AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 29:474–490 (1996)

Review of Occupational Lung Carcinogens

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Lung cancer is the most common malignancy in the United States and is ranked second only to bladder cancer in the proportion of cases thought to be due to occupational exposures. We review the epidemiology of occupational lung cancer, focusing on agents identified as pulmonary carcinogens by the International Agency for Research on Cancer. We derive estimates of overall relative risks from the major studies of these lung carcinogens, and we also provide estimates of the number of exposed workers. Using our data as well as estimates from other authors, we estimate that approximately 9,000–10,000 men and 900–1,900 women develop lung cancer annually in the United States due to past exposure to occupational carcinogens. More than half of these lung cancers are due to asbestos. This estimate is likely conservative, in that we have restricted our analysis to confirmed lung carcinogens and have ignored occupations with documented excess risk but for which the specific agents are unknown. Also, our estimate of the proportion of workers exposed in the past is probably too low. Our estimate should be viewed only as a broad approximation. Nevertheless, it is in line with other estimates by authors using different methods. The current number of cases estimated to be due to occupational exposures reflects past high exposures and is likely to drop in the future, unless other occupational lung carcinogens are confirmed or new carcinogens are introduced into the workplace.

KEY WORDS: lung cancer, occupation, attributable risk, asbestos, arsenic, chromium, radon, silica, beryllium, nickel, cadmium, diesel exhaust

INTRODUCTION

In this paper we will focus on agents determined by the International Agency for Research on Cancer (IARC) to be definite (Group 1) or probable (Group 2A) lung carcinogens (Table I). Exposure to these agents usually occurs in occupational settings, although two of these agents also occur commonly in the general environment: radon in homes and diesel fumes.

We review the epidemiology for most of these substances and estimate the likely number of lung cancers caused yearly in the United States by occupational exposures. We omit detailed discussion of those agents in Table I for which relatively few workers are exposed (less than 30,000). These include bis-chloro-methyl ether, coke oven and coal gasification fumes, and soot. One recent study implicates coal-tar pitch volatiles (Armstrong et al., 1994) as a lung carcinogen; this agent is not included in Table I. However, relatively few workers are exposed, and detailed discussion of coal-tar pitch volatiles is also omitted.

We also omit detailed discussion of the role of smoking. Regarding confounding, some of the studies reviewed here have been able to adjust for smoking. Most show excess risks that are beyond the approximately 10–30% that might be expected due to positive confounding in realistic situations [Blair et al., 1985; Siemiatycki et al., 1988]. Most also show a positive exposure-response, suggesting that confounding is not likely to account for the overall association. Regarding interaction, two general points can be made. First, observed interactions (e.g., asbestos, radon) often fall somewhere in between additive and multiplicative [Steenland and Thun, 1986; Saracci, 1987]. Second, there

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Accepted for publication May 8, 1995.

TABLE I. Definite and Probable Lung Carcinogens as Classified by the International Agency for Research on Cancer (IARC)*

Agent	Animal evidence	Human evidence	IARC ref.
Probable			
Acrylonitrile	Sufficient	Limited	1979, 1987a
Diesel exhaust	Sufficient	Limited	1989
Silica	Sufficient	Limited	1987b
Definite			
Arsenic	Inadequate	Sufficient	1980, 1987a
Asbestos	Sufficient	Sufficient	1977, 1987a
Bis-chloro-methyl ether (BCME)	Sufficient	Sufficient	1974, 1987a
Beryllium	Sufficient	Sufficient	1993
Cadmium	Sufficient	Sufficient	1993
Chromium VI	Sufficient	Sufficient	1990
Coke oven and coal gasification fumes	Sufficient	Sufficient	1984, 1987a
Nickel	Sufficient	Sufficient	1990
Radon	Sufficient	Sufficient	1988
Soot	Sufficient	Sufficient	1985, 1987a

*Agents classified as definite or probable carcinogens based primarily upon evidence at other sites, but with some evidence of lung carcinogenesis, have generally been omitted (e.g., formaldehyde, sulfuric acid mists). NIOSH considers all agents on this list to be carcinogenic, while OSHA considers all, to be carcinogenic with the exception of silica, diesel exhaust, nickel, chromium, and beryllium (OSHA has no standard for soot; chromium VI is actively under consideration).

frequently are insufficient data to characterize with confidence the nature of the interaction. This is true because lung cancer among nonsmokers is so rare; it is difficult to determine with any precision the lung cancer relative risk for nonsmokers, and hence it is difficult to distinguish it statistically from the relative risk for smokers. Despite this imprecision, for most of these agents there is good evidence that exposed nonsmokers do in fact have increased risks compared with nonexposed nonsmokers.

Summary relative risks for specific agents are calculated using inverse-variance and a random effects model (Coldiz et al. 1995). Use of a random effects model is motivated by the fact that relative risks for all but one of the agents considered here show substantial heterogeneity across studies. Such heterogeneity is expected given the widely varying exposure levels of the studies in question. We then use these relative risks and the estimated proportions of workers exposed to determine the risk of lung cancer attributable to occupational exposures to the specific agents considered here. We rely on cohort studies of specific agents, rather than population or hospital-based case-control studies that consider occupation and cannot, in general, determine risk for specific agents. While a calculation of attributable risk based on occupation rather than specific agents is certainly worthwhile, it is beyond the scope of this paper.

AGENTS

Silica

In the 1980s, there were an estimated 1.7 million U.S. workers exposed to crystalline silica [NIOSH, 1991], outside of the mining industry. Some of the principal industries in which exposure occurs are masonry and stonework, concrete and gypsum, and pottery. Silica exposure is common among miners yet is highly variable depending on the silica content of the ore. The Occupational Safety and Health Administration (OSHA) standard for quartz is 100 $\mu g/m^3$.

In rats inhaled silica causes both fibrosis and lung cancer, while in mice silica causes fibrosis but not lung cancer. In hamsters it causes neither [Saffioti, 1992]. Recent data indicate that inhaled silica can cause lung cancer in rats at relatively low doses (1 mg/m^3) [Muhle et al., 1989]. The mechanism by which silica induces lung cancer in animals is not clear, whether directly through effects on the DNA or indirectly by promoting the growth of already initiated cells [Hesterberg et al., 1986; Saffioti, 1992].

There have been a large number of epidemiologic investigations [for a recent review, see Goldsmith, 1994]. A general summary of the evidence is that the studies of silica-exposed workers suggest an increased lung cancer risk, but they are not consistent. The evidence for a lung cancer association is stronger for the many studies of workers with silicosis. Most of these have shown elevated lung cancer risk, often statistically significant and often beyond the range of excess risk that might be caused by confounding by smoking or other occupational exposures.

Cohort and case-control studies of silicotics are shown in Table II (studies in mines that might involve confounding exposures, autopsy, and proportionate mortality studies that may involve possible selection biases, as well as data from presentations or proceedings, are omitted from this table). The summary relative risk for these 15 studies is 2.80 (95% CI 2.50–3.15). These data suggest that either the relatively high doses of silica that are required to cause silicosis in turn result in lung cancer, or that some aspect of the fibrotic disease itself accounts for the observed excess lung cancer risk. Generally the data are insufficient to determine which is the case.

Table III lists the larger studies of silica-exposed workers. All are studies in which high exposure to silica occurred, as documented through actual measurements or an observed high prevalence of silicosis. Emphasis has been placed on studies without confounding exposures. The studies in Table III suggest a moderate excess, with a combined relative risk of 1.33 (95% CI 1.21–1.45). Results of dose-response analyses were inconsistent in the seven studies that

TABLE II. Cohort and Case-Control Studies of Silicotics

Study	Lung cancer SMR or OR (95% CI)	Control for smoking; comment
Westerholm et al. (1986)	SMR = 4.4 (2.95–8.10)	Yes; 712 men compensated for silicosis from 1959 to 1977
Kurppa et al. (1986)	SMR = 3.12 (2.30–4.14)	No; 961 men diagnosed 1935–1977 in Finland, consistent across industries
Forastiere et al. (1987)	OR = 3.9 (1.8–8.3)	Yes; 72 cases, area of pottery industry, OR = 1.4 (0.7–2.8) for exposed nonsilicotics
Mastrangelo et al. (1988)	OR = 1.9 (1.1–3.2)	Yes; 309 cases, area in Italy with quarries, OR = 0.9 for exposed nonsilicotics
Finkelstein et al. (1987)	SMR = 3.02 (1.73–4.89)	No; 276 silicotics not employed in mines or foundries in Canada
Zambon et al. (1987)	SMR = 2.28 (1.69–3.02)	Yes; smoking explains some of excess, 1,234 men diagnosed 1959–1963 in Italy
Infante-Rivard et al. (1989)	SMR = 3.47 (3.11–3.90)	Yes; 1,165 silicotics compensated in Quebec 1938–1985
Merlo et al. (1990)	SMR = 6.85 (4.47–10.00)	Yes; 520 silicotics diagnosed in Italian hospital, 1961–1980
Tornling et al. (1990)	SMR = 1.88 (0.85–3.56)	No; 280 silicotic ceramic workers in Sweden
Ng et al. (1990)	SMR = 2.03 (1.35–2.93)	Yes; 1,419 men in a silicosis registry, estimated 50% of excess due to smoking
Chiyotani et al. (1990)	SMR = 6.03 (5.39–6.77)	Yes; 3,355 hospitalized pneumoconiosis patients, SMR = 2.22 for never smokers
Amandus and Costello (1991)	SMR = 1.96 (1.19–3.23)	Yes; U.S. miners x-rayed 1951–1961, silicotics compared with 9,543 nonsilicotics
Amandus et al. (1981)	SMR = 2.6 (1.8–3.6)	Yes; 760 silicotics diagnosed 1930–1983 in No. Carolina
Hnizdo and Sluis-Cremer (1991)	OR = 0.9 (0.5–1.6)	Yes; nested case-control study among miners, OR = 3.9 (1.2–12.7) for silicosis of hilar gland
Chia et al. (1991)	SMR = 2.01 (0.92–3.81)	Yes; 104 silicotic granite cutters registered 1980–1984 in Singapore
Carta et al. (1991)	SMR = 1.29 (0.8–2.0)	Yes; 724 silicotics diagnosed 1964–1970

SMR = standardized mortality ratio from cohort studies; OR = odds ratio from case-control studies; CI = confidence intervals.

included them. It is possible that the mineralogic characteristics of crystalline silica vary sufficiently such that some varieties of silica induce lung cancer but some do not.

Asbestos

The use of asbestos has been increasingly restricted as its dangers became known. The National Institute of Occupational Health (NIOSH) estimates that in the 1980s approximately 700,000 U.S. workers were exposed to asbestos, primarily maintenance and construction workers exposed to asbestos insulation, and mechanics exposed to asbestos in brake linings [NIOSH, 1991]. Nicholson et al. [1982] estimated that from 1940 to 1979, 27.5 million workers were potentially exposed, 18.8 million of whom had exposure in excess of the equivalent of 2 months in primary manufacturing of asbestos. These authors estimated that excess lung cancer deaths due to asbestos exposure

TABLE III. Cohort and Case-Control Studies of Silica-Exposed Workers

Study	Lung cancer SMR, PMR, or or OR (95% CI)	Control for smoking; comment
Davis et al. al. (1983)	PMR 1.3 (1.0–1.6)	No; 969 dead granite workers, no trend with estimated dust exposure
Steenland and Beaumont (1986)	PMR = 1.19 (0.97–1.46) PCMR = 1.09 (0.89–1.33)	No; 1,905 dead granite cutters with high levels of silica exposure and silicosis before 1950
Neuberger et al. (1986)	SMR = 1.48 (1.22–1.74)	No; 1,630 Austrians exposed to nonfibrous dust, no change in SMR after excluding foundries
Costello and Graham (1988)	SMR = 1.16 (0.96–1.39) SMR = 1.27, shed workers	No; 5,414 granite workers employed 1950–1982, high exposures, especially for shed workers
Guenel et al. (1989)	SMR = 2.00 (1.49–2.69)	No; 2,071 Danish stone workers with high historical rates of silicosis, 44 incident lung cancers
Koskela et al. (1990)	SMR = 1.56 (1.05–2.21) SMR = 2.81, 25+ yr emp	No; but smoking habits probably similar to referents, 1,026 granite workers, 31 lung cancers
Siemiatycki et al. (1990)	OR = 1.3 (1.0–1.8) OR = 1.7 for 20+ exp	Yes; cases (n = 161) restricted to nonadenocarcinoma (no risk for adenocarcinoma, n = 37)
Winter et al. (1990)	SMR = 1.34 (1.03–1.73)	Yes; 3,669 pottery workers aged <60, surveyed for dust and smoking in 1970–1971, positive dose-response
Merlo et al. (1991)	SMR = 1.51 (1.04–2.12) SMR = 1.77, hired <1957	Yes; 1,022 brick workers, high historical silica exposure and silicosis excess, 28 lung cancers,
Hnizdo and Sluis-Cremer (1991)	OR = 1.97 (1.17–3.30)	Yes; case-control study among 2,209 gold miners, + dose response, 77 cases, low radon exposure
McLaughlin et al. (1992)[a]	OR = 2.1 (0.7–7.0) OR = 0.5 (0.3–1.0) OR = 0.7 (0.2–2.3)	Yes; case-control studies among Chinese pottery, tungsten, and iron workers, ORs for high silica vs. none,—dose-response for tungsten miners
Steenland and Brown (1995)	SMR = 1.13 (0.93–1.36)	Yes; 3,328 gold miners, high historical exposures, no dose-response, low radon/arsenic
Checkoway et al. (1993)	SMR = 1.43 (1.09–1.84)	No; 2,570 diatomaceous earth miners with high past exposures, 59 lung cancers, positive dose-response

[a]95% CIs calculated from raw data, and adjusted ORs. Tin miner data omitted due to arsenic confounding.
SMR = standardized mortality ratio from; OR = odds ratio from case-control studies; PCMR = proportionate cancer mortality ratio; PMR = proportionate mortality ratio; CI = confidence interval.

would occur at the rate of about 5,400 annually in the mid-1990s, then gradually decrease until the year 2030. The current OSHA standard is 0.1 fibers/ml for fibers greater than 5 microns in length [Code of Federal Regulations, 1994], which are thought to be the most dangerous [Stanton et al., 1981].

Asbestos minerals are divided into two broad groups, serpentine (chrysotile) and amphibole (amosite, tremolite, and others). Inhalation studies among rats have shown that both serpentine and amphibole fibers cause both fibrosis, lung cancer, and mesothelioma [Davis et al., 1978; Wagner et al., 1974]. All types of asbestos are known to cause lung

TABLE IV. Cohort Studies of Asbestotics

Study	Lung cancer SMR (95% CI)	Control for smoking; comments
Liddell and McDonald (1980)	SMR 3.50 (2.73–4.42)	Some; 4,559 chrysotile miners, SMR for men with less than normal x-rays vs. general population, unchanged with compared with men with normal x-rays, few smoking differences between normals/abnormals
Berry (1981)	SMR = 9.1 (7.5–11.0)	Some; 665 certified asbestotics, 109 lung cancers smoking data suggested asbestotics smoked only slightly more than referent group
Finkelstein et al. (1981)	SMR = 7.9 (3.9–14.1)	No; 172 compensated cases, 11 lung cancers
Cookson et al. (1985)	SMR = 5.1 (3.2–7.9)	No; 354 compensated asbestotics, 21 lung cancers degree of profusion on x-ray predicted lung cancer but estimated cumulative exposure did not
Coutts et al. (1987)	SMR = 7.40 (4.69–11.10)	No; 155 compensated asbestotics, 23 lung cancers
Hughes and Weil (1991)	SMR = 4.33 (1.98–8.21)	Yes; 77 exposed men with abnormal x-rays ≥1/0 profusion, internal analyses confirmed risk

SMR = standardized mortality ratio; CI = confidence interval.

cancer in humans. There is some debate about mesothelioma. Some have suggested that the mesothelioma observed among chrysotile-exposed workers may have been due to the small amounts of tremolite that invariably contaminate chrysotile.

Like silica, asbestos is not a classic gene mutagen in bacterial systems, although it does have the capacity to induce gross chromosomal aberrations and transformation in mammalian cells. Asbestos may induce cancer directly in humans by these mechanisms, or indirectly by the production of free radicals consequent to immune response [Walker et al., 1992].

Asbestos is much like silica in that cohort studies of subjects with asbestosis have shown a consistent and high rate ratio for lung cancer. Table IV shows the results of cohort studies of asbestotics or men with radiographic abnormalities. Rate ratios ranged from 3.5 to 9.1, beyond the range of possible confounding by smoking. The combined relative risk for these studies is 5.91 (95% CI 4.98–7.00).

Cohort studies of workers exposed to asbestos have shown a consistent excess of lung cancer. Table V lists the larger cohort studies, concentrating on those with some estimate of dose and citing only the most recent updates. The combined relative risk from Table V is 2.00 (95% CI 1.90–2.11). Several of the studies shown in this table include estimates of a linear dose-response, in the form of a prediction equation in which the rate ratio (or SMR) for lung cancer between exposed and nonexposed is equal to 1.0 + (slope × fiber/ml-years). OSHA (Code of Federal Regulations, 1994) estimated an average slope across eight studies as 0.01 (95% CI 0.003–0.03). It should be noted that good estimation of exposure-response is difficult because (1) most studies have few historical measurements, and (2) even in those studies that do, conversion of historical data in units of millions of particle of dust per cubic foot (mppcf) to current gravimetric units is problematic.

For asbestos, like silica, the argument can be made that lung cancer cannot occur without preceding fibrosis. This hypothesis is difficult to assess epidemiologically because (1) those with fibrosis are those who also had higher doses and higher doses would be expected to cause more lung cancer, and (2) few studies have good data on the three variables necessary to test this hypothesis, that is, dose, radiographic changes, and smoking (Browne, 1986). Recent studies with reasonable data on these three variables provide some evidence that only those with observable radiographic fibrosis develop lung cancer [Hughes and Weill, 1991; Liddell and McDonald, 1980; Sluis-Cremer and Bezuidenhout, 1990]. However, each of these three studies has its own limitations, and very large populations are needed to truly confirm a negative hypothesis (that those without fibrosis do not get lung cancer; see Roggli et al., 1994 and Abraham, 1994 for a recent discussion).

Most of the epidemiologic studies showing a lung cancer effect have been of workers exposed at very high historical levels, several orders of magnitude higher than most

TABLE V. Cohort Studies of Asbestos Workers

Study	Lung cancer SMR (95% CI)	Control for smoking; comment
Selikoff et al. (1979)	SMR = 4.06 (3.93–4.98)	Yes; 17,800 insulation workers, 429 lung cancers, OSHA (1986) estimated dose-response as SMR = 1 + .02*f/ml-yr
Henderson and Enterline (1979)	SMR = 2.70 (2.07–3.45)	No; 1075 men retired 1941–1967, 63 lung cancers, in an asbestos factory, OSHA estimated SMR = 1 + (.005*f/ml-yr)
Finkelstein (1983)	SMR = 7.4 (4.4–11.6)	No; 241 men hired before 1960, 19 lung cancers, OSHA (1986) estimated SMR = 1 + .048*f/ml-yr
McDonald et al. (1983)	SMR = 1.05 (.77–1.42) (20+ yr since hire)	No; 4,137 men in chrysotile/amphibole textile plant, 59 lung cancers, dose-response SMR = 1 + .051*f/ml-yr
McDonald et al. (1984)	SMR = 1.49 (1.18–1.87)	No; 3,641 in chrysotile friction products, 73 lung cancers, no dose-response, average level 2 mpcf
Newhouse et al. (1985)	SMR = 2.96 (2.62–3.33)	No; 5,100 textile plant workers, 233 lung cancers, positive dose-response by low, medium, high jobs
Peto et al. (1985)	SMR = 1.31 (1.10–1.55) (principal cohort)	No; 3,211 men in chrysotile textile plant, 132 lung cancers, OSHA (1986) estimated SMR = 1 + .005*fiber/ml-yr
Seidman et al. (1986)	SMR = 4.97 (4.05–6.03)	No, 820 men in amosite factory, 102 lung cancers, no dose data but OSHA estimated SMR = 1 + .045 f/ml-yr
Hughes et al. (1987)	SMR = 1.34 (1.14–1.45) (>20 yr since hire)	Some; 5,492 chrysotile textile plant workers, OSHA (1986) estimated SMR = 1 + .011*f/ml-yr
Gardner et al. (1988)	SMR = 2.05 (1.65–2.51)	No; 4,825 amosite factory workers, 93 lung cancers, positive dose-response by 4 exposure levels
Armstrong et al. (1988)	SMR = 2.64 (2.15–3.64)	No; 6,915 crocidolite miners with brief exposures to 20–100 f/ml, 91 lung cancers, 30% lost to follow-up
Newhouse and Sullivan (1989)	SMR = 1.04 (.88–1.18)	No; 12,571 in chrysotile friction products, low doses, 242 lung deaths, OSHA estimate SMR = 1 + .001*f/ml-yr
Piollato et al. (1990)	SMR = 1.1 (0.69–1.67)	No; 1,058 chrysotile miners, 22 lung cancers, no dose-response analysis, 1/3 of cohort with >400 f/ml-yr
Neuberger and Kundi (1990)	SMR = 1.04 (0.79–1.41)	Yes; 2,816 workers at chrysotile cement plant after 1950, 49 lung cancers, low exposures, no dose analysis
Botta et al. (1991)	SMR = 2.68 (2.18–3.26)	No; 2,608 men in chrysotile/crocidolite cement plant, 100 lung cancers, little exposure data
Cheng and Kong (1992)	SMR = 3.15 (1.95–4.81)	Some; 1,072 workers in chrysotile plants, 21 lung cancers, positive dose-response by job categories
Sluis-Cremer et al. (1992)	SMR = 1.72 (1.32–2.21)	No; 7,317 miners mining amosite and crocidolite, 63 lung cancers, no dose-response analyzed
Raffn et al. (1993)	SMR = 1.82 (1.48–2.20)	No; 8,000 men in chrysotile/amosite cement plant, 104 lung cancers, exposures 10–800 f/ml in 1950s
McDonald et al. (1993)	SMR = 1.33 (1.22–1.45)	Yes; 11,379 men exposed to chrysotile in mines/mills, 20+ yr latency, 545 lung cancers, follow-up 1951–1988
Dement et al. (1994)	SMR = 1.76 (1.49–2.09)	Some; 3,041 in chrysotile textile plant, dose-response SMR = 1 + .011 f/ml-yr

SMR = standardized mortality ratio; CI = confidence interval.

current levels. Little excess lung cancer is expected to result from the low levels of exposure of today, although there continues to be controversy regarding the potential of very low levels of exposure to cause mesothelioma [Health Effects Institute, 1991].

Diesel Engine Exhaust

Diesel exhaust is a complex mixture of substances, characterized by polycyclic aromatic hydrocarbons surrounding an elemental carbon core. The gas phase includes carbon monoxide and nitrogen oxides. Diesel exhaust has been shown to be a lung carcinogen in animals [Ishinishi et al., 1986]. The particulate phase of the exhaust rather than the gas phase appears to be implicated.

Outside of mining, there were approximately 1.4 million U.S. workers exposed to diesel exhaust in the early 1980s, principally in the trucking and construction industry [NIOSH, 1990]. There is currently no OSHA standard specifically for diesel exhaust, although there are standards for components of the exhaust such as carbon monoxide or nitrogen dioxide. Environmental Protection Agency (EPA) regulations have been gradually tightened over the last decade to diminish the amount of diesel exhaust permitted from trucks.

Human epidemiologic studies have been difficult to conduct because there are few data documenting past exposures, and most such data are nonspecific measurements of surrogates for diesel exhaust, such as nitrogen oxides. Recently a more specific measure, elemental carbon, has been developed (Zaebst et al., 1992).

Recent studies of diesel-exposed populations have improved on earlier ones because smoking data have been collected and an attempt has been made to measure diesel exhaust currently, and then to extrapolate back to likely historical levels. Table VI lists more recent studies that have had relatively good documentation of exposure or have been based on self-reported diesel exposure. Most have been able to adjust for smoking as well. These studies would indicate a combined relative risk of about 1.31 (95% CI 1.13–1.44) for diesel-exposed populations vs. nonexposed populations. These studies are reasonably consistent, and the weight of the evidence to date tends to confirm IARC's 1989 judgement that occupational diesel exhaust is a probable lung carcinogen.

Radon Progeny

Radon (^{222}Rn) is radioactive noble gas formed during the radioactive decay series through which uranium (^{238}U) decays to stable lead. The radioactive decay of radon gas itself produces short-lived radioactive isotopes of bismuth, polonium, and lead, known as radon progeny or "radon daughters." Unlike radon gas, which is chemically inert, the radon progeny are metal ions that adhere to particles suspended in the air. When inhaled, these particles are deposited on the surface of the respiratory tract, where they irradiate surrounding tissues with alpha particles, which are capable of breaking chromosomes. In most studies, ambient exposure to radon progeny is measured in working levels (WL), and cumulative exposure is expressed in working level-months (WLM, the product of exposure level in WL and the number of 170-hour "working months" of exposure). One WL is any combination of radon progeny in air that ultimately releases 1.3×10^5 MeV of energy during decay. Exposure to radon progeny is also sometimes expressed in picocuries/liter (pCi/l), a unit measuring decay; 0.005 WLM is approximately equal to the progeny in equilibrium with 1 pCi/l of radon. The current standard for radon exposure in mines is 4 WLM per year.

Occupational exposures to radon and its progeny occur in underground mining for uranium and other metals, and in processing ores and radioactive materials. Most uranium mines in the United States have closed, and the number of currently exposed miners is relatively small. However, there is potential exposure to large numbers of workers in poorly ventilated buildings. Although radon concentrations in homes and buildings are far lower than in mines, the long periods of time that people spend at home and at work can result in significant cumulative exposures, although generally far less than a miner's exposure. A person spending 70 years in a residence and 45 years working lifetime in buildings, both with the U.S. average radon concentration of 1.5 pCi/l [Samet, 1989] would accumulate approximately 20 WLM of exposure to radon progeny from the home and approximately another 5 WLM from buildings. By comparison, the median exposure to a uranium miner in the United States has been about 430 WLM.

Studies of uranium miners and other miners exposed to radon daughters have consistently shown excesses due to lung cancer [Hornung and Meinhardt, 1987; Damber and Larsson, 1982; Howe et al., 1986; Morrison et al., 1988; Radford and St. Clair Renard, 1984; Sevc et al., 1993; Solli et al., 1985; Tinmarche et al., 1993; Hodgson and Jones, 1990; Woodward et al., 1991; Samet et al., 1991; Xuan et al., 1993]. Animal data confirm these observations [Cross et al., 1982a,b]. In all of the major cohorts of miners that have been studied, mortality increases monotonically with cumulative exposure in WLM. The excess relative risk of lung cancer among miners is generally 1–2% per WLM [Samet and Hornung, 1990]. The observation of excess lung cancer mortality at low cumulative exposures (less than 50 WLM) is an important finding in several studies of miners [Radford and St. Clair Renard, 1984; Sevc et al., 1976; Howe et al., 1986; Morrison et al., 1988; Tinmarche et al., 1993; Woodward et al., 1991]. These observed risks at low levels and the linear fit of the dose-response function can be taken as supporting the view that radon carcinogenesis is a stochastic

TABLE VI. Recent Studies of Lung Cancer and Diesel Exhaust

Study	Lung cancer SMR (95% CI)	Control for smoking; comment
Gustafsson et al. (1986)	SMR = 1.32 (1.05–1.66) 6,000 stevedores vs. general population	Yes, via later case-control study (Emmelin et al., 1993), which found highest risk for highest exposed based on 50 cases and diesel fuel consumption survey; RR for lung cancer incidence = 1.68 (1.36–2.07)
Garschick et al. (1987)	OR = 1.41 (1.06–1.88) long-term railroad workers vs. nonexposed	Yes; 1,256 cases, 20+ years exposed, parallel exposure survey of job categories, findings similar in subsequent cohort study
Boffetta et al. (1988)	SMR = 1.18 (0.97–1.44) self-reported vs. nonexposed	Yes; self-reported diesel exposure in Am. Cancer Soc. cohort of 1 million, 174 exposed lung cancers deaths, RR increased with duration of exposure, SMR = 1.24 for truck drivers, SMR = 1.59 for railroad workers
Gustavsson et al. (1990)	SMR = 1.15 (0.67–1.84) vs. nonexposed	No, but internal analysis showed highest risk for 695 bus garage workers highly exposed (OR = 2.4), parallel exposure survey, 17 lung cancer deaths
Steenland et al. (1990)	OR = 1.89 (1.04–3.42) long-haul diesel truck drivers vs. nonexposed	Yes; 996 cases in teamsters Union, risk highest for mechanics and drivers, parallel exposure survey, next-of-kin report of engine type, OR = 1.55 for long-haul drivers based on teamster records
Boffetta et al. (1990)	OR = 1.21 (0.78–2.02)	Yes; 477 cases, self-reported diesel exposure, + trend with increasing duration

SMR = standardized mortality ratio; OR = odds ratio; CI = confidence interval; RR = note ratio.

process with no risk threshold [NCRP, 1984]. With this presumption, data from studies of miners with very large cumulative exposures have been used to estimate risks for individuals exposed at much lower levels in homes and workplaces.

Arsenic

Arsenic occurs in organic and inorganic forms. Inorganic arsenic may occur as arsenate [As(V)] or arsenite [As(III)]. Metabolism of As(V) results in As(III), which is then detoxified by methylation. Arsenic is unusual in that there is inadequate animal evidence of its carcinogenicity, while the human epidemiologic data are quite strong. Arsenic appears to interfere with DNA repair and has been shown to cause chromosomal aberrations but does not cause mutations in bacterial systems. Inhalation studies in rodents have been negative, but some studies with intratracheal injection have had positive results [Smith et al., 1992].

The principal occupations exposed to substantial inorganic arsenic levels in the past are workers in copper smelters, workers manufacturing arsenical pesticides, and some miners. In the early 1980s there were an estimated 58,000 U.S. workers exposed to airborne arsenic [NIOSH, 1990] outside of the mining industry. The current OSHA standard for airborne inorganic arsenic is 10 $\mu g/m^3$. There is some limited evidence that inorganic arsenic in drinking water is carcinogenic; excess lung cancer has been found in Taiwan in association with drinking water contamination [Smith et al., 1992]. The principal human epidemiologic studies are shown in Table VII. These studies show a consistent lung cancer risk at high levels, with a clear dose-response. The combined relative risk from these studies is 3.69 (3.06–4.46). It would appear from the epidemiologic data that the excess lung cancer risks in worker populations are primarily due to high exposures, which occurred largely in the past. No excess lung cancer was noted in the study by Enterline et al. [1987] at smelters where exposures were estimated to be at the current OSHA level, 10 $\mu g/m^3$.

Acrylonitrile

Acrylonitrile is a colorless, volatile, flammable liquid with the chemical formula CH_2=CH-CN. Acrylonitrile cur-

TABLE VII. Selected Studies of Inorganic Arsenic and Lung Cancer

Study	Lung cancer SMR (95% CI)	Control for smoking; comment
Ott et al. (1974)	SMR = 3.45 (2.11–5.32)	No; 603 men in pesticide plant, 20 lung cancers, 100–5,000 $\mu g/m^3$ in 1940s–1950s, + dose-response
Lee-Feldstein (1986)	SMR = 2.85 (2.57–3.16)	No; 8,000 workers at copper smelter, 302 lung cancers, + dose-response, range of exposure 400–62,000 mg/m^3
Enterline et al. (1987)	SMR = 1.31 (1.07–2.65)	Yes; 6,000 workers at 8 copper smelters, 93 lung cancers excess seen only at the one plant with the highest mean exposure (69 $\mu g/m^3$), other plants had 7–13 $\mu g/m^3$
Enterline et al. (1987)	SMR = 1.98 (1.64–2.38)	No; 2,800 workers at copper smelter, 104 lung cancers, positive dose-response, 10–2,100 $\mu g/m^3$ exposures
Taylor et al. (1989)	OR = 15.2 (4.9–52.7)	Yes; case-control study among tin miners, 107 cases, positive dose response, mean exposures 420 $\mu g/m^3$ before 1951, 10–60 $\mu g/m^3$ thereafter
Jarup et al. (1989)	SMR = 3.73 (3.04–4.50)	Yes, via later case-control study of 107 cases (Jarup and Pershagen, 1991), 3,900 in cohort at copper smelter, + dose-response, exposures 50–50,000 $\mu g/m^3$ before 1940, 50–5,000 $\mu g/m^3$ in 1940s, 50–200 $\mu g/m^3$ thereafter

SMR = standized mortality ratio; CI = confidence interval; OR = odds ratio.

rently serves primarily as a key component in acrylic fibers used in textile manufacturing, and is also used in pipes, fittings, and other products. NIOSH estimates that in the early 1980s, 335,000. U.S. workers were potentially exposed to acrylonitrile on the job (NIOSH, 1990), primarily via inhalation. Absorbed acrylonitrile is primarily excreted through the urine following metabolism by the liver. The OSHA standard is 2 ppm (TWA). Rats exposed to acrylonitrile by inhalation or ingestion have shown elevated tumor rates, although rates were elevated for sites other than the lung.

A finding of 8 lung cancers vs. 4.4 expected (rate ratio of 1.83, 95% CI 0.78–3.68) in a cohort of workers at an acrylic fiber plant prompted initial concern about lung carcinogenicity [O'Berg, 1980]. Since this 1981 study, there have been three relevant studies with reasonable sample size. A further follow-up through 1984 of the original cohort studied by O'Berg et al. [Chen et al., 1988a,b] failed to observe a substantial lung cancer excess (SMR of 1.06). Collins et al. [1989] reported on 1774 acrylonitrile-exposed workers employed between 1951 and 1973 at one acrylonitrile and one acrylic fiber production plant. The SMR for lung cancer was 1.00. Swaen et al. [1992] followed 2,842 Dutch workers employed at eight plants producing or using acrylonitrile. The SMR for lung cancer was 0.82 (95% C.I. 0.47–1.33). Neither the Collins et al. nor the Swaen et al. studies showed a consistent dose-response. In summary, the epidemiologic evidence does not indicate that acrylonitrile exposure is related to lung cancer.

Chromium

Chromium is a metal that can exist in any oxidation state between −2 and +6. Most chromium compounds contain the metal in the +3 (trivalent) or +6 (hexavalent) state, and most natural chromium is found as oxides in chromite ore. Cr(VI) causes cancer in animal studies, but Cr(III) does not [IARC, 1990; Cohen et al., 1993].

Chromium adds rust and acid resistance as well as hardness to alloys. Stainless steel accounted for 82% of all chromium consumed in the United States in 1987 [IARC, 1990]. Worker exposures occur in the production of stainless steel, other chrome alloys, chrome-containing pigments, chrome plating, and welding (of stainless steel). NIOSH [1990] estimates that in the early 1980s, 551,000 workers in the United States were exposed to hexavalent chromium. OSHA considers Cr(VI) to be carcinogenic, and the OSHA standard for chromic acid and chromates containing Cr(VI) is 0.1 mg/m^3. Historical exposures in chromate production and chromate plating were generally 10 times higher than the current standard [IARC, 1990].

Over 50 epidemiologic investigations addressing lung

TABLE VIII. Selected Studies of Chromium-Exposed Workers

Study	SMR (95% CI)	Control for smoking; comment
Enterline (1974)	SMR 9.43 (7.33–11.93)	No; respiratory cancer
Hayes et al. (1979)	SMR 2.03 (1.55–2.63)	No; respiratory cancer, chromate plant, increase with duration
Alderson et al. (1981)	SMR 2.42 (2.00–2.90)	Some; U.K. chromate plant, heavy smokers rarer in cohort than in refernts
Satoh et al. (1981)	SMR 9.23 (6.27–13.10)	No; chromate producers, increase with duration
Korallus et al. (1982)	SMR 2.10 (1.56–2.76)	No; respiratory cancer, chromate plant
Frentzel-Beyne (1983)	SMR 2.04 (1.23–3.19)	No; pigment plant, maximum risk at high exposure
Davies (1984)	SMR 1.82 (1.37–2.43)	No; 3 pigment plants, no increase at low exposures, smoking prohibited in workplace
Sorohan et al. (1987)	SMR 1.50 (1.17–1.89)	No; chrome and nickel platers, increase with duration
Hayes et al. (1989)	SMR 1.43 (0.93–2.13)	No; pigment workers, increase with duration
Takahashi et al. (1990)	SMR 1.87 (0.81–3.69)	Some; platers, 1.7 for platers using other metals, estimated 30% increase due to smoking

SMR = standardized mortality ratio; CI = confidence interval.
Results are for lung cancer mortality unless otherwise noted in the comments.

cancer in occupational groups exposed to chromium compounds have appeared to date. Extensive tabulations of study results are available in the IARC review [1990]. The largest and best-designed studies of chromium production workers, producers of chromate paints, and chromate plating workers are included in Table VIII. The overall relative risk is 2.78 (2.47–3.52). Those studies that addressed tobacco smoke, asbestos, and nickel exposure ruled out these factors as the major source of the observed association.

Beryllium

Occupational exposure to beryllium occurs principally in mining, refining, and in the manufacture of ceramics, and electronic and aerospace equipment. NIOSH estimates that 44,000 workers were exposed to beryllium dust or fumes in the United States in the early 1980s [NIOSH, 1990]. In 1949, a new standard for beryllium exposure (2 $\mu g/m^3$ TWA) was introduced to avoid berylliosis. Before this time, beryllium exposures were considerably higher than this limit, which is still the OSHA standard (NIOSH recommends 0.2 $\mu g/m^3$). A study of a U.S. beryllium-alloy plant conducted in 1947–48 by the NIOSH showed beryllium concentrations ranging from 411 $\mu g/m^3$ in the general air surrounding mixing operations to 43,000 $\mu g/m^3$ in the breathing zone of alloy operations [NIOSH, 1972].

In a 1980 review, IARC [1980] concluded that there is sufficient evidence that beryllium metal and several beryllium compounds were lung carcinogens in rats and monkeys, but that epidemiologic evidence of lung carcinogenicity was limited, based on three studies. Since 1980, two cohort mortality studies have been reported, in each of which a significant excess of lung cancer was observed. Steenland and Ward [1991] expanded the mortality follow-up of the Beryllium Case Registry cohort to include 689 women and men of all races. The lung cancer SMR was 2.00 (95% CI, 1.33–2.89). Based on limited smoking data (32% of the cohort) and the magnitude of the observed excess, the authors believed it would be unlikely that smoking was a major confounder of the observed excess lung cancer, and selection bias was also judged unlikely.

Ward et al. [1992] reported the results of a cohort mortality study of 9,225 male workers from seven beryllium plants in Ohio and Pennsylvania. The overall SMR for lung cancer was 1.24 (95% CI, 1.10–1.39). Plants having a high SMR for pneumoconiosis and therefore presumably higher beryllium exposure consistently also had an elevated SMR for lung cancer. Lung cancer SMRs increased with increasing latency. After a smoking adjustment based on limited smoking data, the authors concluded that smoking was unlikely to fully account for the observed excess. The SMR at the plant with the highest exposures and longest latency remained elevated (smoking-adjusted SMR = 1.49). In 1993, a working group of the IARC concluded that the evidence was now sufficient to conclude that beryllium is carcinogenic to humans [IARC, 1993].

Nickel

The principal current uses of nickel and nickel salts are in the production of stainless steel, nonferrous alloys, electroplating, and in the manufacture of batteries [IARC,

1990]. Data from NIOSH [1990] indicate that about 147,000 workers in the US were exposed to nickel and nickel compounds in the early 1980s (metallic nickel and nickel alloys excluded; see later). The OSHA standard is 0.1 mg/m^3 for soluble compounds, and 1 mg/m^3 for nickel metal and insoluble nickel compounds.

IARC [1990] concluded that there is sufficient evidence in experimental animals for the carcinogenicity of metallic nickel, and for nickel oxides and sulfides. From epidemiological studies of nickel-exposed workers, IARC considered the evidence sufficient for the carcinogenicity of nickel sulfate and for "the combinations of nickel sulfides and oxides encountered in the nickel refining industry". However, the evidence in humans for the carcinogenicity of metallic nickel and nickel alloys was deemed to be inadequate.

The most current and comprehensive review of carcinogenic effects among nickel-exposed workers is presented in the 1990 report of the International Committee on Nickel Carcinogenesis in Man [ICNCM, 1990]. This report presents updated analyses of nine cohort studies and one case-control study of nickel. Lung cancer and nasal cancer were consistently and significantly increased among exposed workers at nickel refineries. Using data from this report (Table 83), the combined relative risk across 13 studies is 1.56 (95% CI 1.41–1.73).

In contrast to these positive results, cohort mortality studies of workers engaged in the manufacture of high-nickel alloys showed no consistent significant overall excess of lung cancer [ICNCM, 1990], and positive studies were often potentially confounded by other lung carcinogens. The role of nickel in lung cancer excesses observed among stainless steel welders is also unclear, as these welders are also exposed to chromium VI.

Cadmium

Cadmium is principally used in electroplating, in compounds that serve as stabilizers for plastics and as pigments, in electrodes in batteries, and in alloys. [IARC, 1976; Schaller and Angerer, 1992]. Most exposure occurs via inhalation. In the past, cadmium concentrations in workplaces were high; air levels of 1–10 mg/m^3 were found in alkaline battery factories in the 1950s, but with modern technology it is possible to reduce air cadmium concentrations to less than 0.02 mg/m^3 (Schaller and Angerer, 1992). NIOSH estimates that 250,000 workers were exposed to cadmium in the early 1980s [NIOSH, 1990]. The current OSHA standard is 0.1 mg/m^3 for cadmium fumes (cadmium oxides) and 0.2 mg/m^3 for cadmium dust.

Experimentally, cadmium induces tumors of the prostate [Waalkes et al., 1992a], lymphocytic leukemia [Waalkes et al., 1992b], and lung tumors [Heinrich, 1992]; all tumors were induced in rats, and the incidence of tumors was dose dependent.

Until recently, the various epidemiological studies of cadmium exposed workers did not enable any definite conclusion to be reached due to concomitant exposures to other occupational carcinogens, mainly nickel and arsenic [Boffetta, 1992]. New evidence comes from a study of a U.S. plant where cadmium oxide, sulfide, and metal were recovered from the waste of lead and zinc smelters beginning in 1926 [Thun et al., 1986; Stayner et al., 1992, 1993]. The most recent follow-up showed a lung cancer relative risk of 1.49 (95% CI, 0.96–2.22); the relative risk increased with estimated cumulative exposure to cadmium and was statistically significant for workers in the highest exposure category (RR = 2.72; 95% CI, 1.24–5.18). In order to control for the potential confounding effect of arsenic, subgroups of workers known to have little arsenic exposure were studied and also showed a significant excess of lung cancer. In 1933, a working group of the IARC concluded that there now was sufficient evidence in humans for the carcinogenicity of cadmium [IARC, 1993].

ATTRIBUTABLE RISK

There are approximately 90,000 lung cancer deaths per year among U.S. males and approximately 100,000 newly diagnosed cases per year. The comparable figures for U.S. females are approximately 45,000 and 60,000.

There have been several estimates of the proportion of male lung cancers that are due to occupational exposures. Recent estimates of 9% [Morabia et al., 1992] and 3–17% [Vineis et al., 1988] have come from large case-control studies and refer to the proportion of lung cancers attributable to work in occupations with excess risk of lung cancer, rather than to lung cancer attributable to specific occupational carcinogens. In earlier work, Doll and Peto [1981] estimated that approximately 15% of male lung cancers and 5% of female lung cancers were due to occupational exposure, without using any formal methodology.

Estimates based on a case-control study using occupational categories rather than exposure to specific substances have the advantage that they will take into consideration occupations at excess lung cancer risk, even though the occupational agent is unknown. However, the case-control/occupation approach usually relies on a single large study, or on a few large studies in which the same occupational categories have been analyzed. As a result, the relative risks for specific occupations may not be very precise and also may not be representative of the population as a whole.

Our method here will be based on estimating the proportion of the population exposed to specific occupational carcinogens and will use estimated relative risks for these carcinogens. The number of exposed workers in the 1980s and estimated relative risks have been presented earlier. We use a standard formula for calculating the attributable risk, also known as the etiologic fraction [Kleinbaum et al.,

TABLE IX. Summary of Relative Risks from Selected Studies of Occupational Lung Carcinogens and Estimated Number of Workers Exposed

Agent	Relative risk	Number of exposed workers in early 1980s	Proportion of workforce aged 20–65 (126 million)[a]
Cadmium	1.49	258,000 (69% male)	0.20%
Nickel	1.56	147,000 (78% male)	0.12%
Arsenic	3.69	58,000 (78% male)	0.04%
Chromium	2.78	551,000 (83% male)	0.43%
Diesel fumes	1.31	1,350,000 (96% male)	1.07%
Silica	1.33	1,700,000 (90% male)[b]	1.35%
Beryllium	1.49	44,000 (95% male)	0.03%
Asbestos[c]	2.00	700,000 (90% male)[b]	0.50%

[a]Estimated to be 61 million men, 65 million women.
[b]Data on exposure by sex not available, estimated 90% male.
[c]For asbestos, number of attributable lung cancer cases taken from Nicholson et al. (1982).

1982]. For two substances, asbestos and radon, we rely on estimates of the number of attributable lung cancers made by other authors.

Our method has the disadvantage that one must assume that the historical relative risks available from epidemiology are applicable to the exposed workers of interest. For lung cancer in the 1990s, the exposed workers of interest would have generally been exposed 20–50 years earlier if we assume these agents are cancer initiators, or in more recent periods if we assume these agents are promoters. We will make the broad assumption that the relative risks available from the epidemiology (presented earlier) are broadly applicable to the exposed workers of interest. We will base our estimates on the proportion of the population exposed from NIOSH data for the early 1980s, because these are the best data available [NIOSH, 1990], and make another broad assumption that the proportion of the population exposed has remained constant over time (clearly untrue for asbestos, see later). While an earlier NIOSH survey of exposures done in the early 1970s was also available, discussions with NIOSH staff suggest that the later survey benefitted from the experience of the first one (better quality control during the data collection phase), so that the later survey may be more reliable.

First we will consider seven agents: diesel exhaust, silica, arsenic, chromium, nickel, cadmium, and beryllium (asbestos and radon are treated separately later). Very small number of workers are exposed to other agents in Table I (<30,000 each), while the data indicating lung carcinogenicity are doubtful for others (e.g., acrylonitrile). Approximately 6% of the male U.S. population aged 20–65 (n = 61 million) was occupationally exposed to these seven agents in the early 1980s (Table IX). Approximately 0.7% of the female population (n = 65 million) was exposed. Approximately 3% of male lung cancers, or 3,000 cases per year, are estimated to result from exposures to these seven agents. Another 300 cases are estimated to occur among females due to these exposures.

For asbestos, we accept the estimates of 5,400 excess lung cancer deaths among males annually in the mid-1990s attributable to asbestos exposure as estimated by Nicholson et al. [1982], which corresponds to about 6,000 annual attributable incident cases. No comparable figures are available for females, but if we assume the same 10:1 male: female ratio, as we observed earlier, another 600 lung cancers might be attributable to asbestos exposure among women.

Indoor radon exposures at work may also cause some lung cancers, based on the assumption of no threshold, analogous to the situation for indoor radon exposures at home [Lubin, 1994]. Estimates of the number of lung cancers due to residential exposure to radon in homes are about 10,000 per year [Samet, 1989]. Based on relative dose at home and at work (approximately 5:1, see the earlier section on radon), occupational exposure to radon in buildings may account for another 2,000 annual cancers, presumably equally divided between males and females.

Excluding the contribution of radon at work, approximately 9,000 annual lung cancer cases among U.S. males can be attributed to occupational exposure (approximately 9% of all cases). Among females, perhaps 900 cases annually may be attributable to occupational exposures, accounting for 2% of the annual cases in the United States Asbestos exposure accounts for the majority of the attributable cases. If radon exposure at work is considered, the numbers increase to 10,000 cases per year among males and 1,900 among females.

Our estimates are in line with the estimates of prior

authors. However, it must be stressed that our quantitative estimate of attributable cancers is likely to be quite imprecise and serves primarily as a broad approximation. The major limitations of our estimate include the reliance on historical relative risks, which may lead to overestimation; the restriction to confirmed carcinogens, which may lead to underestimation; inaccurate estimates of the proportion of exposed workers in the relevant time period, which may lead to underestimation; and the lack of data to appropriately consider the effects of the interaction between smoking and the agents in question.

Most occupationally related lung cancers occurring today are the result of heavy exposures in the past. In the future the number of attributable cases is likely to diminish, unless new occupational carcinogens are introduced into the workplace, or unless we discover other unknown occupational lung carcinogens to which workers are being or have been exposed. On this last point, there are a number of animal carcinogens that have been identified in the last 10–15 years that are used in the workplace but have not been studied epidemiologically. Some of these may eventually be implicated as human occupational carcinogens.

ACKNOWLEDGMENTS

Alice Greife and Randy Young at NIOSH kindly provided estimates of the numbers of workers exposed.

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