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Contribution of Metals to Respiratory Cancer

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This paper reviews studies on the adverse health effects of exposure to metals, using arsenic and cadmium as examples. The carcinogenic potential of arsenic has been studied in various settings. Inhalation is clearly related to the development of lung cancer in (copper) smelting and arsenical pesticide manufacturing, and also in heavily exposed wine merchants who had an additional source of exposure by ingestion. Animal studies have shown cadmium to be a lung carcinogen, while a study by Thun et al. provides the best evidence to date that cadmium inhaled as CdO particles may be a human lung carcinogen. On the basis of this latter study, EPA estimates the risk due to cadmium at 1.8×10^{-3} cases/$\mu g/m^3$, which results in more than 100,000 excess lung cancers (lifetime). For arsenic, the risk estimate of 4.29 cases/1,000 $\mu g/m^3$, based on epidemiologic data also results in more than 100,000 lung cancers (lifetime). This paper reviews the bases for these estimates and presents recommendations for further research. Lung cancer risks also exist for other metals such as nickel, chromium, and beryllium. Further study is required before a definitive conclusion can be reached about the significance and magnitude of environmental exposures to metals as a cause of lung cancer.

This discussion of the contribution of metals, using arsenic and cadmium as examples, will be presented as follows: calculations of the excess deaths that might be attributable to cadmium and arsenic are presented; descriptions of how these numbers were derived, based on estimates of exposure, toxicologic information, epidemiologic information, and risk estimation; and research recommendations.

Four environments are considered: general air, around smelters, smoking, and occupational exposures. Exposures have been estimated on the basis of micrograms per cubic meter in general air and around smelters. Estimates of arsenic and cadmium from cigarette smoking are described below. For the occupational environment, the proposed TLV was used as level of exposure. The numbers of persons at risk are NIOSH's or the authors' best estimates. Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or by the U.S. Department of Health and Human Services.

EPA's upper bound unit risk estimate for cadmium of 1.8×10^{-3} cases/$\mu g/m^3$ results in more than 100,000 lifetime excess lung cancers (*1*); for arsenic, the unit risk estimate of 4.29 cases/1,000 $\mu g/m^3$ (*2*) also results in more than 100,000 lung cancers over the lifetime of those currently exposed (see Table 1 and Risk Assessment section).

Pulmonary Carcinogenicity of Inhaled Cadmium

A recently reported increase in lung cancer mortality among cadmium production workers seems to confirm an earlier experimental study in which a pulmonary carcinogenic effect of inhaled cadmium in rats was demonstrated (*3,4*). However, many open questions remain, and at present, inhaled cadmium compounds cannot generally be categorized as lung carcinogens. The present state of knowledge on this subject is summarized in the following overview of experimental animal data and epidemiologic studies. This is supplemented by a brief discussion about differences between animal and human studies in order to point out some future research needs.

Water-soluble cadmium salts injected subcutaneously were found to cause both injection site tumors and tumors of distant organs such as testes and pancreas (*5,6*). It appears, therefore, that cadmium is a chemical carcinogen that may induce tumors in different organs and

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Table 1. Estimate of number of excess lung cancer cases (lifetime) attributable to arsenic and cadmium.[a]

	General air	Around smelter	Smoking	Occupational
Cadmium				
$\mu g/m^3$	0.002–0.05	0.2–0.6		50 (TLV)
μg/day	0.008–0.2	0.8–2.4	2.4	100
At risk	220×10^6	100,000[b]	50×10^6 [b]	100,000[b]
Excess cases in lifetime				
EPA 1.8×10^{-3}/ $1\ \mu g/m^3$ [c]	790–19,800	36–108	45,000–90,000	3,214
Arsenic[d]				
$\mu g/m^3$	0.02–0.07	1–2		10
μg/day	0.08–0.28	4–8	0.3	20 (5 days/week)
At risk	220×10^6	500,000[b]	50×10^6 [b]	1.5×10^6 [e]
Excess cases in lifetime				
Brown and Chu[f] 1.25 cases/1,000 $\mu g/m^3$	5,500–19,250	625–1,250	4,688	6,696
EPA 4.29 cases/1,000 $\mu g/m^3$	18,876–66,066	2,145–4,290	16,088	22,982

[a]Assumptions: At work, 10 m^3 of air inhaled per day, 20% Cd or As retained. General, 20 m^3 of air inhaled per day, 20% Cd or As retained. Occupational exposures adjusted by 5/7 for days worked per week.
[b]Peters/Thomas estimates (unpublished).
[c]EPA data (*1*).
[d]EPA data (*2*).
[e]NIOSH estimates (unpublished).
[f]Data of Brown and Chu (*59*).

by different routes of administration. This was confirmed by a long-term inhalation study with $CdCl_2$ aerosols in rats by Takenaka et al. (*4*). Three groups of 40 male Wistar rats were each exposed to the following concentrations of $CdCl_2$ aerosols (expressed as Cd): group I, to 12.5 $\mu g/m^3$; group II, to 25 $\mu g/m^3$; group III, to 50 $\mu g/m^3$. A control group of 41 animals was exposed to filtered air. The particle size was 0.55 μm (mass median aerodynamic diameter). After 18 months of continuous exposure, an additional observation period of 13 months was added before the animals were killed for histopathological examinations.

Primary lung tumors had developed in 15% of the animals of group I, in 53% of group II animals, and in 71% of animals in group III. None of the control animals developed lung tumors, and most of the tumors were adenocarcinomas of alveolar origin. This study provides sufficient evidence that cadmium inhaled as $CdCl_2$ aerosols causes lung tumors in rats. In another study using intratracheal instillations of CdO (25 μg weekly for 3 weeks) in rats, Sanders and Mahaffey could not induce lung tumors (*7*). Obviously, the method of pulmonary administration (inhalation vs. instillation) as well as the duration of administration are of prime importance for demonstrating a carcinogenic effect on the lung.

Ten epidemiologic studies have been reported since 1965 (Table 2), but effects on the lung—in particular lung cancer—have been mentioned in only a few of those. Lemen et al. studied cause-specific mortality in a cohort of 292 cadmium production workers who had been employed from 1940 through 1969 for a minimum of 2 years (*8*). The exposure was mainly to CdO, but exposure to arsenic in some areas of the plant could not be excluded. An increased mortality due to cancer of the lung and prostate was found. However, since no attempts were made to correct for smoking habits and for arsenic exposure, this result cannot be used as evidence of a carcinogenic effect of inhaled cadmium in humans.

Armstrong and Kazantzis reported on a very large cohort mortality study involving 6995 workers from 17 different plants (*9*). The workers were exposed to CdO (as dust and as fume), CdS, and dust from cadmium stabilizers. No increased lung tumor risk was found. However, workers of the "ever high exposure group" were at a significantly increased risk to die of bronchitis.

Sorahan and Waterhouse conducted a prospective mortality study of 3026 nickel-cadmium workers (*10*). The workers were grouped according to "high exposure," "moderate exposure," and "minimal exposure." Although a significant risk of lung cancer was found in the moderate-exposure group, the authors attributed this to exposure of oxyacetylene in welding fumes, as this was not observed in the high-exposure group.

In an update of the Lemen et al. study, Thun et al. expanded the original cohort to 602 workers who had been employed at the plant for at least 6 months between 1940 and 1969 (*3*). Vital status was determined through 1978. Mortality from respiratory cancer was significantly increased among the workers employed for two or more years (16 observed vs. 7 expected). A central finding was also that lung cancer mortality increased significantly with increasing cumulative exposure to cadmium. The risks of developing lung cancer due to smoking or arsenic exposure alone were calculated but did not explain the observed significant increase in lung cancers.

In contrast, White et al. came to a different conclusion

Table 2. Epidemiology of cadmium carcinogenesis.

Study group	Exposure	Findings	Reference
74 workers of alkaline battery factory	CdO dust	3 cancer of prostate 1 cancer of bronchus (no comparison group)	(*61*)
246 workers	CdO dust	Cancer of prostate significantly increased (0.6 expected, 4 observed)	(*62*)
536 workers of alkaline battery plant	$Cd(OH)_2$; $Ni(OH)_2$	No excess cancer	(*63*)
64 renal and 74 colon cancer patients	Cigarette smoking, Cd industry	Increased risk of renal cancer (also exposure to other pollutants)	(*64*)
292 cadmium smelter workers	CdO (some As)	Increased mortality due to lung cancer and prostate cancer; no correction for As and smoking	(*8*)
269 workers of cadmium-nickel factory and 94 cadmium-copper alloy workers	$Cd(OH)_2$; $Ni(OH)_2$	Excess cancer of nasopharynx (Ni?)	(*65*)
347 cadmium-copper alloy workers and 624 vicinity workers	CdO (fume)	Excess deaths from pulmonary disease (not cancer); elevated risk of lung cancer in vicinity workers (As? smoking?)	(*66*)
6,995 male cadmium workers of 17 different plants	CdO, dust and fume; CdS; dust from Cd stabilizers	No significant excess lung cancers; high risk of dying from bronchitis in "ever high" exposure group	(*9*)
3,026 nickel-cadmium battery workers	CdO	Significant increase in respiratory cancer in "high to moderately" exposed workers but not in "high-exposure" group (confounding factor?)	(*10*)
602 cadmium production workers	CdO, dust and fume; CdS, $CdSO_4$ (some As)	Lung cancer incidence increases significantly when employed for 2 or more years and with cumulative exposure; smoking and arsenic exposure do not account for increase	(*3*)

(*11*). Their study cohort consisted of 672 cadmium production workers at the same plant as the Thun et al. study. These authors confirmed an increased lung cancer mortality among the workers, which was significantly correlated with estimated cumulative cadmium exposure. However, they contend that smoking and arsenic exposure might explain this excess of lung cancer mortality. A detailed analysis of the data to support this claim is not possible because the full paper has not yet been published.

The study by Thun et al. provides the best evidence to date that cadmium inhaled as CdO particles may be a human lung carcinogen (*3*). However, because of the possibility that confounding factors may be involved, this evidence is limited according to the criteria of the International Agency for Research on Cancer (*12*).

Several differences have to be considered when comparing the positive results of the rat study by Takenaka et al. and the results of the human epidemiologic studies (*4*). First of all, workers were exposed to CdO as dust or fume, which could act differently than the water-soluble $CdCl_2$ aerosols. The particle sizes of the dust could be considerably larger than the submicronic $CdCl_2$ particles administered in the rat study. Deposition in the respiratory tract is determined by particle size, among other things. This is indicated in differences in tumor sites in the respiratory tract of rats and humans: the tumors were mostly of alveolar origin in the rats and mostly of bronchogenic origin in the cadmium workers. Other factors that have to be considered are differences in the metabolism of inhaled cadmium (retention and accumulation), induction of metallothionein, combined exposures of cadmium, and other pollutants that may add to or protect from cadmium toxicity. The importance of the recovery period for detoxification and repair processes should also be considered.

Several basic questions remain to be answered before cadmium compounds in general can be classified as human lung carcinogens. With regard to epidemiology, a major point that is often overlooked is the different physicochemical form of a cadmium compound to which humans are exposed. It would be desirable in epidemiologic studies to group cohort members not only according to duration and level of exposure but also according to the cadmium compound to which they were actually exposed. For example, the large cohort studied by Armstrong and Kazantzis included workers exposed to CdO as dust and fumes, CdS particles, and dust from Cd stabilizers, yet they were all grouped together (*9*). Workers in the studies by Thun et al. (*3*) and White et al. (*11*) had been exposed to CdO (as dust or fume), $CdSO_4$, or CdS. It is conceivable that cadmium in CdS particles is less bioavailable than in CdO particles (*13*). However, CdO may also exhibit different toxic effects depending on whether it is inhaled as freshly generated CdO fume or as aged CdO dust.

In addition to separating worker cohorts according to the physicochemical form of cadmium, attempts should also be made to quantify exposure; that is, the question

of the dosimetry of inhaled cadmium should be addressed. This includes exposure concentrations, duration of exposure, and particle sizes in order to estimate the dose deposited in the deep lung or in the conducting airways. As a supplement, biological monitoring of cadmium levels in urine should be performed, as this reflects body cadmium burden, if kidney damage is absent. If available, cadmium organ burden in autopsy material should be determined. Combined exposures to other metals should also be taken into account, as they may explain additive, synergistic, or even antagonistic effects. Levels of other air pollutants that may affect the respiratory system (bronchitis, effect on clearance mechanisms) should also be monitored, as they may indirectly influence induction of lung cancer by cadmium. It is mandatory that epidemiologic studies on lung cancer correct for smoking histories.

With regard to animal studies, data are needed on the carcinogenic effect of inhaled cadmium compounds other than $CdCl_2$, in particular CdO (both as dust and as fume) and CdS (both fired and unfired). These are the relevant cadmium compounds to which workers are exposed. The studies should be long-term inhalation studies, and in addition to the rat, another species should be chosen, with both sexes included. Also of interest is a comparison of the effects of continuous versus intermittent (8 hr/day, 5 days/week) exposures in order to study the importance of the recovery phase. Combined exposure to cadmium plus zinc aerosols would address the question of a possible protective effect of zinc. Nothing is known about lung retention and translocation of inhaled CdS particles, which could be quite different from inhaled $CdCl_2$ and CdO. This should be investigated, as it may be helpful for calculation of the accumulated dose in the lung. Finally, the bioavailability of different cadmium compounds—in particular CdS—to the lung should be investigated in short-term studies. These would include effects on the integrity of bronchial and alveolar epithelium, the free cell pool of the lung, and induction of metallothionein in different cells of the respiratory system.

Pulmonary Carcinogenicity of Arsenic

The carcinogenic potential of arsenic has been studied in a number of settings. Exposure by inhalation is clearly related to the development of lung cancer in (copper) smelting and arsenical pesticide manufacturing (*2,14*) and apparently also in heavily exposed vintners who had an additional source of exposure by ingestion. Exposure by ingestion (through arsenic contamination of drinking water or by past use of medicinal arsenic preparations) is related to the development of nonmelanoma skin cancer (*15*) but rarely to hepatic angiosarcoma.

Table 3 lists and briefly summarizes key information related to the studies discussed below.

Occupational Exposures

In the United States, three smelters have been studied in detail, and several follow-up studies have been done, at different time intervals, of workers at the Anaconda, MT, and the Tacoma, WA, smelters. Studies have also been done at smelters in Sweden and Japan.

Results of the studies are consistent in that a significantly increased risk for respiratory cancer has been demonstrated among employees at all five smelters, ranging from about 2-fold to 5-fold among all workers studied. In the smelters studied in detail, a dose-response relationship to arsenic was found, with the "highest" exposed groups having relative risks in the range of 5 to 10. (The relative risks for the Japanese cohort were outside these ranges, with the relative risk of 9 for all workers and 25 for the highest exposed group.)

In these studies, mortality was analyzed for varying lengths of time between 1938 and 1977, although exposure goes back further than 1938 for many workers included in these studies. In general, arsenic-exposure data are sparse; limited data from periodic industrial hygiene surveys or urine-monitoring programs were available for ranking or estimating exposure, particularly in the Anaconda and Tacoma smelters. These data and knowledge of smelter operations appear to be adequate for qualitative grouping of exposure levels.

Exposure data at the Anaconda and Tacoma smelters have also been used for quantitative risk assessment. While sufficient data are available to carry out the assessment, the limitations of the exposure data, particularly at high-exposure levels (where the range, peak, and mean exposure levels are incompletely characterized), are significant.

The studies summarized in Tables 3 and 4 have varied comparison groups as reference populations for establishing risks (i.e., national data, state data, and local or internal comparison data). This should be kept in mind when relative results are being considered.

Other factors that might have influenced risk estimation are smoking and the presence in smelters of potential respiratory toxins in addition to arsenic. Data on the interaction of smoking and arsenic exposure are available in three studies and are presented in Table 4. The results of Pershagen et al. (*16*) indicate a multiplicative effect, although those of Rencher et al. (*17*) suggest an effect intermediate between additive and multiplicative. The data from Welch et al. are consistent with a multiplicative effect but are based on very small numbers (*18*).

In summary, the relationship of arsenic to increased risk of lung cancer in smelter workers appears unequivocal. Data from two cohorts have been used by the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and others for quantitative risk assessment. Data are limited in relation to smoking history, arsenic exposure, and exposure to other potential respiratory toxins. There are virtually no studies of pulmonary morbidity in these groups of smelter workers.

Table 3. Risk of lung cancer to workers at copper smelters and pesticide manufacturing plants.

Occupation	References	Type of study	Size	Years of study[a]	Risk[b] Observed vs. expected
Smelters					
Anaconda, MT	(*18,57,67,68*)	Cohort	8,047 workers	1938–63	147 vs. 44.7 SMR = 329[c]
		Cohort	5,403 workers	1964–77	146 vs. 88.7 SMR = 165
		Cohort	1,800 workers	1938–77	Heavy exp.: 24 vs. 4.6 SMR = 527 Other exp.: 56 vs. 20.9 SMR = 267
		Cohort	8,045 workers	1938–77	302 vs. 105.8 SMR = 285
Tacoma, WA	(*60,69–71*)	PMR	229 deaths	1946–60	18 vs. 8.6
		Cohort	—	1950–71	40 vs. 18
		Cohort	527 pensioners	1949–73	32 vs. 10.5 SMR = 304.8
		Cohort	2,802 workers	1941–76	104 vs. 54.9 SMR = 189.4
Magna, UT	(*17*)	PMR	244 deaths	1959–69	17 (7.0% vs. 2.7%)
		Cohort	—	—	Mort. ratio = 3.06
Sweden	(*72,73*)	Case-control	29 cases	1960–76	Rate ratio = 4.6
		Cohort	3,958 workers	1928–77	76 Observed SMR = 288
Japan	(*74,75*)	Case-control	19 cases	1967–69	Relative risk = 9.0
		Cohort	839 copper smelters	1949–71	29 vs. 3.18 SMR = 912 (ICD 160-3) 29 vs. 2.44 SMR = 1,189 (ICD 162)
Pesticide manufacturing plants					
England	(*76*)	PMR	75 deaths	1910–43	7 vs. 2.5
Midland, MI	(*47*)	PMR	173 deaths	1940–72	28 Observed (16.2% vs. 5.7%)
		Cohort	603 deaths	1940–73	20 vs. 5.8 SMR = 345
Baltimore, MD	(*46*)	Cohort	1,393 workers	1946–77	23 vs. 8.7 SMR = 265 (U.S. white male comparison) 23 vs. 13.7 SMR = 168 (Baltimore City white male comparison)

[a] Years of study refers to observation period for development of respiratory cancer, not to years of exposure.
[b] Observed and expected numbers refer to deaths from respiratory cancer or lung cancer, whichever is used in original article.
[c] SMR: Standardized mortality ratio.

Table 4. Smoking and arsenic exposure in relation to lung cancer risks: data from occupational cohort studies at three smelters.

	Arsenic (+)	Arsenic (−)	Arsenic exposure category: Very high	High	Medium	Low	Reference
SRR in lung cancer case-control study[a]							(*16*)
Nonsmokers	3.0	1.0					
Smokers	14.6	4.9					
Percentage of deaths at each location due to lung cancer							(*17*)
Nonsmokers	3.3[b]	0.7[c]					
Smokers	9.2[b]	3.3[c]					
Respiratory cancer SMR[d]							(*18*)
Nonsmokers			620	286	89	95	
Smokers			803	359	312	120	

[a] Standardized rate ratio.
[b] Smelter.
[c] Mine.
[d] Standardized mortality ratio.

Cohort studies have been conducted at arsenical pesticide manufacturing plants in Baltimore, MD, and Midland, MI, and a proportional mortality study was done at a sheep-dip manufacturing plant in England. All three of these studies demonstrate a relationship between arsenic exposure and increased risk for lung cancer. The increased risk is somewhat less (see Table 3) than that for smelter workers, but the risks cannot be directly compared because different arsenical compounds were used in these settings. Characterization of arsenic exposure levels in the Ott study (Midland, MI) was sufficient for quantitative risk assessment, with the same caveats as above. In the last 25 years, however, the production of arsenical pesticides has dramatically decreased as their uses have been phased out.

In addition to the summary data in Table 3, several features of these studies should be noted. All the data are for males, except in the Mabuchi study, which included a female study cohort. In most of the studies, either arsenic exposure levels were not measured or qualitative estimates were used. A dose-response relationship between arsenic exposure (based on qualitative or quantitative categorization of exposure status) and lung cancer is consistently seen. Other chemicals to which the study groups were exposed were usually not measured or evaluated in detail; when this was done, no dose-response relationship to lung cancer was seen. Elevated mortality from causes other than lung cancer (e.g., cardiovascular disease, cerebrovascular disease, digestive cancer, lymphoma, and anemia) was seen in individual studies (or in sequential studies at single locations), but no consistent patterns emerged. In the cohort studies, reference data came from local, state, or national data; in a few studies, two sets of reference data were used. Finally, in some studies data for cancer of the respiratory system were used, but in others, only data for lung cancer were used. In several studies, data for both were provided, but in others, the particular International Classification of Diseases (ICD) Codes or the disease categorizations were not provided. All these differences in circumstances and methods suggest caution when quantitative results are directly compared among the studies.

In other occupational exposures involving arsenical pesticide applicators, an autopsy study of a group of presumably heavily exposed vintners demonstrated a strikingly increased proportion of lung cancer, although the selection procedures and methods used are not fully defined (*19*). Eleven of 27 had lung cancer; 4 of 27 had liver cancer. The latter may be due to simultaneous exposure through ingestion of an arsenic-containing drink made from grape skins. A follow-up study by Luchtrath lends further support to this relationship; in this update, lung cancer was found in 66% of an autopsy series of 163 former Moselle vintners (*20*).

Environmental Exposure

Analysis of U.S. county mortality data (1950–69) demonstrated increased lung cancer rates for 31 counties containing nonferrous smelters (*21*). The environmental exposure data and the plausibility of county-wide exposure are not detailed. Rom et al. and Lyon et al. found no evidence of a relationship between lung cancer mortality and distance between residence and smelter (up to 20 km) for the smelter counties they studied (*22,23*); again, few environmental exposure data are provided, and it is not clear whether significant exposure would extend beyond several kilometers from the plant. Matanoski et al. did find an elevated lung cancer rate in males in the census tract in which an arsenical pesticide manufacturing facility was located (*24*). Brown et al. showed 2-fold risks for lung cancer associated with residence near a zinc smelter and increased exposure to arsenic, cadmium, and several other metals, but the authors did not consider their results to be conclusive (*25*). Several additional studies have been done with differing and not definitive results (*26–28*). In summary, further evaluation and study are required, particularly for smelter counties, before a definitive conclusion can be reached about the significance of environmental arsenic exposure as a cause of lung cancer. In addition, the relative contributions of air and soil/dust arsenic levels need to be considered.

Occasional case reports of lung cancer related to ingestion of medicinal arsenic have appeared (*29*). Reports from Argentina mention cases of lung cancer in relation to arsenic-contaminated drinking water in Cordoba Province, but this relationship is not well characterized. Several studies suggest an increased risk for lung cancer in individuals with arsenic-induced skin disease or skin cancer (*30*), but the data are limited.

Experimental Carcinogenesis

For many years, arsenic has been considered to be a human carcinogen, even though there is no experimental model for carcinogenesis. Several recent studies have suggested that intratracheal installation of arsenic, along with particulate matter or compounds that increase retention in the lung (i.e., inhibit absorption), can lead to lung tumors, particularly in the Syrian golden hamster (*31–34*). It is unclear how this relates to humans.

Issues

1. Is occupational exposure to arsenic a significant and continuing problem? Are there industries in which exposure exceeding the OSHA standard (10 $\mu g/m^3$) is likely to continue or to appear? Is there an international problem from (copper) smelters?

2. Heavy arsenic contamination of soil (and potentially of groundwater, surface water, air, etc.) exists near abandoned copper smelters. (a) Are nearby populations at significant risk of exposure? (b) Should lung cancer risk in relation to past exposure from air or current exposure from soil be further evaluated? (c) Should the extent of the Comprehensive Environmental Response Compensation and Liability Act of 1980 (Superfund) re-

medial action (i.e., environmental cleanup) at these sites be dependent on the results of such studies?

3. At the current occupational standard, are workers still at significant risk? If risk assessment calculations suggest that this is so, should the standard and/or the risk assessment approach be reconsidered?

4. How relevant are recent experimental carcinogenicity data to human arsenic carcinogenesis? How relevant are they to other particulate respiratory carcinogens?

5. Is a unique histologic type of lung cancer associated with arsenic exposure? Results of the two studies already done show different histological distributions from those expected, but they disagree on which histological type is increased (*35*,*36*).

Exposure Assessment for Arsenic and Cadmium

The goal of environmental health is to control or eliminate risks of lung cancer from environmental exposures. When exposure cannot be eliminated, control can best be achieved if the quantitative relationship (dose-response curve) for exposure and risk is known.

The general relationship between exposure and cancer is diagrammed in Figure 1 (*37*). Exposure is defined as the composition and concentration of the agent in the breathing zone; dose is defined as a time function of the concentration of the causal agent at the site of action, such as metal ions in the pulmonary tissues. Dose is quantitatively related to the intensity of the cellular effect, whereas measures of external exposure may not be. The cancer risk is related to the intensity and duration of the cellular effects and additional biological factors associated with the natural history of the disease (e.g., the lag or induction time) and with host factors (e.g., age, sex, and race), quantitative effects of which are included in the weighting function, $g(T\text{-}t)$. Several key factors are indicated in this diagram. (1) Agent characteristics affect both the dose and the effect: *in vivo* solubilization of metal compound, ability of the active form (e.g., metal ion) to enter target cells, and ability of the active form to cause damage or contribute to the cancer-development process. (2) Exposure conditions control the amount deposited in various parts of the respiratory tract: air concentration, water solubility of gases (e.g., arsine), and size distribution of particles. (3) Personal factors, including pulmonary geometry and pharmacokinetics, control the dose by controlling the tissue concentration: fraction of particles deposited and rates of absorption, transport, storage, metabolism, and excretion; personal factors such as age, age at first exposure, sex, and race are also important for cancer risk. (4) Time factors control the dose and development of the effect: duration of exposure at various levels and the occurrence of sufficient lag time. (5) The mechanism of the cellular effects and the natural history of the cancer are summarized. All these factors work in concert to produce a cancer risk. The chemical form of the metal and its route of entry are especially important.

The chemical form of the metal is important because it controls the bioavailability, the time course of tissue concentration, and the ability to cause damage or contribute to the cancer process. Figure 2 shows how acid solubility may affect tissue concentration of cadmium ions Cd^{+2} produced by the same size particles of three different compounds with different rates of solubiliza-

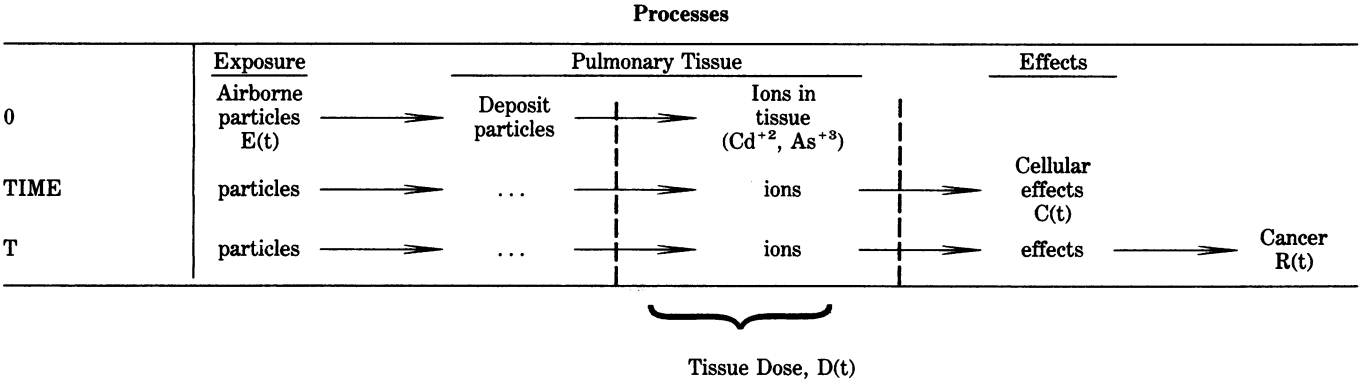

FIGURE 1. Model of environmental lung cancer for metal exposures. The exposure-dose relationship is

$$D(\tau) = \int_0^{\tau} E(t)\, f(I,F,\tau - t)\, dt$$

where $E(t)$ is the breathing zone concentration over time and $f(I,F,\tau - t)$ is a function that depends on the inhalation rate I, the fraction deposited at the target site F, and other pharmacokinetic factors controlling the ion concentration within the target cells. The dose-cellular effect relationship is

$$C(\tau) = 1 + \beta D(\tau)$$

where β is an effect factor characteristic of the specific chemical compound. The cellular effect-cancer risk relationship is

$$R(T) = \int_0^{\tau} C(\tau)\, g(T,\tau)\, d\tau$$

where T is the total time exposed and $g(T,\tau)$ is a weighting function that reflects the latency and host factors such as age, age at first exposure, sex, and race.

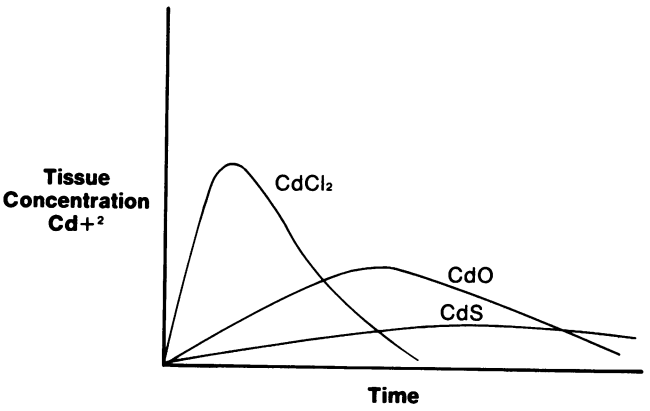

FIGURE 2. Hypothetical tissue concentrations of free ion (excluding protein-bound) produced by cadmium compounds with various acid solubilities ($CdCl^2$ > CdO > CdS) after a single exposure.

tion and total solubility. All produce the same total amounts of Cd^{+2} in the tissues (assuming no clearance of the particles), but the time course and peak concentration are different. Thus, even though all the compounds produce the same active agent, the risks of effects may be different. Particle-size distribution is similarly very important, because it affects where the particles are deposited in the respiratory tract and their solubilization rates. In addition to controlling the tissue dose, chemical form controls the ability of the agent to cause effects. For example, arsenic trioxide in smelter dust has a different toxicity than arsenic in cacodylic acid used as a herbicide.

Route of entry is also important for lung cancer risk. This may be seen in Figure 3, which shows a simple four-compartment model of the body. Metal compounds entering by inhalation may be deposited on the target tissues, whereas those entering by the gastrointestinal (GI) route must pass through the liver, where they may be partially metabolized: arsenic methylated, or cadmium bound to metallothionein, and then diluted with blood returning to the lungs from the other organs. As a result, the pulmonary tissues generally will not experience the same dose with GI exposure as with inhalation unless the amount ingested is massive. This is consistent with the lack of increased lung cancer for either arsenic or cadmium exposures by the GI route. Patients ingesting Fowler's solution, which contains large amounts of arsenic trioxide, have been reported to be at risk of lung cancer, but populations ingesting arsenic-contaminated drinking water are not (*38*).

Arsenic and cadmium are both found extensively throughout the environment as a result of both natural and human activities, and there is a natural cycle of these compounds through the environment (*39–42*). However, aside from arsenic trioxide from volcanic activity, only human activities produce significant air concentrations. Hot metallurgical processes, especially primary and secondary nonferrous smelters (copper, lead, zinc, and their alloys), are the main sources of high occupational and local community exposures to cadmium

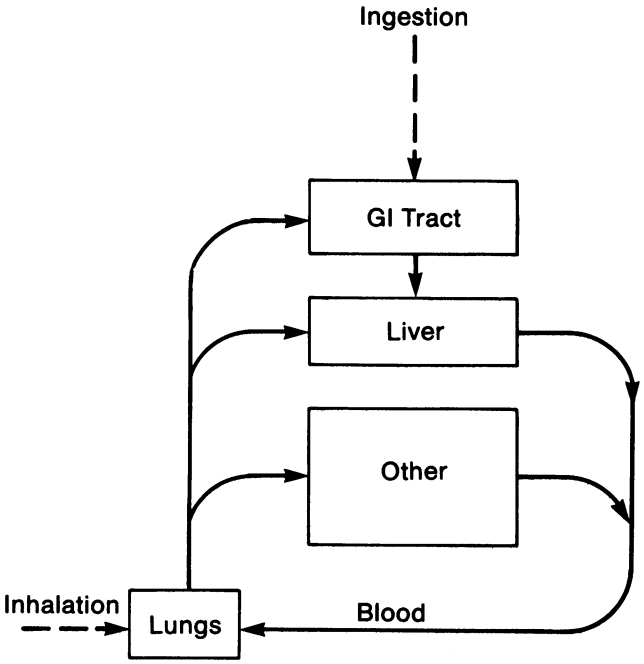

FIGURE 3. Four-compartment model of the body for evaluation of lung tissue dose by inhalation and ingestion routes of exposure.

oxide and arsenic trioxide (*43–45*). Although large total amounts of arsenic and cadmium may be released by coal combustion and municipal incinerators, the air concentrations produced are low because the metal content of the materials burned is low (*41*). There are many other processes that may be limited local sources of occupational exposures to inorganic arsenic: combustion of wood-containing preservatives or wastes containing arsenic compounds, glass and enamel making, and production of high-purity arsenic metal, semiconductor alloys, lead shot, and some lead and copper alloys (*3*). In the past, various arsenic oxides have been used in pesticides and have been associated with major inhalation exposures (*46,47*). Significant occupational exposures are produced in the use of cacodylic (dimethylarsinic) acid as a dessicant for cotton and in forestry applications (*48*). The production of organic arsenic compounds may also lead to local community and occupational exposures, but the levels of exposure have not been documented. Examples of these processes are textile printing; tanning; and production and use of antifouling paints, lubricants, and arsenic-based pesticides, herbicides, and wood preservatives (*43*). Trivalent arsenic (As^{+3}) is oxidized to pentavalent arsenic in the outdoor environment, so smelter emissions deposited in the soil around the plant are converted to less toxic pentavalent arsenic. However, some arsenate is reduced *in vivo* to arsenite, as the environmental oxidation is not fully protective (*49,50*). Thus, soil contamination around industrial sources may be a source of inhalation exposures, as has been noted for soil around smelters contaminated with lead (*51*). Production of nickel-cadmium batteries is also an important source of occupational inhalation

exposure to cadmium oxide (*52*). Limited amounts of cadmium are used as the metal and sulfate for plating and alloys, as the oxide and sulfide for pigments, and as various compounds for additives to plastics and rubber. It is also present as an impurity in zinc products, phosphate fertilizer, and waste products from many operations producing nonferrous metals. Cadmium in particulate urban air pollution is probably predominantly oxide from hot-metal operations and combustion of products containing trace amounts of cadmium; however, it may also be other compounds if there are industrial operations that produce or use cadmium.

The levels of exposure to arsenic and approximate daily pulmonary input by inhalation have been summarized in Table 5 from several sources. The pulmonary inputs for occupational and general exposures were estimated for particles with a mass median diameter of 2 μm by either assuming that 10 m^3 are inhaled by a worker per 8-hr day and 20% of the inhaled dust is deposited in the respiratory tract, or that, for a general community exposure, 20 m^3 are inhaled per 24-hr day and 20% is retained. (These figures do not indicate where in the respiratory tract the particles are deposited, and they are sensitive to the particle-size distribution, the average rate and depth of inspiration, and the fraction of time the subject is exposed, which may be affected dramatically by indoor/outdoor differences for air pollution exposures.) The past respiratory exposures associated with most occupational settings, such as copper smelting or herbicide applicators, are dramatically higher than any of the other environmental exposures, where the range of occupational pulmonary intakes is 200 to 20,000 μg/day of arsenic trioxide or pentoxide. Clearly, the composition will vary with the specific chemical compound being used or produced. Under the current permissible 8-hr OSHA occupational exposure of 10 μg/m^3 of inorganic arsenic, the arsenic intake by inhalation should be less than 20 μg/day, although the actual distribution of exposures is not known. This may be contrasted to the exposures of residents living near a copper smelter, who may inhale 1 to 2 μg/m^3 of arsenic trioxide during a 24-hr exposure and have a pulmonary intake of 4 to 8 μg/day if their indoor exposure is the same as outdoors (which it probably is not). There are other localized exposures to industrial sources of arsenic compounds and to airborne dusts contaminated with pesticides or herbicides. Urban residents would have an approximate range of pulmonary doses of 0.08 to 0.28 μg/day. Cigarettes may be the major source of inhalation exposure to arsenic (probably trioxide), <3 μg/day, if exposure is not occupational, but this is uncertain because of insufficient data.

Table 5. Sources of arsenic and cadmium inhalation exposure.

	Arsenic (25–40% deposition and absorption depending on particle size and chemical form)	Cadmium (25–90% deposition and absorption depending on compound and particle size distribution)
Occupational exposure (8-hr exposures)		
Past cancer studies		
Pesticides	0.1–50 mg/m^3 (Pb, Ca, Mg arsenate, Cu acetoarsenite) 200–20,000 μg As/day	—
Smelters	0.3–11 mg/m^3 (As_2O_3, As sulfide) 600–22,000 μg/day	0.04–17 mg/m^3 (Cd oxide, sulfate, sulfide) 80–34,000 μg/day
Current exposure limits		
OSHA	< 10 μg/m^3 (inorg. As) < 20 μg/day	< 100 μg/m^3 (CdO fume) < 200 μg/day
TLV	None, inorganic As cancer agent	< 50 μg/m^3 (CdO fume) < 100 μg/day
Cigarettes		
Occupational contamination	—	< 20 μg/cigarette < 40 μg/day
General contamination	< 0.15 μg/cigarette < 0.3 μg/day	1–2 μg/cigarette 2–4 μg/day
Air pollution (24-hr exposure)		
Near source	1–2 μg/m^3 near smelter 4–8 μg/day	0.2–0.6 μg/m^3 0.8–2.4 μg/day
General	0.02–0.07 μg/m^3 0.08–0.28 μg/day	0.002–0.05 μg/m^3 0.008–0.2 μg/day

It has been possible to determine total arsenic content of environmental and tissue samples for the last 30 years (*43*). Only recently has it become possible easily to determine arsenite and arsenate and the two common methylated forms (monomethylarsenic and dimethylarsenic acids, and their salts) (*53*). Because the toxic and probably carcinogenic properties of arsenic are determined by its chemical form, application of these methods is very important. Dimethylarsinic acid in the urine is the best biological index of exposure to inorganic or methylated forms of arsenic (*54*). The lack of specific chemical information on arsenic forms has made it difficult to interpret the risk represented by some environmental data on total arsenic exposures.

A summary of the levels of cadmium exposure and approximate daily doses by inhalation intake are given in Table 5. As with arsenic, past and current occupational exposures are the highest source of respiratory intake and are probably orders of magnitude higher than any other source of airborne exposure. Cigarettes are a major source of respiratory intake in the absence of occupational exposure, which may equal or exceed the intake from air pollution from point sources.

Accurate analysis of total cadmium in environmental samples has been possible since the early 1970s (*55*). However, because of the analytical difficulty, no attempt has been made to determine the chemical form of the cadmium, which makes it difficult to estimate the bioavailability of cadmium in these materials. This has occurred in spite of Friberg and co-workers' recommendation in 1974 that the composition of cadmium compounds in air pollutants should be determined. Internal doses can be estimated with biological monitoring data

obtained from analysis of urine or blood samples or by *in vivo* measurement of liver and kidney burdens (*56*).

Risk Assessment

Arsenic

The epidemiological data on the carcinogenicity of arsenic has been reviewed by the EPA (*2*) and used for purposes of quantitative risk assessment. The analysis was confined to data from three reports on the Anaconda smelter workers (*57–59*), the American Smelting and Refining Company (ASARCO) smelter workers (*60*), and the Dow pesticide manufacture workers (*47*). The latter was deemed the least reliable for quantitative estimates, in part because it also included exposures to pentavalent arsenic whereas the others involved only trivalent arsenic, and it was excluded from their final risk assessment. Each of these data sets (with the exception of the Brown and Chu analysis based on multistage models described below) was fitted by Poisson regression techniques to four models: relative risk or absolute risk, as both linear and quadratic functions of cumulative exposure. In all data sets, linear models fit better than quadratic models, and absolute risk models fit better than relative risk models. Thus, only the linear absolute risk model fits were retained for the purpose of risk assessment. For the ASARCO smelter workers, two versions of the data were available, one with no lag in the exposure and one with a 10-year lag; no lags were used in either the Lee-Feldstein or the Higgins et al. data. The resulting slope coefficients were then applied to a standard life table calculation to derive a "unit risk" estimate, being the excess lifetime risk of lung cancer resulting from a constant exposure to 1 $\mu g/m^3$. The estimates obtained in this way ranged from 2.8 to 4.9 excess cancers per 1,000 person-$\mu g/m^3$ for the Anaconda smelter and from 6.8 to 7.6 for the ASARCO smelter.

With the exception of the 10-year lag involved in one of the ASARCO estimates, none of these risk estimates take any account of latency. The 10-year lag allows for a period of no effect immediately following exposure but assumes that the effect remains constant thereafter. An alternative is posed by the use of multistage models in the analysis of the Anaconda smelter by Brown and Chu (*59*). This involves a weighting of each increment of exposure by a power function of both age at exposure and time since exposure, the exponents of each depending on the stage of the carcinogenic process that is influenced by arsenic exposure. Brown and Chu contrasted a first and penultimate stage effect and found the latter to give a much better fit to the data. Integration of this weighting function over ages at exposure then allowed the slope coefficient they derived to be expressed in a similar manner as a unit risk, resulting in an estimate of 1.25 per 1,000 person-$\mu g/m^3$, much smaller than the other two estimates from this smelter. The difference is easily explained by the fact that, under the assumption of a late-stage effect, the increased risk occurs rapidly after exposure and then tapers off after cessation of exposure. Thus, a high slope coefficient estimated from truncated followup of an occupational cohort translates into a much lower lifetime risk estimate.

The final unit risk estimate suggested by EPA of 4.29 per 1,000 person-$\mu g/m^3$ was obtained by taking a geometric mean of the five risk estimates (*2*).

Cadmium

The EPA risk assessment for cadmium is based on the data of Thun et al. (*3*). Restricting the cohort to those first employed after 1925 with at least 2 years of employment, 16 lung cancers were observed, with 7.0 expected. Using a mean cumulative exposure estimate of 1741 $\mu g\text{-day}/m^3$ and methods similar to those described above, a unit risk estimate of 1.8×10^{-3} per person-$\mu g/m^3$ was derived (*1*).

The EPA risk assessment document for arsenic (*2*) includes a comparative table of "relative carcinogenic potencies" among 52 chemicals evaluated by the carcinogen assessment group as suspect human carcinogens, based largely on toxicologic evidence. The potency index given for arsenic is 2000; for cadmium it is 700.

Research Recommendations

Using currently available data on levels of inhalation exposure to arsenic in the most likely settings for exposure (ambient air, small communities around smelters, occupational exposure, and cigarette smoking), and applying the respective total population at risk for each type of exposure, estimates of national exposure to arsenic and cadmium in the United States were derived. The application of the standard risk assessment models for extrapolating arsenic and cadmium dose-response data to national exposure estimates led to the prediction of more than 100,000 excess cases of lung cancer (lifetime) due to both arsenic and cadmium exposure in the U.S. population (see Table 1). Additionally, lung cancer risks exist for other metals such as nickel, chromium, and beryllium.

If these estimates are correct, significantly increased prevention activities are called for. If the estimates are incorrect or if there are large areas of uncertainty that can be resolved, it is important to identify such problems so that scarce resources can be better used elsewhere. The following recommendations have been identified to resolve this issue. Analogous recommendations could be developed for other metals that are or may be lung carcinogens.

Exposure Assessment

Recommendation 1: A national effort should be mounted to estimate the populations exposed to specific metal compounds by level of exposure so that priorities and the magnitude of the problem from carcinogenic metals can be determined.

Risk assessment requires knowledge of the number of people exposed to various levels of specific metal

compounds for which dose-response relationships are known. At present, these data do not exist for either occupational groups or local community groups near point sources. NIOSH's National Occupational Hazard Survey attempted to provide some of this information but was limited and did not include determinations of exposure levels. Data on communities around point sources may exist but have not been collected and probably are very uneven.

To acquire needed information, improved dose-response data and risk assessment models are needed. Specifically, the following are recommended.

Recommendation 2: Followup of existing cohorts should continue in order to refine knowledge about the evolution of risk over time.

Recommendation 3: The environmental data base for these cohorts should be further refined by reconstruction of physical and chemical attributes and biological monitoring approaches.

Recommendation 4: To support the above recommended reconstruction, occupational environments in foreign countries that resemble the conditions to which the U.S. cohorts had been exposed should be identified and the necessary environmental measurements be made.

Recommendation 5: Cohorts of foreign workers with these same occupational exposures should be identified, and their cancer experience should be assessed, both retrospectively and prospectively.

Recommendation 6: There should be studies of all sufficiently large populations exposed by virtue of residence in the vicinity of all active or formerly active smelters to arsenic or other metals that can be carcinogenic. They should be studied in terms of cancer incidence or mortality, by cross-sectional, case-control, cohort, or other unspecified approaches, in relation to a thorough environmental assessment.

Recommendation 7: Data from the existing cohort studies, refined as detailed above, should be made available to an appropriate, multidisciplinary team of investigators for analysis of relevant issues. The team should have access to raw data from all studies of the same agent.

Animal Studies

Recommendation 8: Long-term inhalation studies with cadmium oxide, as dust and as freshly generated fumes, as well as cadmium sulfide particles, are needed.

These studies should be performed in the rat and at least one other species and should include both sexes. Such studies would allow comparison of the relative carcinogenic potencies of the different cadmium compounds. For example, the question can be answered as to whether cadmium sulfide, an important occupationally encountered substance, has a higher or lower carcinogenic potency than cadmium oxide.

Recommendation 9: A suitable animal model for studying arsenic and lung cancer needs to be developed.

Recommendation 10: Combined exposures of animals to cadmium and zinc, in both short- and long-term experiments, should be performed to address the question of the possible protective effect of zinc. Zinc is significant in many occupational exposures to cadmium. Likewise, the effects of arsenic and cadmium, in combination with other environmentally relevant pollutants such as cigarette smoke and sulfur dioxide, should be investigated.

Recommendation 11: Animal studies should include animals of varying ages and durations of exposures. The question of a possibly greater effect on the growing lung should be investigated by starting exposure at a very young age. The importance of the recovery phase should be studied by comparing intermittent versus continuous exposure.

Recommendation 12: Studies are needed on the retention of cadmium and arsenic of different chemical forms to obtain more background data for modeling.

Recommendation 13: The acute pulmonary effects of the metals should be studied in more detail. For example, study is needed on effects on the bronchial and alveolar epithelium (using different particle sizes), effects on alveolar free cells and on biochemical markers, and induction of metallothionein by different cadmium compounds. The effects on the immune system after inhalation exposure should also be investigated.

Recommendation 14: Information on mechanisms from animal studies should be supplemented by *in vitro* studies. *In vitro* studies should include cell culture studies on the uptake of the metals into the cells of the respiratory tract. The metabolism of the metals in those cells should also be studied, for example, methylation of arsenic or the involvement of metallothionein in cadmium metabolism. Finally, studies should be performed of metal-DNA interactions, metal uptake into the cell nucleus, and binding of the metal to RNA or DNA.

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