Corr		Italy	M	NA	NA	NA	3.9 (2.1-5.7)	
Magnani and Leporati, 1998 (52)	Mixed	227 cases	Italy	M+F	0.27 (M) 0.21 (F)	NA	3.07 (2.2-4.3) M 2.05 (1.0-0.3) F	18.3 (11.1-25.6) M 10.1 (0-24.6) F	Occupational and domestic

Abbreviations: M, male; F, female; Pop cc, population based case-control study; case-cohort, population-based case-cohort study; Corr, correlation study; mixed, population-based study with mixed design; p(e), proportion of cases/controls exposed to asbestos; OR, odds ratio; PAR, population attributable risk = $(OR-1)/OR \times p(e)$; NA, not assessed/not applicable. Categories are mutually exclusive. bCalculated from data in the publication.

Table 4. Population attributable risks for lung cancer from occupational asbestos exposure as estimated from hospital based case-control studies and studies with mixed design.

Reference	Study design	Cases/controls	Country	Sex	p(e) cases	p(e) controls	OR (95%CI)	PAR, %	Exposures
Martischmig et al., 1977 (57)	Hosp cc	201/201	U.K.	M	0.29	0.14	2.4 (1.4-4.0)	17b	
Kiuis et al., 1986 (62)	Hosp cc	176/176	Norway	M	0.35	0.33	1.4 (0.8-2.3)	9.9b	Possible
					0.13	0.06	2.8 (1.2-6.7)	8.4b	low definite
					0.12	0.03	4.3 (1.5-12.0)	9.1b	High definite
Dave et al., 1988 (58)	Hosp cc	62/198	Sweden	M+F	0.10	0.02	3.3 (1.2-10.3)	6.7b	
Arvholm et al., 1993 (59)	cc mix	100/73+72	Sweden	M	0.34	0.26	1.6 (0.9-2.8)	13b	0.05-0.9 f-y/ml
					0.09	0.06	1.7 (0.6-5.1)	3.7b	>> t-f-y/ml
Kariainen et al., 1994 (63)	Hosp cc	113/297	Finland	M	0.23	0.15	1.7 (0.9-3.2)	9.5b	1-4.99 x 10 ⁵ f/g
					0.03	0.03	5.3 (1.9-14.8)	9.3b	25.0 x 10 ⁵ f/g
Wilkinson et al., 1995 (121)	Hosp cc	271/678	U.K.	M+F	0.34	0.26	1.7 (1.2-2.4)	14b	dried lung tissue
Mollo et al., 1995 (53)	Autopsy cc	31/178	Italy	M	0.29	0.14	4.2 (1.4-12.6)	10.7	>1000 asbestos bodies/g dried lung tissue

Abbreviations: M, male; F, female; Hosp cc, hospital based case-control study; cc mix, case-control study with a mixed design; p(e), proportion of cases/controls exposed to asbestos; OR, odds ratio; PAR, population attributable risk, $(OR-1)/OR \times p(e)$. Categories are mutually exclusive. bCalculated from data in the publication. Adenocarcinoma only.

methods and U.S. mortality rates, it was estimated that for an exposure of 0.5 f/ml for 20 years from age 25 years, the lifetime risk of mesothelioma from chrysotile exposure only would be 5 per 10,000, and for a mixed-fiber exposure (which is most prevalent in downstream use), 27 per 10,000 (19). The influence of exposure pattern (continuous/intermittent) has rarely been studied. A recent French study (20) indicated consistently higher risk for continuous as compared to intermittent exposure for the same cumulative dose. However, misclassification may have attenuated the risk more for intermittent than continuous exposure.

Mesothelioma Incidence. McDonald and McDonald (21) have suggested that mesothelioma incidence in the 1950s probably was 1 to 2 per million, indicating the background level in the absence of significant asbestos exposure in the population. In 1976, they published a population-based review of more than 4,000 mesotheliomas from 22 countries. They used sex- and age-specific rates from Canada as a reference and concluded that especially the Netherlands and the United Kingdom seemed to have a high mesothelioma burden. They also identified regional hotspots, including Dresden, which was an important center for asbestos production in the German Democratic Republic, and several centers for the shipbuilding industry around Europe.

Information from the European cancer registries indicates that mesothelioma incidence has been increasing among men since the 1960s (22). According to data published in *Cancer Incidence in Five Continents-VII* (23), 10 registries in the world present cumulative incidence rates for pleural malignancy in males higher than 15 per 1,000 and 7 of these registries are in Europe. Usually a high male-to-female ratio is observed (23). Mortality data from England, Wales, and Scotland indicate that mesothelioma deaths are increasing and that the rates are determined by age and birth cohort (24). Rates among women were one order of magnitude lower than among the men, but followed the same pattern. For men born in the 1940s, the predicted lifetime risk was 1%. A continued increase in mesothelioma deaths was predicted for another 15 to 25 years. Similar trends, without any indications of effects of preventive measures, due to the long latency time for mesothelioma was observed in France (25) and in Sweden (26). A time trend for pleural mesothelioma incidence

was also observed in the area of Rotterdam (27). Construction and related trades accounted for 24% of the deaths (24).

In Clydebank, a major shipbuilding area in Scotland with a high prevalence of amphibole exposure in the population, mesothelioma incidence peaked in 1989 at a rate of 512 per million (95% confidence interval [CI] from 265-896) (23), equaling the incidence of colorectal cancer in that year.

Mesothelioma risk from domestic and environmental exposures has been studied in different European countries. Studies up to 1987 have been summarized earlier (29). Magnani and co-workers observed that mesothelioma risk was increased for asbestos cement workers' wives (4 deaths vs 0.5 expected) (30) and for nonoccupationally exposed residents in the town in which the asbestos cement plant was operating (rate ratios 4-6 times higher than observed in other regions) (31). Howel et al. (32) observed a relative risk (RR) of 5.6 (95% CI 1.9-16.5) for para-occupational exposure and an RR of 2.0 (95% CI 0.9-4.2) for residential exposure to asbestos in Yorkshire.

Other reports indicate an increase in pleural malignancies in relation to asbestos industries but do not separate cases by route of exposure. An increase in the incidence of primary cancers of the pleura was observed in a Croatian area with an asbestos processing plant (33). Kogan and Nikitina (34) reported that mesothelioma incidence was 5-fold higher in a town with chrysotile mining in the Ural compared to the regional average.

Biologic Indicators of the Proportion of Exposed Cases. Usually the proportion of exposed cases has been estimated from occupational histories only. It has, however, been suggested that the work history, if possible, should be supplemented with biologic indicators of exposure. A few studies combining these exposure indices are available from Europe.

A study from the Helsinki area found that 71% of the 21 cases in males had an occupational history indicating past definite, probable, or possible exposure. The 2 cases in females in the study were classified as having had occupations with no evidence of asbestos exposure. Analysis of lung tissue concentrations by scanning electron microscopy also indicated that 71% had had an occupational asbestos exposure (total fiber concentrations > 1 million/g dry tissue), but the exposed categories were not entirely congruent. Thus, 86% of the cases

in males were assumed to have had at least possible occupational asbestos exposure either from their work history or from lung tissue fiber concentrations (35).

In a study from the Paris area, Paireon et al. (36) estimated from occupational histories that out of 131 patients with pleural malignant mesothelioma (115 men, 16 women), 37% had a definite or probable exposure to significant levels of asbestos dust. Exposure was also estimated by counts of asbestos bodies with light microscopy of bronchoalveolar lavage fluid or lung tissue. Asbestos body counts indicating nontrivial asbestos exposure were found in 34% of the subjects. Overall, 62% had either an occupational history indicating significant asbestos exposure, or a biologic sample indicating nontrivial exposure. The authors conclude that the results may reflect the fact that few asbestos-processing industries are located within the area, but also that it would have been useful to evaluate the cases that did not show elevated counts of asbestos bodies with electron microscopy.

In a series of 85 consecutive mesothelioma (80 males, 5 females; diagnosis accepted after review) from the area of Lund in Southern Sweden, 76% had a history indicating asbestos exposure; 46% had pleural plaques diagnosed by computerized tomography, autopsy, thoracoscopy, or thoracotomy; and 38% had asbestos body counts (light microscopy) in lung tissue, indicating definite occupational asbestos exposure. The authors conclude that 84% had either a history or biologic findings indicating exposure to asbestos (37).

Lung Cancer

Dose-Response Association. For lung cancer, the risk is usually modeled in a linear way. The model may be expressed as: standard mortality ratio (SMR) = $100 + b$ (ce), where b is the slope and ce is cumulative exposure (38). Contributions to the risk from duration and intensity are assumed to have equal weight (39). Estimates of the slope vary considerably between studies and seem to be associated both with fiber type (amphiboles associated with higher risk than chrysotile) (1) and industrial process per fiber length (textiles associated with higher risk than friction products) (19), and to the prevalence of exposure to other lung carcinogens such as tobacco smoking (40).

It has been assumed that the administered dose would correspond to tissue dose, without taking a limited clearance capacity in

the lung into account. This may, as shown by Smith (41), arbitrarily flatten or inflate dose-response relations with accumulated external dose; the first case may occur when workers with short, intense exposures are a significant part of the low-dose category, and the second case may occur when workers with intense exposure predominate in the high-dose category. Only one study (42) published risk estimates for different intensities and found that a cumulative approach, using the same data, overestimated risk at low intensities. It has further been argued that a threshold might exist which is equivalent to the threshold for minimal fibrosis. Some support for this theory is found in epidemiologic studies of subjects with and without small parenchymal opacities at chest radiography [among others, (38)], but has been contested in a recent study (12).

It has been suggested that the difference in risk associated with industrial process is due to different distributions of fiber size (39). Thus, for mining, slope estimates for chrysotile are approximately 0.05, for tremolite 0.7, and for crocidolite 1.0. For chrysotile friction products manufacturing, the slope has been reported as 0.06, and for chrysotile textile manufacturing as 1.0 to 2.0 (1). The U.S. Occupational Safety and Health Administration estimated an average slope across studies of 1 (95% CI 0.3-3.0) (43). The validity of the estimated slope for chrysotile asbestos has recently been questioned (44).

The dose-response relations from asbestos mining and manufacturing (1) imply that for an exposure of 1 f/ml for 40 years, the estimated risk above the background will vary from 2 to 80%, according to fiber type and process. It is also clear from the analyses of mining and manufacturing cohorts (1) that the asbestos dose estimated to double the lung cancer risk is quite high (50-2,000 f-y/ml). It thus seems likely that only a small proportion of all occupationally exposed subjects would experience such a risk, could these estimates be transferred directly to downstream use, for which no direct estimate is available.

Population Attributable Risk. Although relative risks for mesothelioma are extremely high for some amphibole exposures, lung cancer is the most important asbestos-related neoplasm in terms of excess deaths. Ratios between 1:1 and 1:10 between mesothelioma deaths and excess lung cancers have been observed in different cohorts (21). In population-based

case-referent studies, a ratio of 1:2 was estimated from Glasgow and the west of Scotland (high proportion of crocidolite exposure) (28) and a ratio of 1:5 from the greater Helsinki area (high proportion of anthophyllite exposure) (10).

Several estimates have been published on the proportion of lung cancer attributable to asbestos exposure in a population.

The proportion of cases in a population attributable to a certain factor can be estimated as $AR = p(e) \times (RR - 1) / RP$, where $p(e)$ is the proportion of exposed cases (45).

We present in Tables 3 and 4 the European studies, which either presented estimates of the population attributable risk (PAR), or data that allowed us to calculate it. All are case-control studies, except one case-cohort study from the Netherlands, and two studies from Scotland and Italy, respectively, that used the association between mesothelioma and lung cancer risk to estimate the PAR.

Usually the studies were performed in areas with a higher incidence of lung cancer or a higher prevalence of asbestos exposure than the national average and were restricted to males. These aspects must be considered when the results are generalized. A selection of the studies is listed in Table 5 with the crude RR for lung cancer in the study area in comparison with national rates. These crude ratios should be interpreted only as approximations, as it was not always possible to identify the exact areas covered by the study. As seen from Table 5, studies from areas with a lung cancer rate below the national average are less common and tend to have a lower proportion of asbestos-exposed cases and lower PAR, compared to those covering areas with rates above the national averages.

Further, several types of bias might influence the risk estimates made for these populations. The characterization of exposure is usually based on self-reported exposure or exposure reported by the next of kin for deceased subjects. It is likely that these reports lack precision, which would tend to decrease the contrast in exposure between cases and referents. Moreover, the quality of the information may vary between cases and referents. In principle, two types of information bias are likely to be of importance (and operate in opposite directions): a) cases (and their next of kin) might give more consideration to occupational exposures than healthy referents and thus be more likely to recall that a certain exposure has occurred; and b) for a higher proportion of cases than referents, information on the

work history may have to be obtained from the next of kin. Because the next of kin probably is less well informed, it is likely that significant exposures will be missed more often among cases than controls and bias the estimate towards the null hypothesis (see below).

All quoted case-control studies considered smoking either in the matching of cases and referents (46) or in the subsequent analyses (remaining studies). However, adjustment for smoking did not usually alter the risk estimate substantially and the effect of the adjustment was, as previously indicated by Simonato et al. (17), not consistent. Also, adjustments for residential area, type of dwelling, etc., had little effect on the estimates. The estimates from the case-referent studies were usually not adjusted [except in the studies by Ronco et al. (47) and van Loon et al. (48)] for occupational exposure to other carcinogens.

Estimated RR values for definite asbestos exposure are usually greater than 2. This is considerably higher than expected from the dose-response relationships observed in cohort studies of asbestos mining and asbestos products manufacturing (see above). Estimates of the PAR range from 1.8% (U.K.) to 53% (Italy). The individual studies are described below.

Pastorino et al. (49) studied an area in the Lombardy region (northern Italy) in which 74% of the male active population were estimated to be employed in industry, the proportion being substantially higher than the national average. For over half of the cases, information was obtained from next of kin. The corresponding proportion for controls was 10%. Information was collected about job title and industry for each job held > 6 months and no direct questions were asked about specific exposures. Exposures to asbestos, polycyclic aromatic hydrocarbons (PAHs), and other established lung carcinogens were classified as highly probable, uncertain, or absent. RR values were adjusted for tobacco consumption.

Ronco et al. (47) estimated the odds ratio (OR) for ever being engaged in the production of asbestos materials for at least 6 months for males in two areas in the metropolitan belt of Turin. Both cases and controls were deceased. Next of kin were asked about job title and industry, rather than specific exposures. Estimates were adjusted for cumulative cigarette consumption.

Parolari et al. (50) studied the association between respiratory cancer and occupational exposure to amosite in a small community close to a factory producing

Table 5. Population attributable risks for lung cancer in selected case-referent studies from definite occupational asbestos exposure by crude relative risk for lung cancer in the study area in relation to national rates.

Reference	Country/area	p(e) cases	Lung cancer crude RR, study area; national rates ^a	PAR ^b	Sex
Crude RR < 1					
Damber and Larsson, 1987 (57)	Sweden/Norrbottn, Vasterbotten, Västernorrland	0.17	0.83(21.3,18.3.23.1/25.3)	10c	M
Dave et al., 1988 (58)	SE Sweden/bstergotland?	0.10	0.98(24.7/25.3)	6.7°	M+F
Crude RR > 1					
Kjuus et al., 1986 (62)	Norway/Telemark, Vestfold	0.25	1.04(22.0, 30.1/25.2)	18C	M
Kariäläinen et al., 1994 (63)	Finland/Greater Helsinki	0.26	1.06 (81.3/76.9)	19	M
Wilkinson et al., 1995 (12)	U.K./Greater London	0.34	1.06(77.5/72.9)	14c	M+F
Arvholm et al., 1993 (59)	Sweden/Göteborg	0.43	1.13 (28.5/25.3)	16	M
Martischniß et al., 1997 (56)	U.K./Fryne and Wear?, Durham?	0.29	1.21 (001.3,74.8/72.9)	17c	M
Pastorino et al., 1984 (49)	Italy/Varese	0.28	1.33 (64.8/48.6)	16	M
Bovenzi et al., 1993 (54)	Italy/Trieste	0.29	1.53(74.6/48.6)	14	M

Abbreviations: p(e), proportion of cases exposed to asbestos; PAR, population attributable risk = $(OR-1)/OR \times p(e)$; RR, relative risk; ?, uncertainty about study area.

^aCalculated from age-adjusted rates for males. Morbidity data were used for Norway, Sweden, and Finland (72), mortality data for the United Kingdom, and Italy (73). ^bPAR for low and high definite exposures (Tables 3 and 4) have been summarized. ^cCalculated from data in the publication.

amosite insulating material. A case-control study was conducted that included cancer deaths and deaths from other causes (deaths from 1957-1986) as cases and controls, respectively. Exposure was defined as occupation in the factory according to both official rosters and information from senior workers. Results are presented for the respiratory tract as a whole, with no subdivision on laryngeal and pulmonary cancers. No pleural mesotheliomas were observed (51).

Magnani and Leporati (52) estimated the mortality from lung cancer in asbestos cement workers and in the general population in a small town in which an asbestos-cement factory had operated for decades. The lists of workers and their wives were linked to the lists of residents. Former cohort studies of the workers and their wives were used to obtain the distributions of person-years. Person-years for the unexposed population were estimated as the difference between the total and the exposed populations.

Mofo et al. (53) estimated the association between histologic types of lung cancer and indicators of asbestos exposure (asbestos bodies in the lung tissue and occupational history). Lung cancer cases and controls were selected from the same consecutive series of autopsies carried out from 1982 to 1992, matched by age and sex; asbestos-related diseases were excluded. Results are presented for adenocarcinoma and for the other histologic types together.

Bovenzi et al. (54) studied occupational exposure to recognized and suspected lung carcinogens among deceased lung cancer cases and deceased referents in Trieste, Italy. Shipbuilding and ship repair were

predominant industrial activities in this area, prior to and during World War II. An occupational history was obtained by telephone interviews with the next of kin. Classification of exposure was based on occupational title and knowledge about exposure conditions in the local industries. Risk estimates were adjusted for tobacco consumption and residential area. A clear increase in the RR was observed with increasing duration of exposure.

Martuzzi et al. (55) studied the proportion of lung cancer deaths attributable to living in municipalities with increased pleural neoplasm mortality in Piedmont, Italy. Asbestos was mined in this region, and textiles and asbestos-cement products were manufactured.

Several studies have been conducted in Great Britain, covering the Newcastle area (56), Merseyside (46), Glasgow and the west of Scotland (28), and London (12). Martischniß et al. (56) interviewed incident cases submitted for suspected lung cancer and matched referents submitted for other reasons. Direct questions on asbestos exposure were avoided. The interviewer was aware of the case-referent status and assessed the exposure. The RR estimate was obtained from an analysis stratified for the maximum daily cigarette consumption.

Pannett et al. (46) collected information on occupation and industry using a postal questionnaire sent to all male cancer patients, 18 to 54 years of age or, if they were deceased, to their next of kin. The response rate was low (52%). Lung cancer cases and controls (matched on age, county, smoking habits, and vital status) were selected from those who had responded to the questionnaire. Exposure to asbestos,

chromate, cutting oils, formaldehyde, and PAHs was assessed using a job-exposure matrix. As an alternative approach, exposure was graded by direct review of the full occupational histories. The estimates presented in Table 3 were obtained with the latter method, which was deemed more accurate. The authors conclude that the low age of the subjects included in the study may have decreased the relative risk observed from asbestos exposure, as compared to a study including the full age range. Remarkably, the possible bias introduced by the low response rate is not discussed.

De Vos Irvine et al. (28) estimated the PAR for lung cancer from asbestos exposure among men in Scotland in an ecologic correlation study, adjusting for smoking (using mortality from chronic bronchitis as a proxy), social deprivation, and air pollution. The area studied included Clydebank (see mesothelioma incidence).

Wilkinson et al. (12) studied lung cancer risk in relation to asbestos exposure (as estimated from occupational titles held at least 6 months) using two sets of referents with other respiratory diseases and cardiac diseases, respectively. All were incident cases and interviewed in person. The classification of occupational title employed had been shown to discriminate best between mesothelioma cases and controls in a former study. Occupations held within 15 years of the diagnosis were excluded from the analysis. The results were essentially the same using referents with respiratory and cardiac diseases. Estimates were adjusted for tobacco consumption, type of referral, age, and sex (referents were not matched). No clear increase in risk was observed with increasing duration of exposure.

Studies of the PAR for lung cancer from occupational exposures are available from three different regions in Sweden: northern Sweden (57), southeastern Sweden (58), and Gothenburg (59). Damberg and Larsson (57) collected longitudinal information with a postal questionnaire on occupation held at least 1 year, industry, exposure to asbestos, and smoking habits from relatives of decedents from lung cancer (cases) and matched referents (one set of dead and one set of living referents). The study included different areas: mining communities and heavy industrialized and rural communities. Similar results were generally obtained using the two sets of referents, except for asbestos exposure, where no increase in risk was observed in the comparison between dead cases and living referents, but was clearly evident when both cases and referents were deceased, with a higher risk for duration longer than 20 years. The authors suggest that the discrepancy is due to a conservative information bias, as living subjects are more likely to be aware that they are exposed to asbestos than their relatives. They do not attempt to validate the accuracy of reported asbestos exposure, but the explanation seems likely. Asbestos exposure was reported twice as often for referents who were alive as for those who were dead, whereas the proportions ever holding occupations including probable or possible exposure to asbestos (plumbers, electricians, engineers, boilermakers, welders, stokers, mechanics, turners, and seamen) are similar. Olsen (60) recalculated the estimate obtained by Damberg and Larsson (57), stratified for source of information and obtained an estimate of the PAR of 19%. Estimates were adjusted for smoking status.

Dave et al. (58) collected information on occupation and smoking, with a self-administered questionnaire, from incident lung cancer cases and matched (age, sex) hospital referents. The study area was more industrialized than northern Sweden. The estimates were stratified for cumulative tobacco consumption. The CIs were wide because of the small size of the study.

Jarvholm et al. (59) investigated subjects admitted for suspected lung cancer and included verified cancers as cases, and subjects in which no cancer was diagnosed as one set of referents. Another set was selected from the population registry. Gothenburg is an industrial city, with shipbuilding as a major industry until the early 1970s. Questions were asked about different occupational exposures (including

asbestos) and the occupational career. All subjects were classified according to cumulative asbestos exposure. Risk estimates were adjusted for smoking habits. Similar results were obtained with the two sets of referents. No clear increasing trend in the RR was observed for increasing dose, but the CIs were wide and did not reject it. Women were originally included in the study, but were all allocated to the lower dose category (<0.05 fly/ml). If they are included in the calculation of the PAR, it will decrease to 11% for lung cancer in both sexes.

Two other studies have been published from Scandinavia. Kjuus et al. (61,62) in Norway collected at interview detailed information on the occupational history of incident male lung cancer cases and age-matched referents from the same hospital ward. The areas covered by the investigation, Telemark and Vestfold, were reported to be somewhat more industrialized than the national average. Questions were asked on specific exposures. Cross-classification of occupational title and reported specific exposures among cases and referents did not indicate differential recall. Risk estimates were adjusted for average smoking intensity and urban/rural status. A significant increase in the RR was observed with increasing estimated asbestos exposure.

Karjalainen et al. (63) examined pulmonary concentrations of asbestos fibers in surgically treated male lung cancer patients from the greater Helsinki area and men from the same area who had been subject to forensic autopsy due to sudden or unexpected death. Information on smoking habits was obtained in personal interviews with the cases and with next of kin for the referents (participation rate 56%). Subjects with concentrations greater than 1 million Vg dry tissue assessed with scanning electron microscopy were considered as exposed to asbestos, in accordance with a previous study in which that concentration was "highly indicative" of past occupational exposure (10). Estimates of the RR were adjusted for age and smoking. The estimates quoted in Table 4 refer to all asbestos fibers. The corresponding estimates for crocidolite/amosite were: proportion of exposed cases = 15.0%, proportion of exposed controls = 7.7%, OR = 1.9 (95% CI = 0.9-4.1), PAR = 7.1%.

A large case-cohort study from the Netherlands (48) estimated the PAR among men for occupational lifetime exposure to asbestos, adjusted for age, smoking,

diet, and other occupational exposures. Cases were retrieved from a prospective cohort of men born 1917 to 1931, claimed to be fairly representative of the entire male Dutch population. Exposure assessment was made by occupational hygienists based on job title, industry, and calendar period. An association between exposure category and risk was observed.

Among those studies, two obvious outliers are identified on the low side, for which methodologic issues might explain the deviation. The study by Pannett et al. (46) had a very low participation rate which introduced an unknown, but possibly important, bias and included only subjects up to 54 years of age. The study by Ronco et al. (47) estimated only the effect of exposure in asbestos production, whereas the other studies included exposure in downstream use. On the other side, one study (50) had a very high estimate of the PAR. This study investigated a community with an exceptionally high proportion of the population exposed in asbestos work and the CIs are very wide due to a small number of cases. Thus the results are more difficult to generalize than those obtained in the other studies.

Interaction with Smoking. It has been suggested that the variable pattern of interaction (ranging from less than additive to supramultiplicative) observed between asbestos and smoking in epidemiologic studies reflects that both are complex carcinogens that can affect more than one stage of the lung carcinogenesis (64). Further, smokers might have an enhanced accumulation of asbestos fibers in the airways (65) and in the parenchyma (65, 66).

Kjuus et al. (61) estimated the etiologic fractions for lung cancer in Telemark to be 1% for asbestos alone, 22% for smoking and asbestos, and 61% for smoking alone. Thus, although elimination of tobacco smoking is most important for prevention of lung cancer, an important prevention can also be achieved by eliminating asbestos exposure. Langirid (67) estimated that for 3250 expected lung cancer cases in Norway from 1995 to 2015 associated with asbestos exposure, approximately one-third could be prevented if exposed current smokers quit smoking and that each person would gain, on average, 15 years of life.

Future Trends in Asbestos-Related Lung Cancer. The effect of current asbestos exposure in Europe depends on the proportion of the population that is exposed, exposure levels, and the underlying lung cancer risk. Langirid (67) estimated

that the absolute number of asbestos-induced lung cancers would decline in Norway from 1992 to 1993 on, as a consequence of reduced exposure in the late 1970s, combined with a ban during the 1980s. Exposure in the other Scandinavian countries has changed in a similar way and thus a reduction is to be expected.

There is a trend toward a reduction of asbestos use in all European regions, but the differences in per capita consumption of asbestos in 1994 were still high, with the highest levels in Central Europe and in the former Soviet Union.

Trends in tobacco use can have a large effect on asbestos-related lung cancer trends. The prevalence of male smokers has generally decreased in Europe during the last decade. Few data are available on tobacco consumption in Central Europe and even less for the former Soviet Union; the available information shows that cigarette consumption is steadily increasing in these countries (68). Lung cancer mortality among men is at present highest in Hungary, Belgium, the Czech Republic, the Russian Federation, and Poland (69). Underlying cohort effects indicate that the lung cancer rates will increase in Central Europe (22).

The combination of a current high asbestos consumption per capita, high exposure levels, and high underlying lung cancer rates in Central Europe suggests that the lung cancers that will arise from the smoking-asbestos interaction should be a major concern.

Conclusions and Discussion

Trends in asbestos production and use show a reduction in all European countries but with quite different slopes. In Europe, Russia and Greece remain the only important asbestos producers. Domestic asbestos consumption is still very high in the former Soviet Union, while a sharp decrease has occurred in Northern Europe and a moderate decrease has been noted in the rest of Europe.

Asbestos use is banned in several countries in Northern, Western, and Mediterranean Europe. Crocidolite use is severely limited by EC regulation. Although the trend in Western Europe is toward enforcing lower exposure limits, high exposure levels (mean concentration above 1 fl/ml) are still found in asbestos production and use in Central Europe and the former Soviet Union.

Only a small part of asbestos-exposed workers have been engaged in asbestos

mining or manufacturing. Most workers have been exposed in downstream use, mainly in the construction industry (approximately 85% of the asbestos is processed by the asbestos-cement industry) and in shipyards, but also in several other occupations such as car mechanics or railway workers. Those exposures have often been overlooked (70). Little is known also about the number of workers, the exposure levels, and the intensity of exposure in the asbestos removal industry. Estimates of the proportions of men who have had occupational exposure to asbestos range from 14 to 36%; estimated proportions for women are about one magnitude lower.

Mesothelioma incidence is increasing among men in Europe. Studies combining occupational history with analyses of lung fiber content indicate that 62 to 85% of all cases have had occupational exposure to asbestos.

Dose-response associations for lung cancer obtained in cohort studies have been published for asbestos mining and manufacturing. No studies are available for downstream use. These dose-response associations indicate that a high dose is needed to substantially increase the lung cancer risk. It could be assumed that such high doses are seldom acquired in downstream use. However, several population-based case-control studies, one case-cohort study, and two ecologic correlation studies have investigated the association between asbestos exposure and lung cancer. In these studies, downstream exposures prevail, as they are most prevalent in the population. These studies do, overall, provide higher risk estimates than would have been expected from the cohort studies.

Female cases of lung cancer were, in all studies that included both sexes, less exposed than males. Thus, estimates of the PAR that include both sexes tend to be lower than those that include only men. The latter are more numerous. Excluding the outliers discussed above, eight studies of male lung cancer that allow calculation of the PAR from asbestos exposure provide estimates for definite asbestos exposure between 5.7 and 19%. Six of those give estimates between 14 and 19%, representing the experience from industrial areas of Italy, Sweden, Great Britain, Norway, and Finland. Estimates of the PAR including both men and women range from 6.7 to 14%. It is difficult to estimate national PARS from these regional studies. Karjalainen et al. (10) suggest, based on a

comparison with mesothelioma incidence data, that in Finland the national average PAR for lung cancer may be less than half of their estimate (19%) for the greater Helsinki area. The Dutch study (48) is assumed to be representative for the male population of the Netherlands and estimates the PAR to be 11.6%.

Because asbestos and smoking have a synergistic effect on lung cancer risk, a substantial preventive effect for workers who have already experienced asbestos exposure can be achieved with the reduction of their smoking. Future trends for asbestos-induced lung cancer will depend on future consumption and exposure levels, underlying lung cancer rates, and smoking habits. Perspectives for Central Europe and Russia are alarming from this point of view, as all three determinants seem to be increased in relation to the rest of Europe. The smoking reduction strategy, however, is ineffective for mesothelioma, for which asbestos is the only known causative factor.

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