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The global burden of disease due to occupational carcinogens

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Background This paper describes the worldwide mortality and morbidity from lung cancer, leukaemia and malignant mesothelioma arising from occupational exposures to carcinogens, focusing on cases in the year 2000 resulting from relevant past and current exposures.

Methods The proportions of workers exposed to the carcinogens of interest, and their levels of exposure, were estimated using workforce data and the CAREX (CARcinogen EXposure) database. These were combined with relative risk measures (for lung cancer and leukaemia) or absolute risk measures (for malignant mesothelioma) to develop estimates of deaths, disability-adjusted life years (DALYs) and attributable fraction (for lung cancer and leukaemia).

Results There were an estimated 152,000 deaths (lung cancer: 102,000; leukaemia: 7,000; malignant mesothelioma: 43,000) and nearly 1.6 million DALYS (lung cancer: 969,000; leukaemia: 101,000; malignant mesothelioma: 564,000) due to exposure to occupational carcinogens.

Conclusions Occupational carcinogens are an important cause of death and disability worldwide.

INTRODUCTION

The International Agency for Research on Cancer [IARC, 2002] has classified 150 chemical or biological agents or exposure situations as known or probable human carcinogens. IARC has classified 87 agents, mixtures or exposure circumstances as Group 1 (carcinogenic to humans), including various chemical compounds, pharmaceuticals and bacterial and viral infections. Many of these are encountered in occupational settings, e.g. asbestos and cadmium. An additional 63 agents, mixtures or exposure circumstances have been classified as Group 2A (probably carcinogenic to humans). Those with occupational significance include diesel fumes and benzidine-based dyes [IARC, 2002].

Work-related malignancies can arise from a large variety of occupational exposures. However, three cancers (lung cancer, leukaemia and malignant mesothelioma) account for most occupationally-induced cancers. The exposures selected for assessment in this study were based on how common they may be, the risk arising from exposure, the strength of evidence and the availability of data. Table I shows each of the chemical and physical agents included, along with the related cancer.

Table I Occupational carcinogens and health outcomes included in the study

Occupational carcinogen	Outcome
Arsenic, asbestos, beryllium, cadmium, chromium, diesel exhaust, nickel, silica	Cancer of the trachea, bronchus or lung
Benzene, ethylene oxide, ionizing radiation	Leukaemia
Asbestos	Malignant mesothelioma

Other conditions have insufficient relevant exposure data, insufficient risk data, or insufficient number of cases worldwide to allow them to be usefully included. These conditions (and their causative exposures) include bladder cancer (aromatic amines, benzidine dyes, MOCA), nasal cavity and middle ear (hardwood dust, chromium VI compounds, nickel compounds), bone and articular cartilage (ionizing radiation), skin (arsenic, by-products of distillation, ionizing radiation), and lung cancer due to passive smoking in the workplace. In particular, bladder cancer had to be excluded because adequate global data on exposure were not available.

MATERIALS AND METHODS

The general methodology used in this study is described in detail elsewhere [Nelson et al., 2005]. In summary, the methods used to determine appropriate exposure-risk relationships varied depending on the condition in question. The proportions of workers exposed to the carcinogens of interest and their levels of exposure were estimated using workforce data and the CAREX (CARcinogen EXposure)

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database (described below). For lung cancer and leukaemia, relative risk measures obtained from the literature were applied to these exposure estimates to develop estimates of attributable fraction (AF). To calculate the attributable fraction of deaths or DALYs due to exposure to a specific health risk factor, the estimates of the proportion of a population (f_i) exposed to the risk factor at k levels of exposure,[1] and the relative risks of morbidity and/or mortality from a specific adverse health effect due to that exposure (RR_i) were combined in the following equation:

$$AF = \left(\sum_{i=0}^{k} f_i \, RR_i - 1\right) / \left(\sum_{i=0}^{k} f_i \, RR_i\right)$$

The attributable fraction estimates were applied to WHO estimates of deaths and DALYs (described below) for relevant causes of death in each of the 14 WHO subregions (termed "region" for the rest of this paper for simplicity – see [Nelson et al., 2005] for a description of the regions), to develop estimates of deaths and DALYs arising from the exposures included in the study.

A different approach was taken for malignant mesothelioma, for which the burden is best estimated by using absolute risk rather than relative risk, because virtually all malignant mesothelioma is caused by exposure to asbestos. This means that the attributable fraction for asbestos is essentially one, and the vast majority of asbestos exposure occurs in an occupational context. Therefore, the number of deaths was estimated by applying absolute risk estimates (deaths per year per fibre/ml.yr) to estimates of absolute asbestos exposure (measured in fibre/ml.yr). The proportion of deaths due to mesothelioma in a larger disease category (other neoplasms - Global Burden of Disease Code 77) was used to derive an estimate of DALYs due to mesothelioma; we multiplied this proportion by the number of DALYs in the category "other neoplasms" to estimate the DALYs due to mesothelioma.

Estimating risk factor levels

Assessment of the proportion of exposed workers was based on the distribution of the economically active population by economic sector [ILO, 2002], because the primary exposure data sources used in this analysis reported the percentage of workers exposed to specific carcinogens by economic sector (such as the agriculture, manufacturing and finance sectors). An adjustment factor of four was used to account for turnover in jobs with exposure to occupational carcinogens; i.e. the number of currently exposed workers was multiplied by four to estimate the number of ever-exposed workers. The factor of four was derived assuming a steady state exposed population with 10% turnover per year, a median exposure duration of 10 years and a follow-up period of 40 years, based on cohort modelling (Steenland and Driscoll, personal communication, 2002) (see [Nelson et al., 2005]).

The primary data source on the proportion of workers exposed to carcinogens for each economic sector was the CAREX database [FIOH, 1998], which presents data on the proportion of workers in the European Union exposed to 139 carcinogens (IARC Group 1, 2A and selected 2B agents) at levels above background in 1990–1993. These estimates were based on national workforce data and exposure prevalence estimates from Finland and the United States, adjusted for the economic structure of each country, then refined by national experts (Table II).

[1] Although a CRA analysis can be conducted with only two levels of exposure (e.g., "nonexposed" and "exposed," smaller values of k may compromise accuracy of the analysis.

Table II **Mean proportions of workers exposed to selected carcinogens, by economic sector and subsector, in the European Union[a]**

Carcinogen	Agriculture	Mining	Manufacturing	Electrical	Construction	Trade	Transport	Finance	Services
Lung carcinogens									
Silica	0.00372	0.23049	0.02327	0.01415	0.18860	0.00017	0.00476	0.00002	0.00061
Cadmium	0.00000	0.00000	0.00487	0.00287	0.00291	0.00002	0.00065	0.00000	0.00047
Nickel	0.00000	0.02025	0.01680	0.00352	0.00047	0.00007	0.00003	0.00000	0.00043
Arsenic	0.00054	0.00072	0.00400	0.00148	0.00134	0.00006	0.00000	0.00002	0.00011
Chromium	0.00000	0.00346	0.02079	0.00409	0.00237	0.00017	0.00370	0.00000	0.00225
Diesel fumes	0.00646	0.21970	0.01110	0.03358	0.05816	0.00485	0.13438	0.00000	0.00914
Beryllium	0.00000	0.00055	0.00207	0.00070	0.00004	0.00002	0.00011	0.00000	0.00003
Asbestos	0.01248	0.10248	0.00590	0.01702	0.05203	0.00292	0.00684	0.00016	0.00284
Leukaemogens									
Benzene	0.00100	0.00200	0.00300	0.00100	0.00100	0.01000	0.00500	0.00000	0.02000
Ionizing radiation	0.00000	0.01100	0.00000	0.03400	0.00000	0.00000	0.00400	0.00000	0.00000
Ethylene oxide	0.00012	0.00137	0.00060	0.00006	0.00027	0.00000	0.00002	0.00000	0.00057

It was assumed that the proportion of workers exposed to a particular carcinogen in a specific economic sub-sector was constant throughout the world; and that within a given economic sub-sector, both male and female workers and younger and older workers had the same probability of exposure (this probability of exposure was taken from CAREX, which gave a single combined probability based on both genders and all ages). Data were available on the distribution of males and female in the different economic sectors, and these were taken into account in the analysis.

The U.S. Occupational Safety and Health Administration (OSHA) Permissible Exposure Levels (PELs) were used to classify exposures as Low or High levels. The OSHA PELs for many carcinogens have not changed since their adoption in 1971, allowing a stable benchmark for comparison. Due to the greater prevalence of occupational health and safety regulatory programs and infrastructure in the A regions, it was estimated that a larger proportion (90% vs 50%, see below) of workers was exposed at the lower levels in these regions than in the BCDE regions[2] [Hewett, 1996; Roach, 1992]. Further, where it was necessary to specify an exposure level (to estimate lifetime cumulative exposure to asbestos), the exposure levels in the A regions were estimated to be lower than in the BCDE regions.

The occupational risk factors for cancer involve workplace exposure, at concentrations higher than background level, to various chemical and physical agents that are known to cause malignant neoplasms. Thus, the theoretical minimum risk corresponds to "no occupational exposure to physical, chemical or biological agents or other factors above background levels".

Lung carcinogens and leukaemogens

For lung carcinogens and leukaemogens, the peer-reviewed literature was searched for studies that included proportions of workers exposed above and below particular levels. There are many reports of exposures to contaminants in the literature, and even on the distribution of exposures at low and high levels in developed countries. However, there are few data on distribution of exposure values for developing countries. Using relevant data that could be obtained [Dosemeci et al., 1995; Myers et al., 1989; NIOSH, 2000; NIOSH, 1999; Partanen et al., 1995; Rees et al., 1992; Yin et al., 1987], partition factors were estimated for the A regions and for the B, C, D and E regions. For A regions, it was assumed that 0.90 of exposed workers had Low exposures (at/or below the PEL), and 0.10 had High exposures (above the PEL). For B, C, D and E regions, 0.50 of exposed workers were assumed to be exposed at a Low level and 0.50 at a High level.

Using the above approach, CAREX data, employment data (by economic sector) and population data for each region, the proportion of the population exposed to the lung carcinogens was estimated by region, age, sex and level of exposure. The same was done for leukaemogens.

Using the D region in Africa (AFR D) as an example, the data from Table II were applied to data on the proportion of the male workforce employed in industry sectors (Table III – first row), to produce a table of the proportion of the male workforce exposed to each of the lung carcinogens. These

[2] Regions: AFR = Africa; AMR = Americas; EMR = Eastern Mediterranean; EUR = Europe; SEAR = South-East Asia; WPR = Western Pacific; A: Very low child, very low adult mortality; B: Low child, low adult mortality; C: Low child, high adult mortality; D: High child, high adult mortality; E: High child, very high adult mortality.

were summed to produce an estimate of the proportion of the current, total male workforce in AFR D exposed to lung carcinogens (= 0.048) (Table III). Applying the turnover factor of four, and partitioning the workforce into High (0.50) and Low (0.50) exposed, it was estimated that 0.096 of the male workforce were exposed to lung carcinogens at low levels, and 0.096 at High levels (0.048 * 4 * 0.5 = 0.096). These estimates were multiplied by the proportion of the AFR D population that were in the workforce (0.85), to estimate that 0.082 of the entire population were exposed to lung carcinogens at Low levels, and 0.082 at High levels (0.096 * 0.85 = 0.082). The proportion of the male population who had never been exposed to lung carcinogens was estimated as 0.836 by subtracting the proportion exposed (at High and Low levels) from 1.0 (1.0 – {0.082 + 0.082} = 0.836). The same proportions were used for all age groups, but separate male and female proportions were estimated.

Table III Proportion of the male workforce exposed to lung carcinogens, AFR D

	Agriculture	Mining	Manufacturing	Electrical	Construction	Trade	Transport	Finance	Services	Total
All workforce	0.550	0.011	0.093	0.009	0.036	0.058	0.039	0.029	0.164	1.000
Carcinogen										
Silica	0.002	0.003	0.002	0.000	0.007	0.000	0.000	0.000	0.000	0.014
Cadmium	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001
Nickel	0.000	0.000	0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.002
Arsenic	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001
Chromium	0.000	0.000	0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.003
Diesel fumes	0.004	0.002	0.001	0.000	0.002	0.000	0.005	0.000	0.002	0.016
Beryllium	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Asbestos	0.007	0.001	0.001	0.000	0.002	0.000	0.000	0.000	0.000	0.011
Total										**0.048**

Asbestos

Malignant mesothelioma is virtually only caused by exposure to asbestos. To estimate the risk of malignant mesothelioma from asbestos, values above and below the asbestos PEL were selected to characterize the Low- and High-exposure groups. These values were used to estimate cumulative exposure, because the epidemiological data provided estimates of malignant mesothelioma risk in terms of cumulative asbestos exposure. For A regions, exposure was assumed to be at (for High exposure) or 20% of (for Low exposure) the prevailing PEL in the United States during the relevant years of exposure for various ages. For B, C, D and E regions, exposure was assumed to be 1.5 times (for High exposure) or 0.5 times (Low exposure) the prevailing PEL in the United States during the relevant years of exposure for various ages. Cumulative exposure estimates for workers of different ages were determined by modeling of artificial cohorts to estimate the average cumulative exposure for such a representative cohort in steady state. A steady state working population was produced by randomly assigning durations of exposure to exposed workers based on a log normal distribution with a mean of 9.8 years. Using this, the mean length of exposure (in years) at the end of 40 years could be estimated (by age) for all persons ever exposed in the cohort. Cumulative exposures for asbestos were then estimated by applying these exposure durations to the relevant exposure intensities for Low and High exposures, as described earlier. Cumulative exposures were calculated taking into account changes in the United States PEL for asbestos during the years of interest to the current analysis, with the level before 1972 of 12 fibres/ml decreasing, through several steps, to 0.1 fibres/ml in 1994 [Martonik et al., 2001; Nelson, 1997].

Risk factor–disease relationships

Relative risk estimates were used for lung carcinogens and leukaemogens. For malignant mesothelioma, an absolute rather than a relative risk approach was used. Relative and absolute risk values were obtained from relevant review studies. These review studies assessed risk measures for the main sites of occupational cancer, including the lung (which, for the purposes of this study, includes the trachea, bronchus and lung), the haematopoietic system (represented in this study by leukaemia) and malignant mesothelioma (Table IV).

Table IV Key sources used to assess the risk factor–disease relationship for selected occupational carcinogens

Selected risk factor	Health outcome	Key sources of evidence of causality and of risk measures
Lung carcinogens	Cancer of the trachea, bronchus or lung	[Nurminen and Karjalainen, 2001; Steenland et al., 2003; Steenland et al., 1996]
Leukaemogens	Leukaemia	[BEIR V, 1990; IARC, 1994; Lynge et al., 1997; Steenland et al., 2003]
Asbestos	Malignant mesothelioma	[Hodgson and Darnton, 2000; IARC, 1977; IPCS, 1998; Yano et al., 2001]

Relative risks for lung cancer and leukaemia were taken from studies of cohorts of workers with variable exposure durations and intensities, variable periods from the last exposure and variable lengths of follow-up. They therefore compare exposed with unexposed groups. In preparing relative risk estimates for exposure outcomes of interest, it was assumed that relative risks are the same for men and women; relative risk values are constant with age; and relative risks apply equally to the risk of developing the malignant condition (incident cases) and to the risk of dying from the condition (fatal cases).

Lung cancer

The methodology used in this analysis for all lung carcinogens was similar to that used by Steenland et al. (1996) and Nurminen and Karjalainen (2001), in that the proportion of workers exposed to occupational carcinogens was estimated and applied to relative risk estimates to enable the determination of attributable fractions. A mean relative risk of 1.59 was determined for eight lung carcinogens (not including radon), using data reported by Steenland et al. (1996). This was done by calculating a weighted average of the substance-specific relative risks, weighting the substance-specific relative risks by the proportion of workers exposed to each substance to determine a mean relative risk for workers exposed to the eight lung carcinogens[3] (Table V).

Table V Lung cancer relative risk, substance specific and weighted average[1]

Carcinogen	Combined relative risk[2]	Proportion of workers exposed[3]	Weighted relative risk[4]
Silica	1.33	0.0242	0.4685
Cadmium	1.49	0.0012	0.0258
Nickel	1.56	0.0031	0.0713
Arsenic	3.69	0.0010	0.0518
Chromium	2.78	0.0043	0.1732
Diesel fumes	1.31	0.0226	0.4320
Beryllium	1.49	0.0004	0.0079
Asbestos	2.00	0.0119	0.3466
Total[5]			1.59

1: Source: adapted from [Steenland et al., 1996]
2: Derived from major epidemiologic studies.
3: This is the average proportion, based on all regions.
4: This is the product of columns two and three of the table.
5: Weighted summary relative risk, weighted using proportion of workers exposed to each contributing carcinogen. This is the sum of the substance-specific weighted relative risks.

To produce relative risk estimates for Low and High exposure, it was necessary to partition the mean relative risks into values that correspond to low- and high-level exposure. A mean relative risk (of 1.6) was determined for the United States. Based on the estimates of 90% of American workers exposed at or below the PEL values and 10% exposed at or above the PEL values, and an estimate of the American population-attributable fraction of lung cancer due to occupation of 9% [Steenland et al., 1996], the mean relative risk of 1.6 was partitioned into a relative risk of 1.3 for low-level exposure to lung carcinogens, and 1.9 for high-level exposure[4] (Table VIII).

[3] This was done separately for each region, using the proportion of workers in each region exposed to specific agents to weight the relative risk for each of the agents. However, the resulting average relative risks were not meaningfully different from each other (all were close to 1.6).

[4] The United States ratios of the lower (1.3/1.6) and the higher (1.9/1.6) relative risks to the average relative risk were applied to the average relative risks estimated for each region to produce estimated relative risks at Low and High exposures for each region, but the results were not meaningfully different between regions.

Leukaemia

An approach similar to that used for lung carcinogens was applied to the leukemogens. The separate relative risks for the development of leukaemia arising from exposures to the main relevant occupational carcinogens were combined into single summary relative risks, one for Low exposure and one for High exposure (Table VI)[5]. Unlike lung cancer, the low- and high-exposure relative risks were available for each exposure, and these were directly incorporated into low- and high-exposure summary measures through the weighting process (Table VIII).

[5] Also as for lung carcinogens, this was done separately for each region, using the exposure prevalence of the workforce in each region to weight the exposure-specific risks. However, the resulting average relative risks were not meaningfully different between regions.

Table VI **Leukaemia relative risk, substance specific and weighted average. By exposure level**

Leukaemogen	Low exposure Combined relative risk[1]	Low exposure Proportion of workers exposed[2]	Low exposure Weighted relative risk[3]	High exposure Combined relative risk[1]	High exposure Proportion of workers exposed[2]	High exposure Weighted relative risk[3]
Benzene	2	0.0062	1.66	4	0.0062	3.32
Radiation	1.22	0.0010	0.16	1.57	0.0010	0.21
Ethylene oxide	1.1	0.0003	0.04	3.5	0.0003	0.13
Total[5]			1.86			3.66

1: Derived from major epidemiologic studies.
2: This is the average proportion, based on all regions.
3: This is the product of the preceding two columns of the table.
4: Weighted summary relative risk, weighted using proportion of workers exposed to each contributing leukaemogen. This is the sum of the substance-specific weighted relative risks.

Malignant mesothelioma

Risks were calculated for malignant mesothelioma on the assumption that exposure commenced some time between the ages of 20 and 45 years and ceased at age 65 years. Assuming a mixed fibre type, the lifetime risk of death from malignant mesothelioma is approximately 100 per 100 000/fibre.year per ml. (This combined estimate is based on best estimates of risk of 400 per 100 000/fibre.year per ml for crocidolite, 65 per 100 000/fibre.year per ml for amosite and 2 per 100 000/fibre.year per ml for chrysotile, and the changing mixture of amphiboles and chrysotile that has characterised exposure 20 and 50 years ago [Hodgson and Darnton, 2000].) Using this finding, cumulative risks at various cumulative exposures (and thus at various ages) were estimated, based on the exposure assumptions outlined above. Annual risks were then estimated within age groups by dividing the cumulative risks by 50, on the assumption that the adult lifespan was 50 years (ie death at age 70) (Tables VII and VIII).

Table VII **Annual mesothelioma mortality risk by cumulative exposure to asbestos. By region and exposure level**

	A regions				BCDE regions			
	Low exposure		High exposure		Low exposure		High exposure	
Age	Cumulative exposure[a]	Annual risk[b]	Cumulative exposure[a]	Annual risk[b]	Cumulative exposure[a]	Annual risk[b]	Cumulative exposure[a]	Annual risk[b]
20-29	0.1	0.000002	0.5	0.000011	0.3	0.000005	0.8	0.000016
30-44	1.1	0.000023	5.7	0.000113	2.8	0.000057	8.5	0.000170
45-59	8.4	0.000168	42.0	0.000841	21.0	0.000420	63.1	0.001261
60-69	12.2	0.000244	60.9	0.001219	30.5	0.000609	91.4	0.001828
70-79	17.4	0.000347	86.8	0.001735	43.4	0.000868	130.1	0.002603
80+	23.3	0.000465	116.3	0.002325	58.1	0.001163	174.4	0.003488

a In fibre/ml.yr
b Annual risk of death from malignant mesothelioma

Table VIII Summary of risk measures (relative risk and mortality risk) for occupational carcinogens

Health outcome	Risk measure	Estimate	Comments	Primary data sources
Cancer of the trachea, bronchus and lung	Relative risk	Low exposure: 1.3 High exposure: 1.9	Composite relative risk based on individual relative risk of arsenic, asbestos, beryllium, cadmium, chromium, diesel exhaust, nickel and silica	[Steenland et al., 1996]
Leukaemia	Relative risk	Low exposure: 1.9 High exposure: 3.7	Composite relative risk based on individual relative risk of benzene, ionizing radiation and ethylene oxide	[BEIR V, 1990; IARC, 1994; Lynge et al., 1997; Steenland et al., 2003]
Malignant mesothelioma	Annual mortality risk[a]	A subregions, low exposure[b]: 0.000002 to 0.000465 A subregions, high exposure[c]: 0.000011 to 0.002325 B, C, D and E subregions, low exposure[d]: 0.000005 to 0.001163 B, C, D and E subregions, high exposure[e]: 0.000016 to 0.003488	Mortality risks for malignant mesothelioma, based on cumulative exposure to asbestos, and age-adjusted for mean duration of exposure	[Hodgson and Darnton, 2000]

a The range represents risk at the lowest and highest relevant cumulative exposures.
b At 0.2 times the relevant United States PEL.
c At the relevant United States PEL.
d At 0.5 times the relevant United States PEL.
e At 1.5 times the relevant United States PEL.

DALYs

DALYs are "disability-adjusted life years", a weighted estimate of the number of years lived with disability. The weighting refers to the severity of the disability. DALYs require an estimate of the age at which a disease occurs, an estimate of the duration of the disease, and often an estimate of the life expectancy of the person who is ill. Calculation of DALYs also requires a severity weighting that is based on expert judgement of the relative importance of the disability. In the case of premature death due to the disease, the weighting is 1.0 and DALYs are in effect an estimate of the years of life lost due to premature death. (For this project, disability weights were developed in collaboration with Member States by methods including general and specific population surveys.) The DALY thus represents the gap between the current situation, and an ideal situation where everyone achieves an agreed standard life expectancy in perfect health. More detail is provided in the introductory paper to this series [Nelson et al., 2005] and elsewhere [Ezzati et al., 2004; Murray and Acharya, 1997].

RESULTS

Tables IX to XIII and Figure 1 summarize the attributable fractions, mortality and burden of disease for the occupational carcinogens considered here. For lung cancer, the attributable fraction arising from work varied from 5% in AMR-A to 14% in EUR-C, with overall attributable fractions for lung cancer estimated to be 10% for men and 5% for women (9% overall). There were estimated to be 102,000 deaths due to occupational lung cancer, nearly 90% of which occurred to males, and 969,00 DALYs. For leukaemia, estimates of the attributable fraction varied from 1% in EMR-D to 3% in several regions. There were estimated to be approximately 7000 deaths and 101,000 DALYs from leukaemia each year, with a much more even proportion between males and females than was seen for lung cancer, although approximately two thirds of the deaths and DALYs were due to male cases. There were estimated to be about 44,000 deaths and 564,000 DALYs from malignant mesothelioma. For each condition, deaths were predominantly among older persons up to 79 years, whereas DALYs tended to be highest in the younger age groups.

Table IX Attributable fractions (per cent) for lung cancer and leukaemia caused by workplace exposure

Region[1]	Lung cancer			Leukaemia		
	Males	Females	Total	Males	Females	Total
AFR-D	9	4	7	3	1	2
AFR-E	9	4	7	3	2	3
AMR-A	6	2	5	3	3	3
AMR-B	11	3	8	2	2	2
AMR-D	12	2	8	3	2	3
EMR-B	12	2	9	3	2	2
EMR-D	9	3	7	2	1	1
EUR-A	7	2	6	3	3	3
EUR-B	12	4	10	3	2	3
EUR-C	15	9	14	2	2	2
SEAR-B	10	4	9	2	2	2
SEAR-D	11	4	9	2	0	2
WPR-A	8	3	6	2	2	2
WPR-B	12	7	10	2	2	2
World	10	5	9	2	2	2

1: Regions: AFR = Africa; AMR = Americas; EMR = Eastern Mediterranean; EUR = Europe; SEAR = South-East Asia; WPR = Western Pacific; A: Very low child, very low adult mortality; B: Low child, low adult mortality; C: Low child, high adult mortality; D: High child, high adult mortality; E: High child, very high adult mortality.

Table X **Deaths (000s) from lung cancer, leukaemia and malignant mesothelioma caused by workplace exposure**

Region[1]	Lung cancer			Leukaemia			Mesothelioma		
	Males	Females	Total	Males	Females	Total	Males	Females	Total
AFR-D	0.6	0.1	0.7	0.1	0.1	0.2	0.9	0.5	1.4
AFR-E	0.9	0.2	1.0	0.2	0.1	0.4	1.0	0.7	1.7
AMR-A	6.7	1.6	8.3	0.4	0.4	0.8	0.5	0.2	0.7
AMR-B	3.6	0.4	3.9	0.2	0.2	0.5	1.7	0.5	2.2
AMR-D	0.2	0.0	0.2	0.1	0.1	0.1	0.2	0.0	0.3
EMR-B	1.0	0.1	1.1	0.1	0.0	0.1	0.5	0.1	0.6
EMR-D	1.3	0.1	1.4	0.2	0.0	0.2	1.2	0.5	1.7
EUR-A	11.1	1.2	12.2	0.7	0.5	1.2	0.8	0.3	1.1
EUR-B	5.8	0.5	6.3	0.2	0.1	0.3	1.2	0.7	2.0
EUR-C	12.4	1.5	13.9	0.2	0.2	0.3	2.2	1.7	3.9
SEAR-B	3.1	0.2	3.3	0.2	0.1	0.3	1.4	0.7	2.1
SEAR-D	10.9	0.9	11.8	0.5	0.1	0.6	5.8	3.2	9.0
WPR-A	3.4	0.5	3.9	0.1	0.1	0.2	0.4	0.2	0.5
WPR-B	27.0	7.1	34.1	1.0	0.6	1.6	9.9	5.9	15.8
World	88.0	14.3	102.3	4.2	2.6	6.8	27.7	15.3	43.0

1: Regions: AFR = Africa; AMR = Americas; EMR = Eastern Mediterranean; EUR = Europe; SEAR = South-East Asia; WPR = Western Pacific; A: Very low child, very low adult mortality; B: Low child, low adult mortality; C: Low child, high adult mortality; D: High child, high adult mortality; E: High child, very high adult mortality.

Table XI **DALYs (000s) due to lung cancer, leukaemia and malignant mesothelioma caused by workplace exposure**

Region[1]	Lung cancer			Leukaemia			Mesothelioma		
	Males	Females	Total	Males	Females	Total	Males	Females	Total
AFR-D	6	1	7	2	1	3	12	7	19
AFR-E	9	2	11	4	2	6	13	10	24
AMR-A	53	13	65	4	3	7	6	2	8
AMR-B	34	4	38	4	4	8	22	7	28
AMR-D	2	0	2	2	1	2	3	1	4
EMR-B	10	1	11	2	1	3	7	1	8
EMR-D	14	2	16	3	1	4	16	8	24
EUR-A	89	9	99	6	4	10	9	3	12
EUR-B	60	5	65	3	2	5	15	9	24
EUR-C	127	14	140	2	2	4	26	18	44
SEAR-B	32	3	34	3	2	5	18	10	28
SEAR-D	109	11	120	10	1	11	77	51	128
WPR-A	23	3	26	1	1	2	4	2	6
WPR-B	257	76	333	19	11	30	129	80	209
World	825	144	969	66	35	101	356	207	564

1: Regions: AFR = Africa; AMR = Americas; EMR = Eastern Mediterranean; EUR = Europe; SEAR = South-East Asia; WPR = Western Pacific; A: Very low child, very low adult mortality; B: Low child, low adult mortality; C: Low child, high adult mortality; D: High child, high adult mortality; E: High child, very high adult mortality.

Table XII **Age-specific attributable fractions[a], deaths and DALYs for lung cancer, leukaemia and malignant mesothelioma, males**

	Age group (years)						
	15–29	**30–44**	**45–59**	**60–69**	**70–79**	**80–89**	**All ages**
Attributable fractions (%)							
Lung cancer	11	11	10	10	10	9	10
Leukaemia	3	3	3	3	3	3	2
Deaths (000s)							
Lung cancer	0.3	3.2	20.0	30.5	26.1	7.9	88.0
Leukaemia	0.8	0.5	0.7	0.8	0.9	0.5	4.2
Mesothelioma	0.3	2.6	11.8	6.7	4.7	1.6	27.7
DALYs (000s)							
Lung cancer	10	76	306	279	136	18	825
Leukaemia	29	13	11	7	4	1	66
Mesothelioma	10	66	190	63	24	4	356

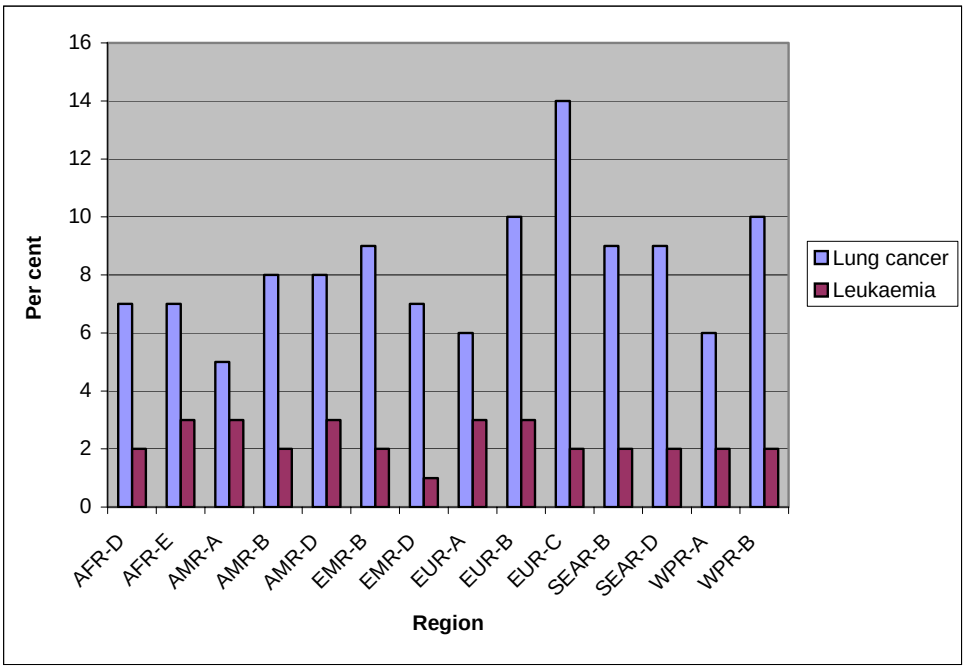
a Attributable fractions are not presented for mesothelioma, because virtually all mesothelioma is due to asbestos exposure, and most exposure is related to work.

Table XIII **Age-specific attributable fractions[a], deaths and DALYs for lung cancer, leukaemia and malignant mesothelioma, females**

	Age group (years)						
	15–29	**30–44**	**45–59**	**60–69**	**70–79**	**80–89**	**All ages**
Attributable fractions (%)							
Lung cancer	5	5	5	5	4	4	5
Leukaemia	2	3	3	3	3	3	2
Deaths (000s)							
Lung cancer	0.1	0.7	3.2	4.1	4.3	1.8	14.3
Leukaemia	0.3	0.3	0.5	0.4	0.6	0.5	2.6
Mesothelioma	0.0	1.3	5.9	3.7	3.0	1.3	15.3
DALYs (000s)							
Lung cancer	3	19	52	41	25	4	144
Leukaemia	10	8	8	4	3	1	35
Mesothelioma	6	41	103	37	18	3	207

a Attributable fractions are not presented for mesothelioma, because virtually all mesothelioma is due to asbestos exposure, and most exposure is related to work.

Figure 1 **Attributable fractions (%)in 2000 from lung cancer and leukaemia caused by workplace exposure. By region.**



DISCUSSION

The estimated overall attributable fractions for lung cancer of 10% for men and 5% for women (9% overall) are similar to those from a recent United States study, based on a review of relevant studies, in which the attributable fraction for lung cancer was estimated to be between 6% and 17% for men, and to be about 2% for women [Steenland et al., 2003]. A similar Finnish study used estimates of 29% (men) and 5% (women) [Nurminen and Karjalainen, 2001].

Estimates of leukaemia attributable risk varied from 1% in EMR D to 3% in several regions. The estimated 2% attributable fraction for leukaemia compares to a range 0.8% to 2.8% for the United States [Steenland et al., 2003], and 18% (men) and 2% (women) for Finland [Nurminen and Karjalainen, 2001]. The higher Finnish estimate seems to arise from the inclusion of occupational exposure to electromagnetic fields, from the reliance on different studies for relative risk estimates, and from the exposure patterns in the Finnish population.

The number of deaths estimated for malignant mesothelioma (43,000) do not have a direct comparison. Recent studies suggest that each year there are about 700 malignant mesothelioma deaths in Australia [Leigh and Driscoll, 2003] and 700 in Japan [Furuya et al., 2003]; 2,600 in the United States [Price and Ware, 2003]; and about 5,000 (male deaths) in Western Europe [Peto et al., 1999]. The vast majority of these will have arisen from work-related exposures. Comparable results from this analysis in terms of deaths are 500 in WPR-A, 700 in AMR-A and 1,100 in EUR-A, respectively. This suggests that the results from this analysis underestimate the overall number of deaths by about a factor of at least two, with larger underestimations probably present for some regions, and overestimations possible for others.

Quantitative and qualitative sources of uncertainty

Estimates of risk reversibility

Lung cancer, leukaemia and malignant mesothelioma typically develop many years after first exposure, with latencies of the order of at least 10 years for lung cancer and leukaemia, and up to 60 years for malignant mesothelioma. It is not clear to what extent the risk of developing cancer diminishes as a result of exposure ceasing, apart from the lack of further exposure meaning that there is no increase in risk arising from a higher cumulative exposure. This uncertainty arises from a lack of relevant data. The studies from which the estimated risks arise are based on cohorts with people exposed for different periods of time, followed up for varying periods of time, and with varying periods of time between exposure cessation and follow-up, with follow-up periods varying between zero (still exposed) and many decades. Therefore, most of the absolute and relative risks produced by the studies are already dependent on whatever change in risk there might be once exposure ceases.

Related to the concept of risk reversibility is disease latency, the period between first exposure and the onset of detectable disease. This means that there will be a delay before the benefits of any reduction in exposure will be evident. Given that the latency between first exposure and the development of lung cancer or leukaemia is of the order of 10 to 20 years, and is between 20 and 60 years for malignant mesothelioma, the last case of lung cancer or leukaemia due to occupational exposures could be expected about 20 years, and of malignant mesothelioma about 60 years, after exposure ceases.

For malignant mesothelioma, absolute risk measurements were made, based on cumulative exposure and thereby related to age to produce age-specific risks. Once exposure ceases, the age-specific-risks should decrease, because persons of a given age will have been exposed for less of their working lifetime and so will have a smaller cumulative exposure. That is, a 60 year old in 1995 is likely to have received a larger cumulative dose of asbestos than a 60 year old in 2010, and so the risk of developing malignant mesothelioma in the latter 60 year old will be less. Although age-specific relative risks are not available for the other agents, the same concept applies. So, the number of deaths from the conditions considered here will fall away rapidly in the last decade in which cases occur, since both the proportion of persons at risk, and the absolute risks, will be declining. This effect will be evident earlier for mesothelioma and, to a lesser extent, lung cancer, since the asbestos exposure levels decreased in the last 20 or 30 years, so the cumulative exposure will decline relatively more rapidly at a given age once exposure is stopped.

Extrapolation from one region to another

For lung cancer and leukaemia, the same basic risk estimates were used to develop summary risk estimates for each region. Summary relative risks were developed taking into account estimates of workforce exposure in each region, but the region-specific summary risks were all similar. For malignant mesothelioma, the same summary risk estimates were used for all regions, as relevant data were not available to allow region-specific estimates. The studies from which the risk estimates are taken were based in single countries, although they are consistent with good studies conducted elsewhere. Some differences in biological effect might be expected in different racial groups, or as a result of different co-exposures in different cultures, but such differences are unlikely to be significant. Most importantly, direct risk data are not available for the exposures of interest in most regions and, apart from the weighting process based on exposure prevalence used here, there is virtually no information available to allow the precise extent of any possible differences to be determined for any of the exposure-disease relationships of interest. In addition, a large degree of uncertainty was introduced because European and American exposure estimates had to be applied to the developing subregions (B, C, D, and E subregions) in many instances because of the lack of high-quality exposure data worldwide.

Incidence and mortality

This analysis assumed that when relative risk values were based on disease incidence studies, the incidence rate ratio was comparable to the corresponding mortality risk ratio. Similarly, the absolute risk of incident cases and fatal cases of malignant mesothelioma were assumed to be the same. For lung cancer and malignant mesothelioma this is probably true, since most people who develop lung cancer or malignant mesothelioma will die directly, or fairly directly, of this disease. Persons with leukemia generally have a higher five-year survival. This means that the number (and rate) of deaths from these diseases is not likely to be the same as the number and rate of incident cases. However, the relative rate is likely to still be the same in many situations. There were insufficient data available to confirm or refute this assumption for the outcomes of interest in this study.

Calculation of relative risk

Summary relative risks related to occupational exposures were calculated for the cancers of interest. Where only a few relevant studies were available, the best quality studies were used to determine the appropriate relative risk. Since only confirmed or probable carcinogens were included in the exposures of interest, there were usually at least several good quality studies available for each exposure on which to base the selected relative risks. The relative risks on which the summary measures were based were determined by individual studies for a particular exposure-outcome relationship, and sometimes varied widely. For example, the summary risk estimates of malignant mesothelioma arising from crocidolite, amosite and chrysotile produced in a recent comprehensive review [Hodgson and Darnton, 2000] had considerable uncertainties - up to two-fold for crocidolite, two to four-fold for amosite and up to a three-fold for chrysotile. This sort of variation is not surprising, given variations in the level of exposure, period of follow-up, level and control of confounders, and opportunity for selection and measurement bias. The summary risk measures are an attempt to identify the best estimate of the "average" risk for the exposure types and levels of interest.

The relative risks have not been related to any absolute measure of cumulative exposure, because the necessary exposure-risk data are not available. The average duration of exposure of all the relevant populations on which the relative risks are based is not known, as some of the summary measures are based on meta-analyses, covering many studies and different countries with a wide range of exposure duration. The average duration in the populations to which the relative risks are to be applied is also not known. The cohorts used in the studies are probably not typical of the entire exposed workforce, as cohort studies tend to be based on workforces that have had fairly stable workforces, but there are no more typical cohorts that have been studied. Most importantly, the relative risks are NOT based on duration. They are simply calculated for exposed versus non-exposed, without consideration of duration. Although more quantitative data would be desirable, they are not available for the risk estimates, and are also unlikely

to be available at the level of detail required for the populations to which the risk estimates are to be applied.

Omitted exposures and conditions

Some occupational exposures potentially causing cancer have been excluded. These include acrylonitrile, BCME, formaldehyde, radon, soot, tetrachloroethylene, trichloroethylene, xenylamine, 4-nitrobiphenyl, and polycyclic aromatic hydrocarbons. This was because of one or more of very low workplace exposure levels, limited evidence of any effect in causing the conditions of interest, and lack of data in CAREX. This will have led to some underestimation of the total burden of malignant conditions arising from workplace exposure, but it is unlikely that these omissions would produce significant underestimations. An important feature of these risk factors and the resulting disease burden is their concentration among the formal working population, especially those in high-risk occupations and sectors. Hazards in workplaces and the resulting illness and injury are understood most accurately in the formal sector, and even there much undercounting occurs. The burden in the informal sector in developing countries, where large proportions of the population work, is high and is largely undescribed. Neither household and family agricultural work of women nor child labor were addressed in our study. As for omitted exposures, the exclusion of some work-related malignancies (e.g. carcinoma of the bladder) will have led to some underestimation of the total burden of malignant conditions arising from workplace exposure, but it is unlikely that these omissions would produce significant underestimations.

CONCLUSION

The aim of this study was to estimate the attributable fractions of selected occupational carcinogens, and the resulting number of deaths and DALYs. The risk factors were selected according to the availability of data, the strength of evidence linking the occupational exposure and the outcome, and the amount of risk arising from the exposure. The analysis has shown that occupational carcinogens are an important cause of death and disability worldwide. Work-related cancers are largely preventable, and the estimated burden of occupational carcinogens can be diminished by improving working conditions, as many examples from different countries have shown.

DISCLAIMER

The views expressed in this article are those of the authors and do not necessarily reflect the position of the World Health Organization.

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REFERENCES

BEIR V (Committee on the Biological Effects of Ionizing Radiation). 1990. Health effects of exposure to low levels of ionizing radiation: BEIR V Washington, DC: National Academy Press.

Dosemeci M, McLaughlin J, Chen J, Hearl F, Chen R, McCawley M, Wu Z, Peng K, Chen A, Rexing S, al e. 1995. Historical total and respirable silica dust exposure levels in mines and pottery factories in China. Scandinavian Journal of Work Environmental Health 21: 39-43.

Ezzati M, Lopez A, Rodgers A, Murray C. 2004. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors Geneva: World Health Organization.

FIOH. 1998. CAREX database Helsinki: Finnish Institute of Occupational Health.

Furuya S, Natori Y, Ikeda R. 2003. Asbestos in Japan. Int J Occup Environ Health 9: 260-265.

Hewett P. 1996. Interpretation and use of occupational exposure limits for chronic disease agents. Occupational Medicine: State of the Art Reviews 11: 561-590.

Hodgson J, Darnton A. 2000. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg 44: 565-601.

IARC. 1977. Asbestos Lyon, France: International Agency for Research on Cancer.

IARC. 2002. IARC monographs programme on the evaluation of carcinogenic risks to humans Lyon, France: International Agency for Research on Cancer.

IARC. 1994. Some industrial chemicals Lyon, France: International Agency for Research on Cancer.

ILO. 2002. Economically active population 1950-2010, 4th edn, rev. 2 Geneva: International Labour Organization.

IPCS. 1998. Chrysotile asbestos Geneva: International Programme on Chemical Safety.

Leigh J, Driscoll T. 2003. Malignant mesothelioma in Australia, 1945 - 2002. Int J Occup Environ Health 9: 206-217.

Lynge E, Anttila A, Hemminki K. 1997. Organic solvents and cancer. Cancer Causes Control 8: 406-419.

Martonik J, Nash E, Grossman E. 2001. The history of OSHA's asbestos rulemakings and some distinctive approaches that they introduced for regulating occupational exposure to toxic substances. Am Ind Hyg Assoc J 62: 208-217.

Murray C, Acharya A. 1997. Understanding DALYs. J Health Econ 16: 703-730.

Myers J, Lewis P, Hofmeyr W. 1989. Respiratory health of brickworkers in Cape Town, South Africa: Background, aims, and dust exposure determinations. Scandinavian Journal of Work Environmental Health 15: 180-187.

Nelson D. 1997. Risk assessment in the workplace. In: Di Nardi SR editor. The occupational environment-its evaluation and control Fairfax, VA: The American Industrial Hygiene Association.

Nelson D, Concha-Barrientos M, Driscoll T, Steenland N, Fingerhut M, Prüss-Üstün A, Corvalan C, Leigh J. 2005. The global burden of occupational disease and injury. Am J Ind Med Submitted.

NIOSH. 2000. Injuries, illnesses, and hazardous exposures in the mining industry, 1986 - 1995: a surveillance report Washington, DC: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

NIOSH. 1999. Work-related lung disease surveillance report 1999 Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

Nurminen M, Karjalainen A. 2001. Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland. Scand J Work Environ Health 27: 161-213.

Partanen T, Jaakkola J, Tossavainen A. 1995. Silica, silicosis and cancer in Finland. Scandinavian Journal of Work Environmental Health 21: 84-86.

Peto J, Decarli A, La Vecchia C, Levi F, Negri E. 1999. The European mesothelioma epidemic. Br J Cancer 79: 666-672.

Price B, Ware A. 2003. Mesothelioma trends in the United States: an Update based on surveillance, epidemiology, and End Results program. Data for 1973 through 2003. Am J Epidemiol 159: 107-112.

Rees D, Cronje R, du Toit R. 1992. Dust exposure and pneumoconiosis in a South African pottery. 1. Study objectives and dust exposure. Br J Ind Med 49: 459-464.

Roach S. 1992. Health risks from hazardous substances at work-assessment, evaluation and control New York: Pergamon Press.

Steenland K, Burnett C, Lalich N, Ward E, Hurrell J. 2003. Dying for work: The magnitude of US mortality from selected causes of death associated with occupation. Am J Ind Med 43: 461 482.

Steenland K, Loomis D, Shy C, Simonsen N. 1996. Review of occupational lung carcinogens. Am J Ind Med 29: 474-490.

Yano E, Wang Z-M, Wang X-R, Wang M-Z, Y-J L. 2001. Cancer mortality among workers exposed to amphibole-free chrysotile asbestos. Am J Epidemiol 154: 538-543.

Yin S, Li Q, Liu Y, Tian F, Du C, Jin C. 1987. Occupational exposure to benzene in China. Br J Ind Med 44: 192-195.